CHAPTER III

Basic Pharmacological Properties

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A. Introduction

This chapter intends to portray the present knowledge on site and mechanism of action of the ergot alkaloids. The presentation is based chiefly on selected work performed in defined isolated systems in which the interference with specific substrates usually called receptors has been sufficiently proven. We hope that this presentation will contribute to the understanding of the complexity of ergot pharmacology as presented in the following chapters.

For many years it was considered that the stimulant activity of ergot alkaloids in different test preparations was due to a "direct" effect on smooth muscle cells, although the antagonism against catecholamines or 5-HT (5-hydroxytryptamine), indicating an affinity to specific receptor sites, was already regarded as a characteristic property of ergot compounds.

It must be assumed now that not only the inhibitory but also the stimulant activities of several ergot alkaloids and related compounds are mediated by interference with those specific constituents of a cell which are called drug receptors. Receptors are thought to be of molecular dimensions and probably form part of the surface of the cell membrane. A characteristic property of receptors is their specificity, which implies that structurally different drug molecules interact with structurally specific receptors. A three-point alignment between drug and receptor may be the minimal requirement for pharmacologic activity of drugs. However, the effect of an interaction of an ergot alkaloid with a receptor depends not only on the type of ergot compound but probably also on the environment in which the receptor exists. Accessory receptor areas might increase the affinity of an ergot alkaloid to the receptor site or lead to the formation of a slowly reversible complex between an ergot alkaloid and a receptor. In addition to the living substrate employed, the time pattern, e.g., the extent of latency period for maximum action of the drug, is also of importance. Nevertheless, drug action throughout this chapter will be considered within the simplified framework of the classical drug-receptor interaction theory.

A brief outline of receptor theory, insofar as it is relevant to the action of ergot alkaloids, is given below.

It is generally assumed that the first event in drug action is the formation of a reversible complex between receptor R and drug D, following the laws of second order reaction kinetics, $R+D \rightleftharpoons RD$, and that this leads to a pharmacologic

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response through several intermediate stages. If the law of mass action applies to the combination between drug and receptor, the proportion y of receptors activated by the drug is

$$y=\frac{K_1 A}{K_1 A+1} \tag{1}$$

where A is concentration of drug and K_1 the affinity constant (reciprocal of dissociation constant) of the drug-receptor complex.

Competitive Drug Antagonism

When an agonist and antagonist compete for the same receptor

$$y=\frac{K_1 A}{K_1 A+1}=\frac{K_1 A x}{K_1 A x+K_2 B+1} \tag{2}$$

where y is the proportion of receptors occupied by agonist, A and B are the respective concentrations of agonist and antagonist, and K_1 and K_2 the respective affinity constants of the agonist-receptor complex and antagonist-receptor complex, and x is the dose ratio. The dose ratio is the multiple of the agonist dose required to maintain an unchanged response in the presence of an antagonist. The dose ratio is particularly relevant in competitive antagonism when the log dose-response curves of the agonist in the absence and presence of antagonist are parallel.

It must be understood that the term y does not refer to a physiologic response but to the fraction of agonist-occupied receptors. Nevertheless, it is usually assumed that in a series of parallel log dose-response curves, equal responses correspond to equal fractions y of agonist-occupied receptors. Competitive antagonists produce parallel log dose-response curves (ARUNLAKSHANA and SCHILD, 1959; SCHILD, 1969). Furthermore, in the simplest type of competitive antagonism in which one molecule of drug or antagonist occupies one receptor, the degree of displacement of the curves obtained in the presence of different concentrations of antagonist is determined. Examples of experimental curves showing competitive antagonism in an isolated preparation are shown in Figures 1 and 2.

From such curves the affinity constant of the antagonist-receptor complex may be obtained. By algebraic transformation of eq. (2)

$$K_2=\frac{x-1}{B} \tag{3}$$

and since the terms x and B are known, K_2 may be calculated. When $x=2$

$$K_2=\frac{1}{B}$$

and

$$\log K_2=-\log B=pA_2$$

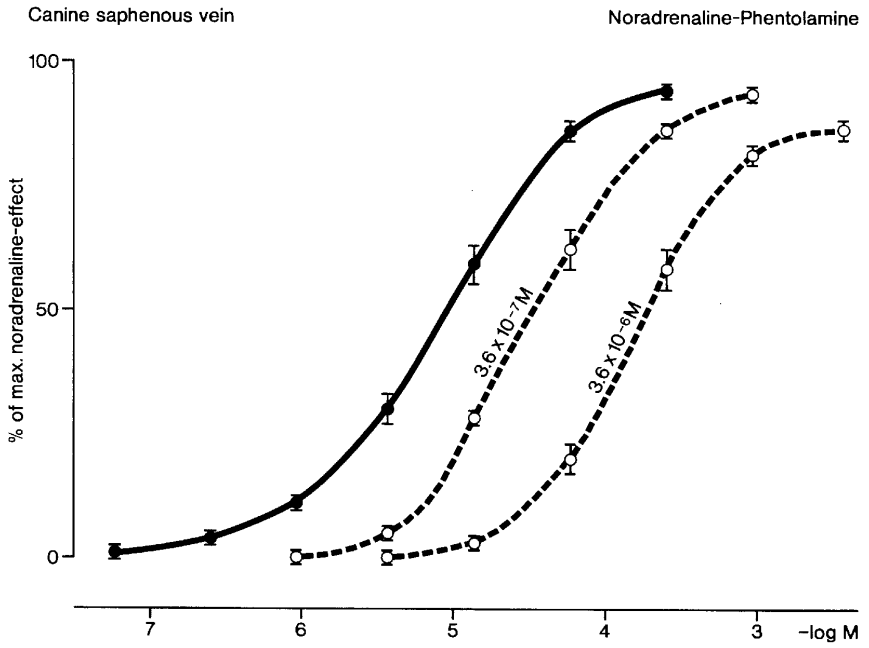


Fig. 1. Cumulative concentration-response curves for noradrenaline without (●—●) and 15 min after phentolamine (○---○) in the final concentrations of 3.6×10^{-7} and 3.6×10^{-6} M on spiral strips from canine saphenous veins. The bars represent ±SEM. [From Figure 4, MÜLLER-SCHWEINITZER, E., STÜRMER, E.: Blood Vessels **11**, 186 (1974)]

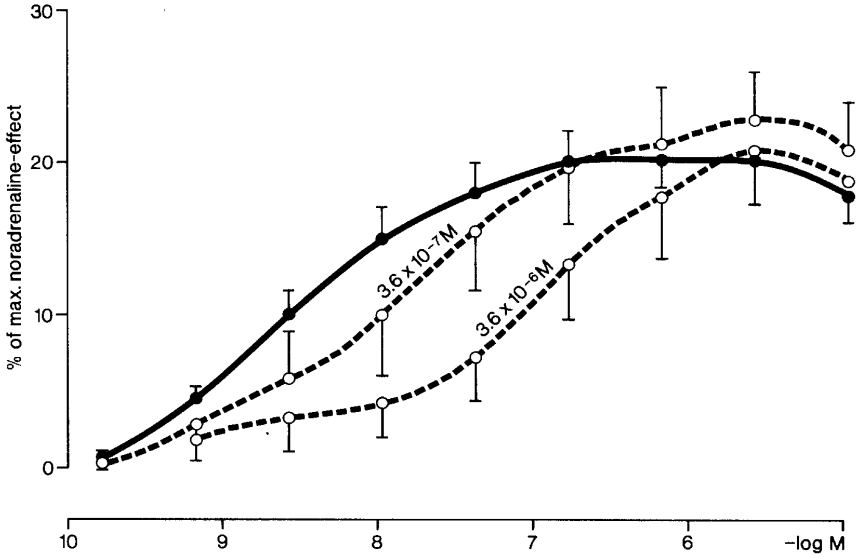


Fig. 2. Cumulative concentration-response curves for ergotamine without (●—●) and 15 min after phentolamine (○---○) in the final concentrations of 3.6×10^{-7} and 3.6×10^{-6} M on spiral strips from canine saphenous veins. The bars represent ±SEM. [From Figure 5, MÜLLER-SCHWEINITZER, E., STÜRMER, E.: Blood Vessels **11**, 187 (1974)]

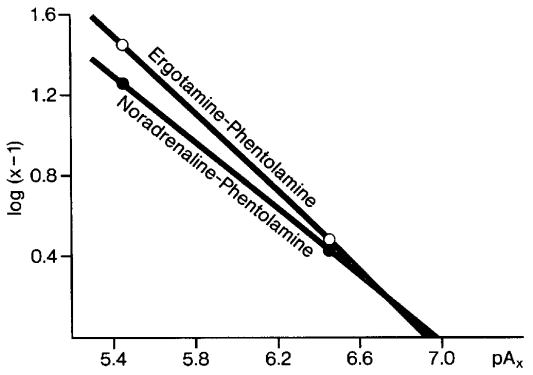


Fig. 3. Plot of the data from Figures 1 and 2 according to ARUNLAKSHANA and SCHILD (1959). The slope of the line for noradrenaline-phentolamine is n = −0.83, whereas the ergotamine-phentolamine line has a slope of n = −0.97. [From Figure 6, MÜLLER-SCHWEINITZER, E., STÜRMER, E.: Blood Vessels **11**, 187 (1974)]

wise, pA_2 can be considered as an empirical measure by which the activity of an antagonist can be expressed. It can then be defined as the decimal logarithm of the molar concentration of antagonist, which reduces the effect of a double dose of agonist to that of a single dose (SCHILD, 1947). It follows from eq. (3) that plotting log $(x-1)$ against log B (or $-\log B$ or pA_x) should give a straight line with slope unity which cuts the x-axis at a point corresponding to pA_2.

Corollaries of Competitive Antagonism

Two important corollaries of the theory of competitive antagonism have been emphasised by ARUNLAKSHANA and SCHILD (1959):

1. When two different agonists acting on the same receptor are tested with the same competitive antagonist, the affinity constant of the latter should be the same. This can be used as a test whether two agonists act on the same receptor. For example, Figure 3 shows that using this criterion ergotamine and noradrenaline probably stimulate the same receptor (α-adrenoceptor) in an isolated preparation of dog veins.

2. Identical receptors in different preparations should produce the same affinity constants with the same competitive antagonist. The method of classifying receptors is quantitative and has been shown to be applicable to receptors for acetylcholine, histamine, noradrenaline and 5-HT (ARUNLAKSHANA and SCHILD, 1959; FURCHGOTT, 1967; MÜLLER-SCHWEINITZER, 1976b).

Affinity and Intrinsic Activity (Efficacy)

The activity of a competitive antagonist at equilibrium is described by its affinity constant. In the case of agonists it was postulated by ARIENS (1954) and STEPHENSON (1956) that in addition to the affinity, a further variable, the intrinsic activity

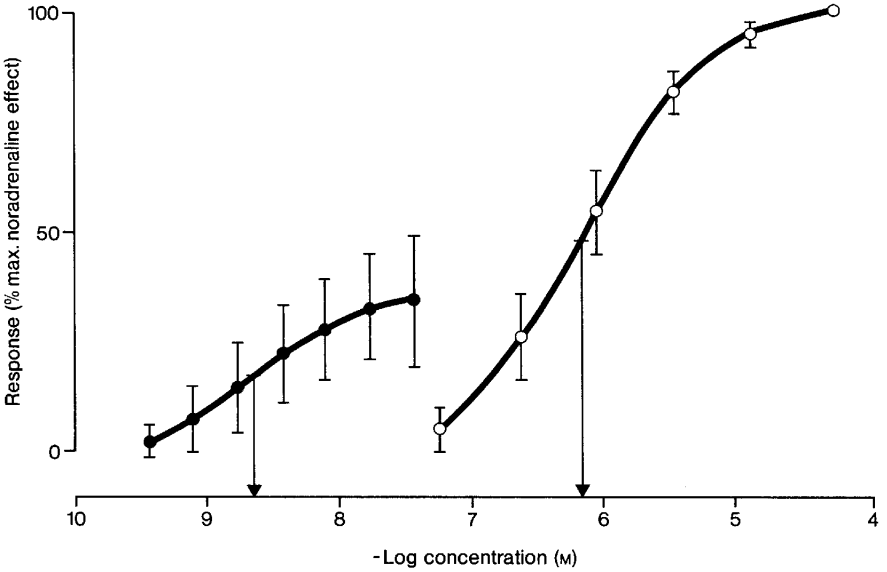


Fig. 4. Cumulative concentration-response curves for ergotamine (●) and noradrenaline (○) on spiral strips from canine femoral veins. pD_2 is represented by an arrow in each case. The bars indicate SD. [From Figure 1, MÜLLER-SCHWEINITZER, E., STÜRMER, E.: Brit. J. Pharmacol. **51**, 442 (1974)]

or efficacy, is needed to account for their effects. Efficacy can be regarded as a measure of the effectiveness with which the drug, once combined, activates the receptor.

Efficacy is an empirical constant which ranges from zero for an antagonist, upwards. Drugs with intermediate efficacy are termed partial agonists and those having the greatest efficacy of which the particular tissue is capable (a not well-defined concept) are termed full agonists. Drugs with high efficacy may be able to produce the maximal response of which the particular preparation is capable by occupying only a small fraction of receptors. The preparation is then said to contain a substantial proportion of spare receptors. Drugs with low efficacy produce flatter log dose-response curves than those with high efficacy, and their maximal responses may be reduced. Figure 4 shows the effects of a drug with low efficacy and high affinity (ergotamine) and a drug with lower affinity and high efficacy (noradrenaline).

Figure 5 shows the effect of combined administration of ergotamine, a partial agonist acting on α-adrenergic receptors, and noradrenaline, a full agonist acting on the same receptors. The partial agonist causes a rise of the base line. With increasing doses it occupies all the receptors and then acts as a typical competitive antagonist of noradrenaline.

Receptor Classification

Two main approaches to receptor classification and identification have been employed:

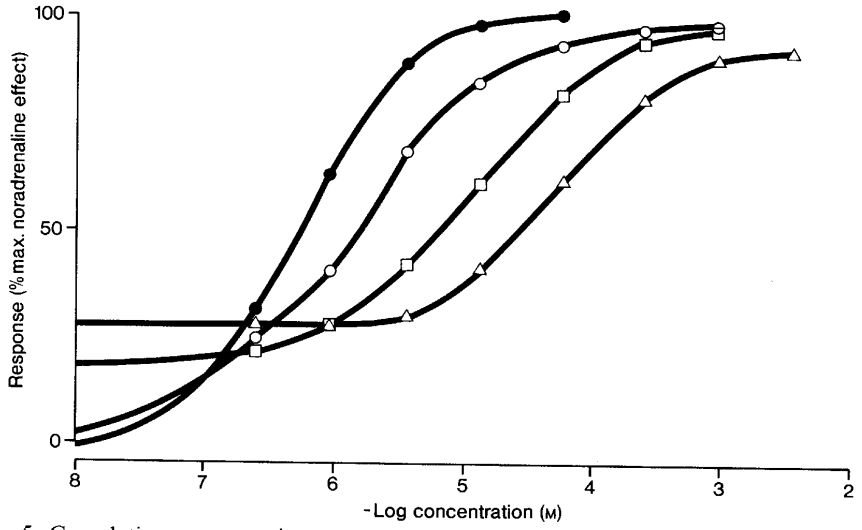


Fig. 5. Cumulative concentration-response curves for noradrenaline without (●) and 15 min after ergotamine in the final concentrations of 1.7×10^{-9} (○), 1.7×10^{-8}(□) and 1.7×10^{-7} M (△) on spiral strips from canine femoral veins. [From Figure 2, MÜLLER-SCHWEINITZER, E., STÜRMER, E.: Brit. J. Pharmacol. **51**, 443 (1974)]

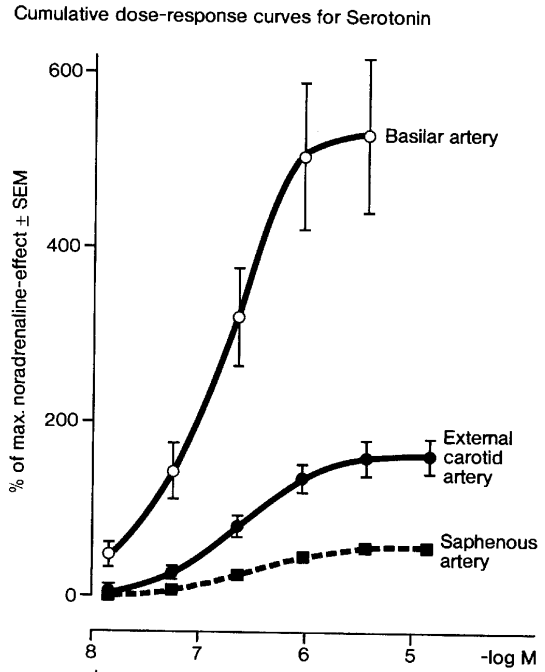


Fig. 6. Cumulative concentration-response curves for 5-HT (serotonin) on spiral strips from canine saphenous arteries (■---■), external carotid arteries (●—●) and basilar arteries (○—○) expressed as percentages of the maximum responses to noradrenaline. [From Figure 1, MÜLLER-SCHWEINITZER, E.: Naunyn Schmiedebergs Arch. Pharmacol. **292**, 114 (1976)]

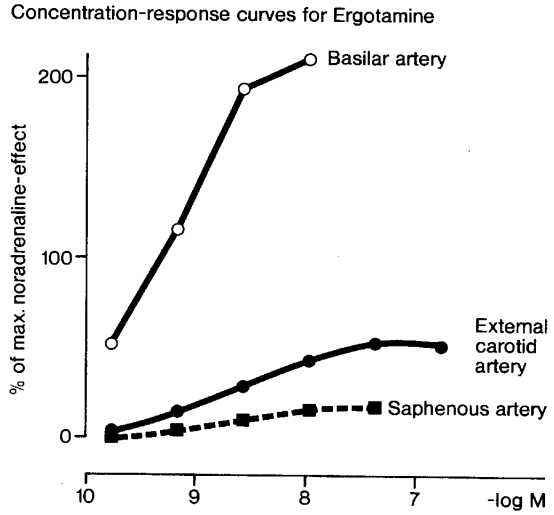


Fig. 7. Concentration-response curves for ergotamine on spiral strips from canine saphenous arteries (■---■), external carotid arteries (●—●) and basilar arteries (○—○) expressed as percentages of the maximum responses to noradrenaline. [From Figure 2, MÜLLER-SCHWEINITZER, E.: Naunyn Schmiedebergs Arch. Pharmacol. **292**, 114 (1976)]

1. Classification by antagonists. This is based on the principle, previously discussed, that similar receptors will give similar affinity constants (pA_2 values) with a competitive antagonist.

2. Classification by agonists. This is based on the idea that the potency ratios of agonists acting on the same receptor are independent of the preparation used. Although this is not strictly correct in theory (FURCHGOTT, 1972), it is a sufficient approximation to be useful in practice which has helped in the classification of beta adrenoceptor subclasses.

A variant of this approach which has been employed in the ergot field is illustrated in Figures 6, 7, and 8. They show that when ergotamine and 5-HT are tested in different arterial preparations their relative efficacies remain the same. This may indicate that the two drugs act on the same (5-HT) receptors in these preparations.

Noncompetitive Antagonism

A mass law equation for noncompetitive drug antagonism may be derived (ARIENS et al., 1956; SCHILD, 1954) based on the hypothesis that the agonist and the antagonist react with accessory sites of the same receptor or with consecutive sites of the activated effector system, so that the effect of the antagonist cannot be overcome (surmounted) by increasing the concentration of the agonist. This assumption gives rise to non-parallel log dose-response curves with decreasing slopes and maxima. Curves of this type are frequently seen: In the ergot field they tend to occur particularly when the ergot alkaloids are used as 5-HT antagonist (cf. Figs. 9, 11, and 12). True noncompetitive antagonists are probably rare, but curves

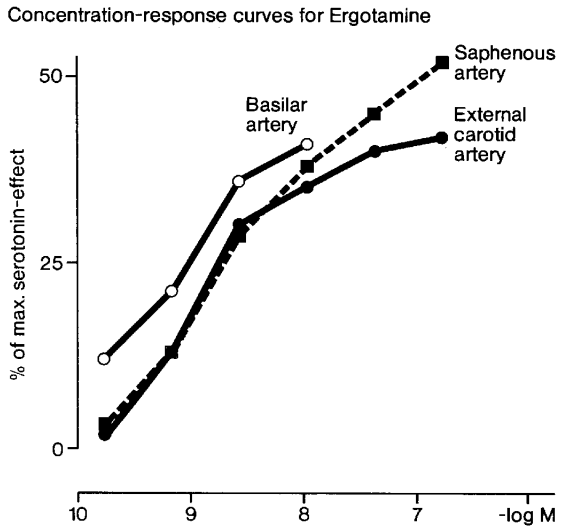


Fig. 8. Concentration-response curves for ergotamine on spiral strips from canine saphenous arteries (■---■), external carotid arteries (●—●) and basilar arteries (○—○) expressed as percentages of the maximum responses to 5-HT (serotonin). [From Figure 3, MÜLLER-SCHWEINITZER, E.: Naunyn Schmiedebergs Arch. Pharmacol. **292**, 114 (1976)]

of the noncompetitive type (pseudo-noncompetitive) are frequently seen experimentally.

As basis of drug antagonism throughout this chapter, it must be presumed that the antagonist will not react chemically with the agonist and will not interfere with the formation or metabolism of the agonist.

Besides specific action of ergot alkaloids on receptor sites, there are also interactions with other cell components such as enzymes and membranes which, however, occur only in 100 to 1000 times higher concentrations compared to those showing affinity to receptor sites. These interactions may be the consequence of the strong affinity of ergot alkaloids to several cell constituents, such as proteins and lipoproteins.

B. Actions of Ergot Alkaloids at 5-HT Receptors

1. Actions of Ergot Alkaloids at Extraneuronal 5-HT Receptors

a) General Description of "Specific Tryptamine Receptors"

Since the discovery of 5-HT as a widely occurring and potent biogenic amine, many investigations have supported the idea of the existence of tissue receptors which preferentially react to 5-HT. The first evidence for an interaction of ergot alkaloids with 5-HT receptor sites was provided when GADDUM (1953) described the marked antagonism between D-LSD (d-lysergic acid diethylamide) and 5-HT on the isolated rat uterus. Testing 5-HT and several antagonists on different isolated organs, GADDUM and HAMEED (1954) concluded that more than one receptor type

for 5-HT must exist. One type was found to be present in the smooth muscle of the rat uterus and rabbit ear artery and could be specifically blocked by D-LSD. The second type was considered to be present in the post-ganglionic nerves in AUERBACH's plexus of the guinea-pig ileum and could be blocked by low concentrations of atropine, indicating the involvement of an indirect cholinergic mechanism, e.g., release of acetylcholine (ROCHA E SILVA et al., 1953; CAMBRIDGE and HOLGATE, 1955). Later studies on the isolated guinea-pig ileum (GADDUM and PICARELLI, 1957) led to the differentiation between D-receptors, which can be blocked by phenoxybenzamine, ergot derivatives or 5-benzyl-oxygramine, and M-receptors, the stimulation of which is antagonized by morphine, methadone, atropine, and cocaine but not by ergot alkaloids. Antagonism of stimulation of M-receptors may be indirect, e.g., atropine is believed to antagonize the effects of acetylcholine released from postganglionic nerve endings of AUERBACH's plexus.

Thus, although in some preparations, e.g., rabbit ear artery (APPERLEY et al., 1974, 1976; FOZARD, 1973b), guinea-pig umbilical vessels (NAIR and DYER, 1974), and cat spleen (INNES, 1962b), 5-HT and catecholamines seem to act on a common receptor, it is probably justified to accept the existence of specific receptor sites for 5-HT.

Evidence for the existence of two types of receptors for 5-HT in the nasal vessels from dogs—a constrictor receptor and a vasodilator receptor—has been provided by VARGAFTIG and LEFORT (1974). Whereas 5-HT activated both receptor types, tryptamine stimulated only the constrictor receptor, leaving the vasodilator unchallenged. GADDUM and PICARELLI (1957) referred to 5-HT receptors as tryptamine receptors, and this has tended to persist in the literature (e.g., VANE, 1960), although there is evidence that receptors for 5-HT and for tryptamine may be either different or at least differentially accessible. A tryptamine receptor different from the classical "D-type" is assumed to be involved in the mediation of the constrictor response of the external carotid vascular bed from dogs to 5-HT and ergotamine (SAXENA and DE VLAAM-SCHLUTER, 1974) and may also be involved in the action of methysergide in this vascular bed (SAXENA, 1974a, b).

A further type of tryptamine receptor mediating the phenomenon of sensitization to the vasoconstrictor activity of biogenic amines has been suggested for the vascular smooth muscle cells of several branches of the external carotid vascular bed (CARROLL and GLOVER, 1973; CARROLL et al., 1974).

b) Ergot Alkaloids as Stimulants at 5-HT Receptors

α) *Common Pharmacologic Properties of Ergot Alkaloids and 5-HT*

5-HT often has a dual action, e.g., stimulation and—especially at higher concentrations—self-blockade, which results in the well-known phenomenon of tachyphylaxis. Both pharmacologic properties are also characteristic of various ergot alkaloids when interacting as agonists with 5-HT receptors. D-LSD was found to be a very potent agonist in human and sheep umbilical vessels. On both preparations, however, concentration-response curves for D-LSD could be established only with single doses, since addition of increasing amounts of D-LSD to the bath without changing the fluid evoked no further contraction (DYER and GANT, 1973;

GANT and DYER, 1971). Similar observations have been made when the vasoconstrictor activity of dihydroergotamine was investigated on perfused human umbilical cords (GOKHALE et al., 1966) and when the mode of action of ergotamine was studied in canine arteries from different vascular beds (MÜLLER-SCHWEINITZER, 1976a) or in the rat stomach strip (FRANKHUIJZEN, 1975). As observed with D-LSD, the stimulating activity of ergotamine could be investigated only with a single dose-response technique. In the rat stomach strip the dose-response curve obtained with ergotamine was bell shaped, reaching its maximum at a bath concentration of 3 μM. The addition of higher ergotamine concentrations resulted in a decrease of the contraction height, indicating self-blockade.

β) Stimulation of D-Receptors by Ergot Alkaloids

As has been mentioned, ergot alkaloids specifically block D-receptors but do not antagonize effects exerted on M-receptors, thus indicating a selective affinity to those receptor sites of smooth muscles which are directly stimulated by 5-HT. When used as serotoninergic blocking agents, ergot compounds often showed considerable stimulant activity suggesting that they may act as partial agonists on 5-HT receptors. Umbilical and placental vessels are usually extremely sensitive to the vasoconstrictor activity of both 5-HT and ergot alkaloids. Human umbilical and placental vessels are stimulated by D-LSD (GANT and DYER, 1971), methylergometrine (PANIGEL, 1959, 1962), methysergide and BOL-148 (DYER and GANT, 1973), and by dihydroergotamine (GOKHALE et al., 1966; PANIGEL, 1959, 1962). Similarly, D-LSD, ergometrine, and ergotamine caused contraction of sheep umbilical vessels (DYER, 1969, 1970, 1974; DYER and GANT, 1973). Using BOL-148 and cinanserin as selective 5-HT antagonists, evidence has been provided that on both human and sheep umbilical vessels the vasoconstrictor activity of D-LSD is mediated through serotoninergic receptor sites. Moreover, since atropine failed to reduce responses to D-LSD, it was confirmed that the LSD-induced vasoconstriction was mediated solely by stimulation of D-receptors (DYER and GANT, 1973). Further evidence for this suggestion was provided by using the technique of selective receptor protection (DYER, 1974).

Methysergide, like 5-HT, caused vasoconstriction of in vitro perfused human temporal arteries. Responses to both 5-HT (0.1 μg) and methysergide (1 μg) could be abolished by perfusion of serotoninergic blocking agents such as cyproheptadine or pizotifen at a concentration of 10 ng/ml, suggesting the involvement of serotoninergic receptor sites in the vasoconstrictor response of the human temporal artery to methysergide (CARROLL and GLOVER, 1973; CARROLL et al., 1972, 1974). Injected at doses of 10 nmol to 2.5 μmol, methysergide also induced reproducible constriction of the rabbit ear artery (APPERLEY et al., 1974, 1976; CARROLL and GLOVER, 1973; CARROLL et al., 1972, 1974; FOZARD, 1973a, b, 1976a, b). As observed with the human temporal artery, this vasoconstrictor effect of methysergide could be prevented by perfusion of 1–10 ng/ml cyproheptadine or pizotifen, concentrations which also selectively antagonized responses to 5-HT but not those to noradrenaline (CARROLL and GLOVER, 1973; CARROLL et al., 1974).

While these observations suggest that methysergide constricts the rabbit ear artery via serotoninergic receptor sites, comparative studies of the antagonism

by pizotifen and phentolamine against methysergide, 5-HT, and noradrenaline provided evidence that in the rabbit ear artery 5-HT and noradrenaline combine with the same receptor, which can also be activated by methysergide. APPERLEY et al. (1974, 1976) found that in the rabbit ear artery 100–300 nM pizotifen and 4–8 nM phentolamine were equipotent in antagonizing methysergide, 5-HT, and noradrenaline, thus indicating that the receptor stimulated by the three agonists may probably be identical with the α-adrenoceptor. These conclusions were confirmed by FOZARD (1976b), who found that on the isolated rabbit ear artery pA_2 values for phentolamine against noradrenaline, 5-HT, and methysergide did not differ significantly from each other.

The mode of the vasoconstrictor action of ergotamine has been investigated on canine arterial strips from different vascular beds, e.g., saphenous, external carotid, and basilar arteries. Compared with the maximum noradrenaline effect, ergotamine, like 5-HT, had different intrinsic activities in different vessels. The intrinsic activity (efficacy) of both ergotamine and 5-HT was found to be in the ascending order of saphenous < external carotid < basilar artery. Expressed as percentages of the maximum 5-HT effects, however, the intrinsic activity of ergotamine was about 50% in the three arteries (Figs. 6, 7, and 8). These results suggested that the relative efficacies of ergotamine and 5-HT in different vascular beds are the same and that in canine arterial vascular smooth muscle the stimulant activity of ergotamine might be mediated through 5-HT receptor sites. Further evidence for this was provided in experiments where 5-HT antagonists such as cyproheptadine and pizotifen and the α-adrenergic blocking drug phentolamine were used. Comparing the concentrations necessary to inhibit ergotamine effects with those required to antagonize responses to 5-HT and noradrenaline, respectively, it could be demonstrated that in canine arterial smooth muscle cells the ergotamine-induced vasoconstriction is mediated mainly through specific 5-HT receptors (MÜLLER-SCHWEINITZER, 1976a, b).

Similar conclusions were reached by FRANKHUIJZEN (1975), who investigated the mode of action of ergotamine on the isolated rat stomach preparation. Using ergotamine, 5-HT, and acetylcholine as agonists and ergotamine, methysergide, and piperoxan as antagonists, it was shown that ergotamine acts as a partial agonist on the classical D-receptors of the isolated rat stomach preparation.

It is interesting to note that ergotamine stimulated the smooth muscle cells from preparations as different as canine arteries and rat stomach strip in similar concentration ranges and with similar relative intrinsic activities compared to the maximum 5-HT effects, which implies structural similarities between the D-receptors in these different smooth muscle preparations.

An example where D-LSD effects could be blocked by 5-HT is the melanophore expansion test on the female guppy *Lebistes reticulatus*. In this test, increasing concentrations of D-LSD caused dose-dependent expansion of the melanophores, thus inducing a progressive darkening of the skin. This effect could be reversed in vivo as well as in vitro by high doses of 5-HT (BERDE and CERLETTI, 1956, 1957; CERLETTI, 1955; CERLETTI and BERDE, 1955). Although the darkening of the skin could be regarded as an agonistic action of D-LSD, the reversal by 5-HT indicates that these experimental results are a typical example of reversed antagonism, where the effect of an antagonist, D-LSD, could be inhibited by an agonist,

5-HT. Nevertheless, these results support the notion that D-LSD and 5-HT combine with the same receptor sites.

In the frog *Rana temporaria* D-LSD, like 5-HT, produces melanin dispersion, an effect which appears to be mediated indirectly through the pituitary, since responses to both D-LSD and 5-HT were absent in hypophysectomized specimens of *Rana temporaria* (KAHR and FISCHER, 1957).

Isolated hearts of various molluscs, e.g., *Venus mercenaria,* which respond to 5-HT at concentrations which are surprisingly small are also stimulated by several ergot alkaloids, e.g., ergometrine (GADDUM and PAASONEN, 1955; WELSH, 1953; WRIGHT et al., 1962), methylergometrine (CHONG and PHILLIS, 1965; WRIGHT et al., 1962), ergotoxine (CHONG and PHILLIS, 1965; WELSH, 1953, WRIGHT et al., 1962), ergotamine (CHONG and PHILLIS, 1965), dihydroergotamine and dihydroergotoxine mesylate (GADDUM and PAASONEN, 1955; WRIGHT et al., 1962), but D-LSD proved to be the most excitatory ergot alkaloid on the molluscan heart (GADDUM and PAASONEN, 1955; GREENBERG, 1960b; LIEBESWAR et al., 1975; SHAW and WOOLLEY, 1956; WELSH, 1955, 1957; WRIGHT et al., 1962). When an isolated *Venus* heart is bathed in a solution of D-LSD in sea-water at a concentration as low as 10^{-16} M, it absorbs a sufficient amount of the drug to produce a maximal increase in frequency and amplitude of heart beats within 1 to 4 h. The generally similar actions of D-LSD and 5-HT on molluscan hearts suggested that both stimulate the muscle cells through the same receptor. Evidence for this was provided by the observation that responses to both D-LSD and 5-HT could be selectively abolished by pretreatment of the heart with BOL-148 or methysergide (CHONG and PHILLIS, 1965; WELSH and MCCOY, 1957; WRIGHT et al., 1962).

The liver fluke *Fasciola hepatica* responds with increased motility to the addition of 5-HT at μM concentrations, which seems to be a peripheral effect since following removal of the central ganglia, isolated strips of the parasite exhibited a smilar response to the stimulatory action of 5-HT. When used at 5–50 nM, D-LSD temporarily reduced the spontaneous activity of the worms. At concentrations of 0.1 μM and higher, D-LSD, like 5-HT, increased the motility of the flukes, thus being more potent than 5-HT. BOL-148, having no or rather depressant effects on spontaneous motility, antagonized the stimulatory activity of both 5-HT and D-LSD, indicating that responses to D-LSD were mediated by stimulation of 5-HT receptor sites (ABRAHAMS, 1974; MANSOUR, 1956, 1957; MANSOUR et al., 1957). BEERNINK et al. (1963) performed a comparative study of a number of lysergic acid derivatives, calculating those concentrations which stimulated 50% of the preparations. It was found that all compounds tested, except for BOL-148 and L-LSD, stimulated the fluke in lower concentrations than 5-HT.

An increase in basal motility by 5-HT has also been observed in *Schistosoma mansoni.* In this preparation, dihydroergotamine was found to be more potent than methysergide in causing excitation (HILLMAN et al., 1974; TOMOSKY et al., 1974).

Experiments with isolated salivary glands from the blow fly *Calliphora erythrocephala* have shown that D-LSD, BOL-148, and lysergic acid, like 5-HT, can stimulate secretion. In this experimental model, D-LSD produced the same physiological and biochemical events that have been associated with the action of 5-HT. For example, the addition of D-LSD caused the transepithelial potential

to go negative, and it also raised the intracellular concentration of cyclic 3′,5′-adenosine monophosphate (cyclic AMP) as did 5-HT. But unlike 5-HT, the D-LSD-induced secretion continued despite repeated washings, indicating that D-LSD disengaged slowly from the receptor. Thus, salivary glands which had been treated with D-LSD appeared to be insensitive to the immediate action of 5-HT antagonists. Prolonged treatment with high concentrations of the 5-HT antagonist gramine, however, caused a gradual inhibition of the D-LSD-induced secretion. Similarly, the D-LSD-induced secretion could be inhibited by prolonged exposure of the salivary glands to high concentrations of either 5-HT or tryptamine. These observations strongly suggest that in salivary glands from the fly *Calliphora erythrocephala* D-LSD causes stimulation by combining with the same receptor site normally occupied by 5-HT (BERRIDGE and PRINCE, 1973, 1974).

γ) Stimulation of M-Receptors by Ergot Alkaloids

Although experiments with isolated organs from animals have not, so far, suggested an interaction of ergot alkaloids with M-receptors, there is some evidence that in longitudinal muscle strips from human intestine ergot alkaloids may stimulate M-receptors, thus causing release of acetylcholine.

Both circular and longitudinal muscle strips from human ileum contracted in response to 5-HT. On circular muscle strips the calculated $pA_{2(2\,min)}$ values against 5-HT were 8.0 for methysergide and 7.7 for cinanserin, indicating that in this preparation responses to 5-HT might be mediated mainly through D-receptors. On longitudinal muscle strips from human ileum, however, cinanserin was about 100 times less potent in antagonizing 5-HT-induced contractions ($pA_{2(2\,min)}$ value = 5.5), while methysergide enhanced responses to 5-HT, suggesting that in these muscle layers D-receptors are not involved in the response to 5-HT (METCALFE and TURNER, 1969; TURNER, 1973). When high concentrations of methysergide (10–50 μg/ml) were tested on specimens of longitudinal muscles from human intestine, they caused a contraction which was similar in nature and additive to that induced by 5-HT, and both were blocked by the same concentration of atropine (60 ng/ml). Moreover, after inhibition of cholinesterase by eserine, responses to methysergide were enhanced, suggesting the involvement of an indirect cholinergic mechanism in the stimulant activity of methysergide on longitudinal muscle strips from human intestine (METCALFE and TURNER, 1970).

c) Ergot Alkaloids as 5-HT Receptor Blocking Agents

Blocking agents, especially selective blocking agents, are the most important means of characterizing and classifying drug receptors. The use of competitive antagonists for the purpose of defining receptors (by their affinities for these antagonists) was discussed in Section A. Although the use of log dose-respose curves in isolated preparations and the use of competitive antagonists is ideal for classifying receptors, the ideal can frequently not be attained, either because the system does not lend itself to isolated organ work but only to in vivo work where the concentrations of antagonist are not well defined or stable, or because no reversible and competitive antagonists are available for receptor analysis.

In the case of 5-HT antagonists, although highly active and specific compounds have been described, they do not generally behave as competitive antagonists. Typically they produce nonparallel log dose-response curves with progressive lowering of maxima, such as are shown in Figures 9 and 12 for D-LSD and ergotamine, respectively. Frequently curves show both depression of maxima and lateral displacement. In the following discussion we have characterized such antagonists by both their pA_2 values at the 50% response level and their pD'_2 values (from the antagonist concentration, reducing the maximum of the dose-response curve to one-half), regarding both as essentially empirical measurements.

Structure activity relationships of lysergic acid derivatives. Small amide derivatives of lysergic acid, e.g., D-LSD, BOL-148, methysergide, ergometrine, and methylergometrine, are among the most potent and selective 5-HT antagonists, whereas peptide alkaloids, e.g., ergotamine, ergotoxine, and their dihydroderivatives, are usually less selective, showing closely similar affinities to both 5-HT receptors and α-adrenoceptors. Ergot compounds possess the indolealkylamine group of 5-HT as a rigid part of the lysergic acid structure, which might be responsible for the high affinity of these substances to 5-HT receptors. The degree of specifity, i.e., the degree of selective affinity to 5-HT receptors, of an ergot compound will, however, largely depend on the environment of the 5-HT receptor, i.e., on the existence and stereochemical arrangement of accessory receptor areas which may be tissue- and species-dependent. As demonstrated by BACH et al. (1974) the side chain at position 8 in an ergolene is not essential for the antagonistic activity of an ergot compound. Ergolene was found to be only three times less potent than methysergide in antagonizing the constrictor response to 5-HT in isolated rat stomach strips. On the other hand, prolongation of the side chain at position 8 of a lysergic acid derivative seems to enhance the affinity to accessory receptor areas, thus leading to very potent and long-acting 5-HT antagonists like GYKI 32084 (1-methyl-9,10-dihydro-d-lysergyl-nitro-argininol). For antagonism of 5-HT effects by GYKI 32084 a pA_2 value of 9.8 on the isolated rat uterus and a pD'_2 value of 9.7 on the rat stomach strip was calculated (BORSY et al., 1973; PIK and BORSY, 1974). A further potent 5-HT antagonist with a very long-lasting activity is MCE (1-methyl-8β-carbobenzyl-aminomethyl-10α-ergoline), which effectively protected guinea-pigs from 5-HT-induced bronchospasm and which was also found to be about 500 times more potent than methysergide in antagonizing response to 5-HT when tested on the isolated rat uterus (BERETTA et al., 1965a, b).

The affinity to 5-HT receptors of an ergot compound will largely depend on the test organ employed, and data obtained on one tissue of a certain species will often not be applicable to another preparation.

D-LSD (d-lysergic acid diethylamide) is a highly potent and selective 5-HT antagonist. Most of the studies investigating the peripheral anti 5-HT activity of D-LSD employed the isolated rat uterus. After 10 min incubation of a rat uterus preparation with D-LSD, a pA_2 value of 8.7 (=2 nM) for antagonism of 5-HT by D-LSD was calculated (GADDUM, 1953; GADDUM and HAMEED, 1954; GADDUM et al., 1955). This antagonism by D-LSD, which appears to be competitive at low concentrations, increases progressively and becomes "unsurmountable" with time of incubation (GADDUM et al., 1955). Prolonged exposure to D-LSD may render the antagonism irreversible. Similar observations have been reported

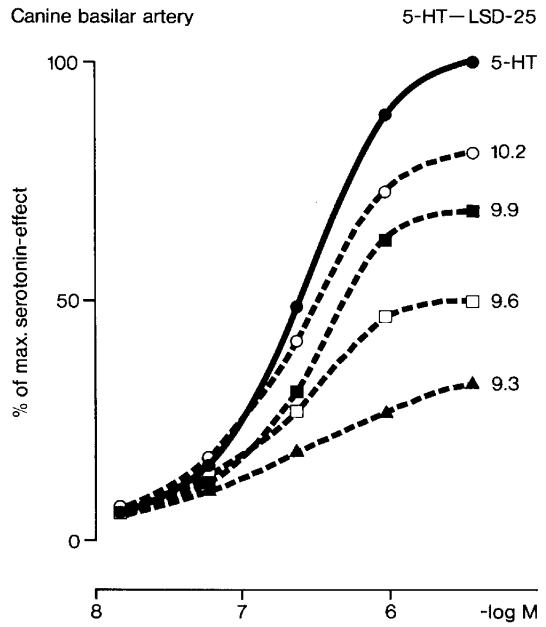


Fig. 9. Cumulative concentration-response curves for 5-HT without (●) and 30 min after D-LSD (LSD-25) in the final concentrations of $10^{-10.2}$ (○), $10^{-9.9}$ (■), $10^{-9.6}$(□) and $10^{-9.3}$M (▲) on spiral strips from canine basilar arteries. (MÜLLER-SCHWEINITZER, unpublished)

concerning intracranial blood vessels from various species. On the isolated circular smooth muscle of the middle cerebral artery from the goat, the vasoconstrictor effect of 5-HT was selectively antagonized by D-LSD. This antagonism by D-LSD was found to progress from surmountable to unsurmountable blockade as the D-LSD concentration was increased. A 10-min incubation with 6 nM D-LSD reduced the maximum response to 5-HT by about 50%. As observed with canine basilar arteries (TODA, 1975), this unsurmountable blockade could be reversed by removal of D-LSD from the bathing fluid (URQUILLA et al., 1974, 1975). Using a 30-min incubation time on spiral strips from canine basilar arteries, D-LSD antagonized responses to 5-HT in a noncompetitive way (Fig. 9). For antagonism of 5-HT by D-LSD a $pD'_{2(30\,\mathrm{min})}$ value of 9.6 (=0.25 nM) was calculated (Table 1).

As has been mentioned, 5-HT stimulates mainly M-receptors in the guinea-pig ileum, causing acetylcholine release. D-receptors are also stimulated but to a lesser extent, and they make only a partial contribution to the stimulant effect. It follows from this that the maximal inhibition of 5-HT effects by ergot compounds (which affect solely D-receptors) is only about 50%. Maximal antagonism of 5-HT effects by D-LSD could be achieved with concentrations of 0.01 to 0.1 μg/ml, whereas higher concentrations caused no further inhibition (GADDUM, 1957; GADDUM and HAMEED, 1954; GADDUM and PICARELLI, 1957; GINZEL, 1957; JAQUES et al., 1956).

Methysergide (1-methyl-d-lysergic acid butanolamide). For several years D-LSD was considered to be the most potent 5-HT antagonist. Studies of structure-activity

Table 1. Antagonism of 5-HT by various ergot alkaloids

	Canine	Bovine
D-LSD	9.6	9.2
Methylergometrine	9.1	
Methysergide	7.7	9.1*
Ergotamine	9.6*	9.2*
α-Ergokryptine	8.6	
Bromocriptine	7.8	
Dihydroergotamine	9.1	8.8*
Dihydroergotoxine mesylate	8.1	7.9
Dihydroergocornine		7.9
Dihydroergocristine		7.9
Dihydro-α-ergokryptine	7.8	7.7
Dihydro-β-ergokryptine	8.4	7.8

Note: pD'_2 values were calculated after an incubation time of 30 and 60 (*) min on spiral strips from canine and bovine basilar arteries (MÜLLER-SCHWEINITZER, unpublished)

relationships of lysergic acid derivatives, however, have shown that the 5-HT receptor blocking activity of these compounds can be increased by substitution of different radicals, mainly in position 1 and 2 of the ring complex of lysergic acid (CERLETTI and DOEPFNER, 1956; 1958a, b; CERLETTI and KONZETT, 1956; FREGNAN and GLÄSSER, 1968; ROTHLIN, 1957a, b; STOLL and HOFMANN, 1956). It was found that the introduction of a methyl group at position 1 of the lysergic acid increased the 5-HT antagonistic activity on the isolated rat uterus of ergometrine by 24 times and enhanced those of D-LSD and methylergometrine by about four times (CERLETTI and DOEPFNER, 1956, 1958a, b).

Methysergide seems to be the most potent 5-HT antagonist on the isolated rat stomach strip showing selective inhibition of 5-HT effects at threshold concentrations of about 1 nM (BAKHLE and SMITH, 1974a; FRANKHUIJZEN and BONTA, 1974b; GÖRLITZ and FREY, 1973; OFFERMEIER and ARIENS, 1966). When investigated on the isolated rat stomach preparation, methysergide shifted the log dose-response curve for 5-HT to the right but also lowered its maximal height, suggesting that methysergide exhibits a dualism in its antagonism of 5-HT consisting of a competitive and a noncompetitive part. As observed with D-LSD the antagonism by methysergide increased with time of incubation.

Figure 10 shows the influence of the time of incubation on the 5-HT antagonism induced by methysergide on the isolated rat fundus. In the presence of 1 nM methysergide the maximum response to 5-HT is progressively diminished by increasing the time of incubation. Thus, the calculated pA_2 values for antagonism of 5-HT by methysergide were found to be 8.9 after 5 min, 9.5 after 30 min and 10.1 after 60 min incubation time (FRANKHUIJZEN and BONTA, 1974b; GÖRLITZ and FREY, 1973), and similarly the calculated pD'_2 values were 8.0, 8.9 and 9.3 after 5, 30 and 60 min, respectively (FRANKHUIJZEN and BONTA, 1974b).

On bovine basilar arteries the $pD'_{2(60\ \mathrm{min})}$ value for antagonism of 5-HT by methysergide was 9.1, indicating that in this vascular tissue methysergide and

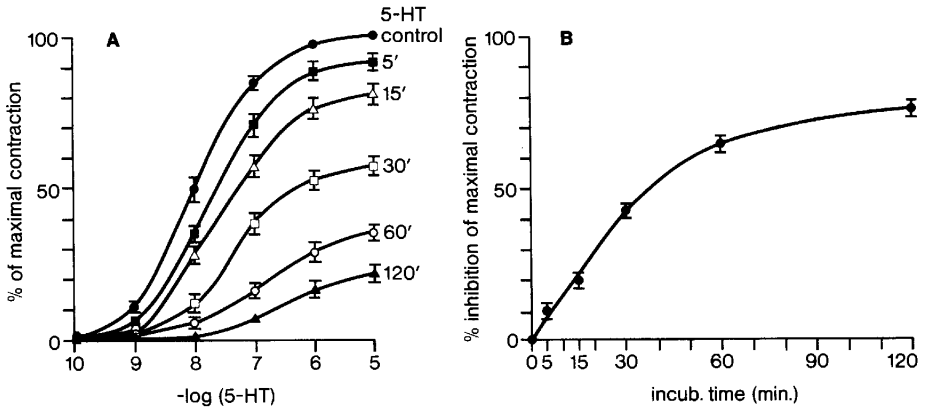


Fig. 10. (A) Dose-response curves for 5-HT without and in the presence of 1 nM methysergide after different incubation times on the rat fundus strip. (B) Dependence of the percentage inhibition of the maximal response to 5-HT on the preincubation time. [From Figure 2, FRANKHUIJZEN, A.L., BONTA, I.L.: Europ. J. Pharmacol. **26**, 223 (1974)]

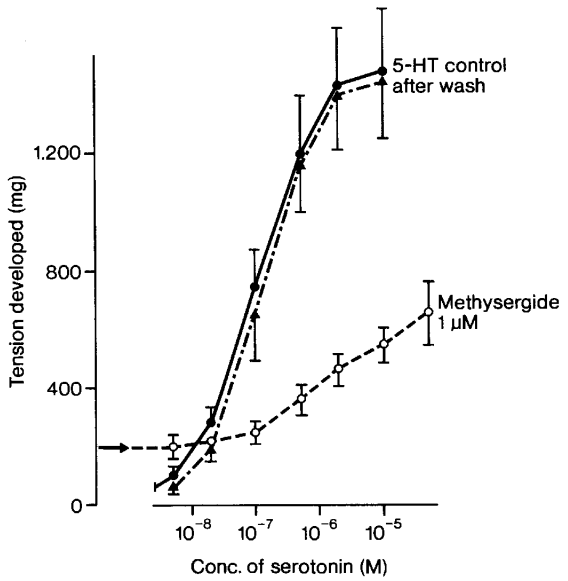


Fig. 11. Dose-response curves for 5-HT without (●), 20 min after 1 μM methysergide (○) and after washout of methysergide (▲) on spiral strips from canine cerebral arteries. [From Figure 2, TODA, N.: J. Pharmacol. exp. Ther. **193**, 387 (1975)]

D-LSD ($pD'_{2(30\ min)}$ value = 9.2) are nearly equipotent in antagonizing responses to 5-HT (Table 1). As observed with D-LSD on canine basilar arteries, the 5-HT antagonism by methysergide could be reversed by removal of the drug from the bathing fluid (TODA, 1975; TODA et al., 1976) (Fig. 11).

On blood vessels from various species methysergide proved to be highly selective in antagonizing the vasoconstrictor responses to 5-HT. For antagonism of 5-HT

effects by methysergide the $pA_{2(2\ min)}$ value on human saphenous veins was 8.2 (METCALFE and TURNER, 1969; TURNER, 1973), and both the $pA_{2(15\ min)}$ value on canine saphenous arteries (MÜLLER-SCHWEINITZER, 1975a) and the $pA_{2(30\ min)}$ value on rabbit aortic strips (APPERLEY et al., 1974, 1976) were 8.5, whereas in both preparations about 1000 times higher methysergide concentrations were necessary to antagonize vasoconstrictor responses to noradrenaline to an equal extent.

BOL-148 (2-bromo-d-lysergic acid diethylamide). In some preparations, e.g., isolated rat uterus, the 5-HT antagonism induced by BOL-148 was found to be somewhat stronger than that induced by D-LSD (CERLETTI and DOEPFNER, 1956, 1958a, b; CERLETTI and KONZETT, 1956; CERLETTI and ROTHLIN, 1955; FANCHAMPS et al., 1960; SOLLERO et al., 1956). In most tissues, however, BOL-148 and D-LSD seem to be equipotent in antagonizing responses to 5-HT. On rabbit aortic strips $pA_{2(10\ min)}$ values for BOL-148 were 9.0 against 5-HT and 6.4 against noradrenaline (KOHLI, 1968), suggesting that in the rabbit aorta 5-HT and noradrenaline combine with different receptor sites, and indicating that BOL-148 selectively antagonized 5-HT receptors, since for blockade of α-adrenoceptors about 400 times higher concentrations of BOL-148 were necessary. Using helical aortic strips from reserpinized rats the 5-HT antagonism by BOL-148 occurred in similar concentrations ($pA_{2(15\ min)}$ value = 8.9) but was less selective than on rabbit aortic strips, since in the rat aorta only about 10 times higher concentrations of BOL-148 were required to antagonize responses to noradrenaline ($pA_{2(15\ min)}$ value = 7.9) to the same extent (KRISHNAMURTY, 1971).

In the rat aortic strip the antagonism induced by BOL-148 was not influenced by prolongation of the incubation time (KRISHNAMURTY, 1971), while that on the isolated rat fundus strip increased progressively with time of incubation (BARLOW and KHAN, 1959a).

Ergot peptides in most preparations also antagonized responses to 5-HT effectively and essentially irreversibly. On the isolated rat uterus for the antagonism of 5-HT by dihydroergotamine and dihydroergokryptine $pA_{2(10\ min)}$ values of 6.9 and 6.8, respectively, were calculated (GADDUM et al., 1955), thus indicating that in this preparation both ergot alkaloids are about 100 times less potent than D-LSD in antagonizing 5-HT effects. Moreover, the 5-HT antagonism by peptide alkaloids is usually much less selective than that induced by amide derivatives of lysergic acid, since ergot peptides besides antagonizing responses to 5-HT also inhibit those to catecholamines in similar concentrations. Furthermore, in doses necessary to inhibit 5-HT effects these ergot alkaloids develop stimulating activity to a greater or lesser extent. This is especially the case for the natural and less so for hydrogenated compounds. Cumulative dose-response curves for 5-HT without and in the presence of ergotamine on spiral strips from canine external carotid arteries are shown in Figure 12. Ergotamine caused a considerable increase in tension on its own and progressively lowered the maximal response to 5-HT, indicating noncompetitive antagonism. Similar curves have been obtained when ergotamine was tested against 5-HT on canine basilar arteries by TODA et al. (1976).

The agonistic and antagonistic activities of ergotamine were investigated in detail on the isolated rat stomach strip by FRANKHUIJZEN (1975). When tested

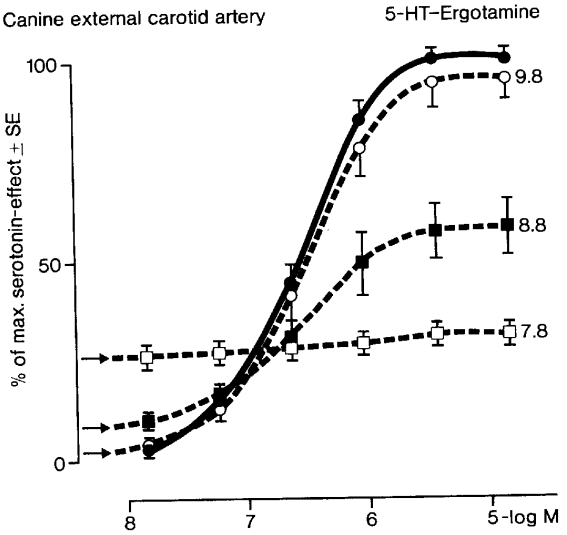


Fig. 12. Cumulative concentration-response curves for 5-HT without (●) and 60 min after ergotamine in the final concentrations of $10^{-9.8}$ (○), $10^{-8.8}$ (■) and $10^{-7.8}$ M (□) on spiral strips from canine external carotid arteries. (MÜLLER-SCHWEINITZER, unpublished)

against 5-HT, ergotamine behaved like a noncompetitive antagonist with considerable intrinsic activity. After an incubation time of 70 min, about 6 nM ergotamine reduced the maximal response to 5-HT by about 50%. Similarly ergotamine acted as a noncompetitive dualist when tested against 5-HT on canine arterial strips. On canine saphenous arteries, ergotamine antagonized 5-HT effects in a noncompetitive way with a $pD'_{2(60\ min)}$ value of 8.9 (=1.3 nM) but showed competitive antagonism against noradrenaline ($pA_{2(60\ min)}$ value=8.7), thus demonstrating that in this vascular preparation ergotamine has affinity for both α-adrenergic and 5-HT receptor sites. However, as already mentioned, the affinity of an ergot compound to a certain receptor area depends on the type of tissue employed. Using canine arteries from different vascular beds, it has been found that the selectivity of the 5-HT antagonism induced by ergotamine shows considerable differences. While on canine saphenous arterial strips ergotamine antagonized responses to both 5-HT and noradrenaline in similar concentration ranges, it failed to inhibit those to noradrenaline on canine basilar and external carotid arteries but developed the same or even stronger anti-5-HT activity as on saphenous arteries (MÜLLER-SCHWEINITZER, 1976c, d; MÜLLER-SCHWEINITZER and STÜRMER, 1975), thus indicating that in arterial vascular smooth muscle cells from the carotid vascular bed ergotamine has a selective affinity to 5-HT receptor sites.

The pD'_2 values calculated for antagonism of 5-HT by different ergot alkaloids (Table 1) demonstrate the strong 5-HT blocking activity of peptide alkaloids on spiral strips from canine and bovine basilar arteries.

At any rate, in most smooth muscle preparations the 5-HT antagonism by peptide alkaloids is usually much less selective than that induced by amide derivatives of lysergic acid, and it must be considered that peptide alkaloids might

also combine with α-adrenoceptors when they are used as 5-HT receptor blocking agents. A number of investigations demonstrating 5-HT receptor blocking activity of ergot alkaloids in various preparations are summarized in Table 2.

Table 2. Methods demonstrating 5-HT antagonism by ergot alkaloids

Preparation, species, references	Observations
Basilar artery – dog (ALLEN et al., 1974; MÜLLER-SCHWEINITZER, 1976c, d; TODA, 1974, 1975; TODA et al., 1974, 1976) – bovine (MÜLLER-SCHWEINITZER, 1975 b) – man (MÜLLER-SCHWEINITZER, 1976c, d)	Selective noncompetitive and reversible 5-HT antagonism by both D-LSD and methysergide at concentrations of 0.6–10 nM. Ergotamine behaved like a noncompetitive dualist.
Middle cerebral artery – goat (URQUILLA et al., 1974, 1975) – cat (HARDEBO and EDVINSSON, 1976; NIELSEN and OWMAN, 1971)	
Ear artery (isolated perfused) – rabbit (CARROLL et al., 1972; FINGL and GADDUM, 1953; FOZARD, 1973b; GADDUM, 1954; GADDUM and HAMEED, 1954; SAVINI, 1956)	Perfusion of 1–10 ng/ml D-LSD, BOL-148 or ergometrine antagonized selectively 5-HT-induced vasoconstrictor effects.
Temporal artery – man (CARROLL et al., 1972)	High concentrations of methysergide, ergotamine or 1-methyl-ergotamine inhibited 5-HT effects.
Maxillary and lingual artery – cat (HARDEBO and EDVINSSON, 1976)	Methysergide antagonized 5-HT effects competitively.
Carotid artery – sheep (SHAW and WOOLLEY, 1953; WOOLLEY and SHAW, 1953)	Both ergotamine and ergotoxine reduced the vasoconstrictor response to 5-HT.
– dog (MÜLLER-SCHWEINITZER and STÜRMER, 1975)	Ergotamine acted as a noncompetitive dualist ($pD'_{2(60\,min)} = 8.4$).
External carotid vasculature – dog (SAXENA, 1972a, b, 1974a, b; SAXENA and DE VLAAM SCHLUTER, 1974; VIDRIO and HONG, 1976)	In vivo ergotamine first reduced and at higher doses reversed 5-HT effects. Methysergide antagonized vasodilator response to 5-HT.
Internal carotid vasculature – dog (MCHEDLISHVILI and ORMOTSADZE, 1974; VIDRIO and HONG, 1976). – monkey (KARLSBERG et al., 1962, 1963)	Methysergide and dihydroergotoxine mesylate antagonized selectively vasoconstrictor effects of 5-HT.
Nasal mucosa vessels – dog (CARPI and VIRNO, 1957; SCHÖNBAUM and LAMAR, 1975; SCHÖNBAUM et al., 1974, 1975; VARGAFTIG and LEFORT, 1974)	Methysergide at high concentrations antagonized both 5-HT-induced vasoconstriction and vasodilatation which occurred in the presence of ergotamine.
Aortic strips – rat (KRISHNAMURTY, 1971) – rabbit (APPERLEY et al., 1974, 1976; GARRETT and BROWN, 1970, 1972; KOHLI, 1968; KOHLI and INNES, 1964; WURZEL, 1966)	Selective 5-HT antagonism by BOL-148 and methysergide, both being about equipotent against 5-HT.

Table 2 (continued)

Preparation, species, references	Observations
Coronary artery in situ – dog (MENA and VIDRIO, 1976)	5-HT-induced dilatation was antagonized by pretreatment of the dogs with methysergide.
Cutaneous vasculature (in situ) – rat (CHAHL and LADD, 1976)	Methysergide antagonized 5-HT-induced vasoconstriction.
Saphenous artery – dog (MÜLLER-SCHWEINITZER, 1975a, 1976c, d; MÜLLER-SCHWEINITZER and STÜRMER, 1975)	Highly selective 5-HT antagonism by methysergide ($pA_{2(15\,min)}=8.5$) less selective noncompetitive inhibition by ergotamine.
Peripheral artery – man (MÜLLER-SCHWEINITZER, 1976c, d)	Noncompetitive 5-HT antagonism by ergotamine of similar potency as observed in dog saphenous arteries.
Saphenous vein – man (METCALFE and TURNER, 1969; TURNER, 1973)	Antagonism of 5-HT by methysergide ($pA_{2(2\,min)}=8.2$).
Hand veins in situ – man (COLLIER et al., 1972; DEL BIANCO et al., 1972, 1975; SICUTERI et al., 1964a, b)	Injection of μg doses of D-LSD, BOL-48, methysergide 1-methyl-ergotamine or nicergoline antagonized 5-HT-induced venoconstriction.
Forearm blood flow – man (GLOVER et al., 1957; WALSH, 1967)	
Pulmonary vessels – rat (BAKHLE and SMITH, 1974a, b) – guinea-pig (STARR and WEST, 1966) – dog (JOINER et al., 1974, 1975) – sheep (EYRE, 1975) – cattle (EYRE, 1971)	Selective 5-HT antagonism has been demonstrated for methysergide and for BOL-148.
Lungs, isolated perfused – rat (ALABASTER and BAKHLE, 1976; BAKHLE and SMITH, 1972, 1974b; FOZARD and LEACH, 1968)	Methysergide, BOL-148 and ergotamine selectively antagonized 5-HT-induced vasoconstriction and release of spasmogens.
– rabbit (HAUGE et al., 1966) – cat (GADDUM et al., 1953; GINZEL and KOTTEGODA, 1953) – dog (DAICOFF et al., 1968; ROSE and LAZARO, 1958). – sheep (HALMAGYI and COLEBATCH, 1961)	D-LSD antagonized 5-HT more selectively than peptide alkaloids. In vivo 5-HT-induced rise in pulmonary arterial pressure was blocked after methysergide, D-LSD and BOL-148.
Mesenteric vessels – rat (HAEUSLER and FINCH, 1972) – dog (HALL and O'CONNOR, 1973; LUDANY et al., 1959; STRONG and BOHR, 1967b) – cattle (HOLROYDE and EYRE, 1975)	Methysergide, D-LSD and BOL-148 were tested as 5-HT antagonists.
Mesenteric vasculature (in situ) – cat (BIBER et al., 1974; CERLETTI, 1955; FARA, 1974)	Dihydroergotamine blocked selectively vasodilator effect of low 5-HT doses. D-LSD reduced selectively vasoconstrictor effect of high 5-HT doses.

Table 2 (continued)

Preparation, species, references	Observations
Ischemic ulcers induced by 5-HT – rat (SCHERBEL, 1960; WILHELMI, 1957; WILHELMI and SCHINDLER, 1959)	Methysergide and D-LSD protected rats from 5-HT-induced gastrointestinal ulcers.
Kidney, isolated perfused – rat (CERLETTI, 1955; CERLETTI and KONZETT, 1956; PASSOW et al., 1960)	D-LSD, acetyl-LSD, and BOL-148 inhibited 5-HT-induced vasoconstriction and protected rats from 5-HT-induced renal infarcts.
Renal infarcts – rat (JASMIN and BOIS, 1960)	
Antidiuretic action – rat (CHODERA, 1963; DEL GRECO et al., 1956; ERSPAMER, 1952, 1953)	Methysergide, D-LSD, BOL-148, dihydroergotamine, and dihydroergotoxine mesylate antagonized 5-HT-induced antidiuresis.
Umbilical vessels – man (ALTURA et al., 1972; ÅSTRÖM and SAMELIUS, 1957; DYER and GANT, 1973; ELIASSON and ÅSTRÖM, 1955; GOKHALE et al., 1966, GULATI and KELKAR, 1971; PANIGEL, 1959, 1962).	Methysergide and BOL-148 antagonized vasoconstrictor response to 5-HT in similar concentrations (0.05–0.1 μg/ml) and caused small contraction. D-LSD antagonized 5-HT-induced vasoconstriction. Dihydroergotamine was less selective.
– monkey (DYER et al., 1972)	
– sheep (DYER, 1969, 1970; DYER and GANT, 1973)	BOL-148 selectively antagonized 5-HT effects.
– guinea-pig (NAIR, 1974; NAIR and DYER, 1974)	BOL-148 antagonized responses to noradrenaline more effectively than those to 5-HT or D-LSD.
Foetal death induced by 5-HT – mouse (FLÜCKIGER and SALZMANN, 1961; HARPER and SKARNES, 1972; POULSON and ROBSON, 1963; TERAKI, 1970)	Methysergide and D-LSD effectively protected the litters against the toxic effect of 5-HT.
– rat (BALDRATTI et al., 1965; PFEIFER et al., 1969)	Ergoline derivative MCE was more active than methysergide.
Atrium – guinea-pig (GREEF et al., 1959; LEVY and MICHEL-BER, 1956; MAGISTRETTI and VALZELLI, 1955; POURRIAS, 1975; TARDOS and ADAM, 1974; TRENDELENBURG, 1960)	D-LSD and BOL-148 reduced but failed to abolish positive inotropic and chronotropic activity of 5-HT.
– hamster (GONZALES et al., 1975)	
– cat (TRENDELENBURG, 1960)	Selective 5-HT antagonism by D-LSD.
– rat (BENFEY et al., 1974)	Inotropic effect of 5-HT was inhibited by 15 μM dihydroergotamine.
Ovarian suspensory ligament – rat (DAVIS, 1976)	Methysergide antagonized 5-HT-induced contraction unmasking a relaxant activity of 5-HT mediated by release of a PGE_2-like substance.
Uterus – rat (ARCARI et al., 1972; BERETTA et al., 1965a; BERNARDI et al., 1975; BORSY et al., 1973; CERLETTI, 1955; CERLETTI and DOEPFNER, 1956, 1958a, b; CERLETTI and KONZETT, 1956; CERLETTI and ROTHLIN, 1955; CHAMBERS and MARSHALL, 1967; COSTA, 1956;	D-LSD at ng concentrations antagonized selectively responses to 5-HT but induced spontaneous contractions at higher concentrations. 5-HT antagonism by methysergide, BOL-148, ergometrine, or methylergometrine was similar in potency to that induced by D-LSD ($pA_{2(10\,min)} = 8.7$).

Table 2 (continued)

Preparation, species, references	Observations
DELAY and THUILLIER, 1956; DOEPFNER and CERLETTI, 1957; DYKSTRA et al., 1967, 1973; ENGELHARDT, 1975; ERSPAMER, 1952, 1953; FANCHAMPS et al., 1960; FINGL and GADDUM, 1953; GADDUM, 1953, 1954; GADDUM and HAMEED, 1954; GADDUM et al., 1955; GOGERTY and DILLE, 1957; PIK and BORSY, 1974; SOLLERO et al., 1956; STONE et al., 1961; TOTHILL, 1967; VOTAVA et al., 1957, 1958)	Peptide alkaloids were about 100 times less potent in antagonizing 5-HT effects and produced more or less spontaneous contractions. For antagonism of 5-HT the $pA_{2(10\ min)}$ values were 6.9 and 6.8 for dihydroergotamine and dihydroergokryptine, respectively.
Esophagus – chicken (BARTLET, 1974; BARTLET and HASSAN, 1968)	Methysergide antagonized contractions but not relaxation in response to 5-HT.
Stomach – rat (BACH et al., 1974; BAKHLE and SMITH, 1974a; BARFKNECHT et al., 1973; BARLOW, 1961; BARLOW and KHAN, 1959a, b; BARZAGHI et al., 1973; CASENTINI and GALLI, 1956; FRANKHUIJZEN, 1975; FRANKHUIJZEN and BONTA, 1974a, b; GÖRLITZ and FREY, 1973; HANDSCHUMACHER and VANE, 1967; MARLEY and WHELAN, 1976; OFFERMEIER and ARIENS, 1966; OGLE and WONG, 1971; PIK and BORSY, 1974; VANE, 1957, 1960)	Most ergot compounds antagonized 5-HT effects in a noncompetitive and nearly irreversible way. D-LSD seems to be slightly less potent than both metysergide and BOL-148. Ergotamine acted as a noncompetitive dualist of 5-HT.
– guinea-pig (YAMAGUCHI, 1972)	
– man (FISHLOCK et al., 1965)	D-LSD (0.1 µg/ml) blocked 5-HT.
– fish (GROVE et al., 1974)	Methysergide antagonized 5-HT.
Duodenum – rat (LEVY and MICHEL-BER, 1956; VOTAVA et al., 1958)	D-LSD inhibited responses to 5-HT.
– mouse (DRAKONTIDES and GERSHON, 1968)	Methysergide blocked muscle receptors for 5-HT.
– rabbit (SOLLERO et al., 1956)	BOL-148 reduced 5-HT effects.
Jejunum – rat (HAYASHI, 1975) – cat (BARABE et al., 1975) – dog (LUDANY et al., 1959) – man (FISHLOCK et al., 1965)	Selective inhibition of 5-HT effects has been demonstrated with D-LSD and methysergide.
Ileum – rat (FURUKAWA and NOMOTO, 1974, 1975) – guinea-pig (BELESLIN and VARAGIC, 1958; BERETTA et al., 1965a; BROWNLEE and JOHNSON, 1963; CHAMBERS and MARSHALL, 1967; DAY and VANE, 1963; GADDUM, 1957; GADDUM and HAMEED, 1954; GADDUM and PICARELLI, 1957; GINZEL, 1957; INNES and KOHLI, 1969; JAQUES et al., 1956; SOLLERO et al., 1956)	Maximal inhibition of 5-HT effects (about 50%) could be achieved with 0.01–0.1 µg/ml D-LSD or BOL-148. Higher concentrations induced contractions but no further inhibition. Dihydroergotamine was less potent and less selective, since it antagonized responses to 5-HT and histamine at the same concentration ranges.
– man (BENNETT and STOCKLEY, 1975; FISHLOCK, 1964; METCALFE and TURNER, 1969, 1970; TURNER, 1973)	Methysergide antagonized 5-HT ($pA_{2(2\ min)}=8.0$).

Table 2 (continued)

Preparation, species, references	Observations
Colon – rat (GAGNON, 1972; JAQUES et al., 1956; PARRATT and WEST, 1957b; REGOLI and VANE, 1964)	Selective antagonism of 5-HT by D-LSD or BOL-148 (0.01–0.2 µg/ml) and by methysergide (0.3 µg/ml).
Rectal cecum – fowls (BARTLET, 1974; CLEUGH et al., 1961)	Potent 5-HT antagonism by methysergide.
Rectum – cockroach (BROWN, 1975)	BOL-148 antagonized selectively 5-HT effects.
Intestine – fish (GADDUM and SZERB, 1961)	Methysergide (50 ng/ml) antagonized responses to 5-HT.
Ureter – pig (CIMA and FRESCHI, 1957)	D-LSD at 0.2 µg/ml antagonized 5-HT effects selectively.
Urinary bladder in situ – dog (GYERMEK, 1960, 1962)	BOL-148 antagonized the prolonged contraction mediated by D-receptor stimulation, leaving the first twitch-like phase unchanged.
Trachea – guinea-pig (CHAHL and O'DONNELL, 1971; CONSTANTINE and KNOTT, 1964)	Methysergide (5–50 ng/ml) inhibited 5-HT effects selectively.
Lungs (isolated perfused) – guinea-pig (BHATTACHARYA, 1955; KING 1956, 1957; MARLEY and WHELAN, 1976) – cat (GADDUM et al., 1953)	D-LSD, BOL-148, methysergide, dihydro-ergotamine, and ergotamine prevented 5-HT-induced bronchospasm.
Bronchospasm, 5-HT-induced, in vivo – guinea-pig (BARZAGHI et al., 1973; BERETTA et al., 1965a, b; BERRY and COLLIER, 1964; CERLETTI, 1955; ENGELHARDT, 1975; HERXHEIMER, 1953, 1955, 1956; HOLGATE and WARNER, 1960; KONZETT, 1956; MARLEY and WHELAN, 1976; SICUTERI et al., 1960) – cat (CERLETTI and KONZETT, 1956; KONZETT, 1956) – rat (CHURCH, 1975)	Selective protection against 5-HT-induced bronchospasm was found with D-LSD BOL-148, and methysergide (1–10 µg/kg). Dihydroergotamine and ergotamine showed only negligible antagonism.
Aggregation, 5-HT-induced	
Platelets – human (BORN et al., 1972; BOULLIN and GREEN, 1975; BOULLIN et al., 1975a; CUMINGS, 1974; CUMINGS and HILTON, 1971; HILTON and CUMINGS, 1971; MICHAL and MOTAMED, 1975, 1976; O'BRIEN, 1964) – sheep (MICHAL, 1969) – pig (DRUMMOND and GORDON, 1974; GORDON and DRUMMOND, 1975) – rat (DRUMMOND and GORDON, 1975a) – duck (BELAMARICH and SIMONEIT, 1973)	5-HT initiates aggregation of platelets by reacting with a receptor similar to the D-receptor of smooth muscle, which can be blocked selectively by D-LSD, BOL-148, methysergide, 1-methyl-ergotamine, and ergotamine at ng concentrations.
Blood cells from various animals (PITZELE and DOBELL, 1973; SWANK and FELLMAN, 1966; SWANK et al., 1963)	

Table 2 (continued)

Preparation, species, references	Observations
Capillary permeability	
Mesenteric vascular bed – rat (MOUTON and DEMAILLE, 1975)	Methysergide inhibited tumoral cell diffusion facilitated by 5HT.
Paw edema – rat (BERDE et al., 1960; BERETTA et al., 1965a; BORSY et al., 1973; CERLETTI and BERDE, 1967; CERLETTI and DOEPFNER, 1958a; CRUNKHORN and MEACOCK, 1971; DOEPFNER and CERLETTI, 1958; ENGELHARDT, 1975; FANCHAMPS et al., 1960; GELFAND and WEST, 1961; MALING et al., 1974; MAWSON and WHITTINGTON, 1970; MÖRSDORF and BODE, 1959; PARRATT and WEST, 1957a, 1958; STONE et al., 1961; VOGEL and MAREK, 1961; VOTAVA and LAMPLOVA, 1959; WEST, 1957)	Methysergide proved to be the most potent ergot compound in antagonizing 5-HT-induced edema of the rat paw. BOL-148 was about four times less potent than D-LSD. The peptide alkaloids, e.g., ergotamine, 1-methyl-ergotamine, and dihydroergotamine, exerted an edema-inhibiting effect only at high concentration ranges.
Skin capillary permeability – mouse (CHURCH and MILLER, 1975) – rat (CRUNKHORN and WILLIS, 1971)	Methysergide inhibited 5-HT-induced inflammation selectively.
Nictitating membrane (in vitro) – cat (THOMPSON, 1958)	D-LSD (1 ng/ml) and dihydroergotamine (10 ng/ml) diminished 5-HT-induced contractions.
Secretion, induced by 5-HT	
Adrenal medulla (in vivo) – cat (MARLEY and WHELAN, 1974, 1976)	5-HT-induced release of adrenaline from adrenal medulla was abolished following intra-arterial injection of methysergide.
Kidney (in vivo) – rat (MEYER et al., 1974)	Methysergide inhibited the stimulation of renin-angiotensin system by 5-HT.
Pancreas (in vitro) – golden hamster (FELDMAN and LEBOVITZ, 1970a, b)	Methysergide antagonized 5-HT-induced inhibition of the insuline release.
Pituitary gland (in vivo) – amphibians (BURGERS and IMAI, 1962; BURGERS et al., 1958, 1962; ITURRIZA, 1965; ITURRIZA and KOCH, 1964)	D-LSD prevented the release of intermedin from the pituitary gland induced by 5-HT.
– crustacean (FINGERMAN and RAO, 1970; RAO and FINGERMAN, 1970)	D-LSD and methysergide prevented 5-HT-induced release of red-pigment-dispersing hormone from neuroendocrine system.
Motility of parasites – *Fasciola hepatica* (BERETTA and LOCATELLI, 1968; MANSOUR, 1957; MANSOUR et al., 1957)	5-HT-induced motor activity could be antagonized by MCE and BOL-148. Dihydroergotamine exhibited only weak 5-HT antagonism.
– *Schistosoma mansoni* (HILLMAN et al., 1974; TOMOSKY et al., 1974)	BOL-148, MCE, dihydroergotamine, and methysergide, but not D-LSD antagonized 5-HT-induced motor activity.
Byssus retractor muscle – *Mytilus edulis* (STEVENS and BAGUET, 1968)	BOL-148 abolished 5-HT-induced relaxation of the contracted byssus muscle.

Table 2 (continued)

Preparation, species, references	Observations
Hearts of certain molluscs	
– *Venus mercenaria* (CHONG and PHILLIS, 1965; GREENBERG, 1960a; HIGGINS, 1974; WELSH and MCCOY, 1957; WRIGHT et al., 1962)	Longlasting and selective antagonism by methysergide and BOL-148 against responses to 5-HT and D-LSD.
– *Cyprina, Buccinum* (WELSH, 1954b, 1956)	D-LSD antagonized 5-HT without stimulating the hearts by itself.
– *Helix aspersa* (KERKUT and LAVERACK, 1960)	D-LSD acted as a 5-HT antagonist with stimulating activity.
– *Helix pomatia* (ROZSA and GRAUL, 1964)	Only BOL-148 antagonized 5-HT effects.

2. Effects of Ergot Alkaloids on 5-HT Metabolism

a) Effects of Ergot Alkaloids on 5-HT Metabolism in Peripheral Tissues

Following the in vivo administration of ergot compounds, such as D-LSD, methysergide or BOL-148, time-dependent changes in the levels of 5-HT in several tissues have been observed. The injection of D-LSD at doses of 50–500 μg/kg caused an increase in the 5-HT level within 10–15 min in rat blood platelets (TORRE et al., 1974a) and in rabbit blood (SANKAR et al., 1964), while 60 min after the i.v. administration of D-LSD into pregnant rabbits a decrease in the 5-HT content in arterial and venous blood was found (ZHABIN and URAZAEVA, 1975). When assayed 120 min after the administration of methysergide, the 5-HT concentration in rat blood was unchanged (OWEN et al., 1971b).

In tissues from rat intestinal tract maximal increase in the level of 5-HT was found 60 min after the injection of a single dose of methysergide (THOMPSON and CAMPBELL, 1967). Chronic administration of methysergide (5 mg/kg/day) for 4 weeks increased the content of 5-HT but also that of noradrenaline, particularly in the rat lung (MIELKE et al., 1973).

Following the injection of [^{14}C] labeled 5-HTP into rabbits an increase in the levels of 5-HT as well as of the radioactivity in several visceral tissues 15 min after the injection of both D-LSD and BOL-148 was observed (SANKAR et al., 1961, 1962, 1964). However, D-LSD increased not only the incorporation of radioactivity following the administration of labeled 5-HTP but also that after [^{14}C]-histidine and that after [^{14}C]noradrenaline. On the other hand D-LSD decreased the levels of histamine and noradrenaline while increasing that of 5-HT. Thus, it cannot be excluded that changes in 5-HT contents induced by ergot alkaloids may be mediated indirectly by mutual interaction with the levels and/or binding of other biogenic amines (SANKAR et al., 1964).

α) *Biological Inactivation of 5-HT in Peripheral Tissues*

In the isolated perfused rabbit heart 1 μg/ml methysergide enhanced metabolite appearance in the perfusion fluid as assessed by the perfusion of [^{3}H]5-HT (FOZARD

and BERRY, 1976; FOZARD and WRIGHT, 1974). Although this observation could suggest that methysergide enhanced the biological inactivation of 5-HT, in vitro studies on suspension of guinea-pig liver and rat fundus showed that neither BOL-148 (BARLOW, 1961) nor methysergide (SEILER and WASSERMANN, 1973) displayed any change of MAO activity.

β) Uptake and Release of 5-HT by Peripheral Tissues

There is good evidence for the existence of at least two different 5-HT receptors on blood platelets from various species: One receptor mediating cellular stimulation (platelet shape change, platelet aggregation) by 5-HT, and the other receptor mediating the uptake of 5-HT (BORN et al., 1972; BOULLIN et al., 1975b; DRUMMOND and GORDON, 1975b; DRUMMOND et al., 1976). Ergot alkaloids were found to be potent antagonists of the stimulatory 5-HT receptors, while causing only weak inhibition of the active transport of 5-HT. Methysergide (BORN et al., 1972; CUMINGS and HILTON, 1971; DRUMMOND and GORDON, 1975a; HILTON and CUMINGS, 1971; MITCHELL and SHARP, 1964; O'BRIEN, 1964; PITZELE and DOBELL, 1973), D-LSD and methergoline (DRUMMOND and GORDON, 1975a; MICHAL, 1969), BOL-148, ergotamine and 1-methyl-ergotamine (CUMINGS and HILTON, 1971) caused about 50% reduction of 5-HT-induced stimulation when used at nM concentrations. However, when tested as inhibitors of the platelet 5-HT transport system, 130–150 μM of D-LSD, BOL-148 or methysergide were necessary to cause a 50% reduction of 5-HT uptake (BORN et al., 1972; CUMINGS and HILTON, 1971; TRENCHARD et al., 1975; STACEY, 1961). The peptide alkaloids ergotamine and dihydroergotamine (LINGJAERDE, 1970; STACEY, 1961) were only two to 10 times more potent than the lysergic acid derivatives in decreasing the 5-HT uptake by blood platelets. Thus, ergot alkaloids were at least 10,000 times less potent as inhibitors of the platelet 5-HT transport system as compared to their blocking activity against the stimulatory 5-HT receptors on blood platelets.

Using chlorprothixene isomers as blocking agents, DRUMMOND et al. (1976) found that cis-chlorprothixene was about 200 times more potent than its trans-isomer as an inhibitor of the 5-HT-induced aggregation, while the latter was twice as inhibitory as its cis-isomer when tested against the active uptake of 5-HT. It was suggested that 5-HT adopts different conformations for binding to its two platelet receptors: A less extended form of its side chain when binding to the stimulatory receptors but an extended form of its side chain when binding at the uptake receptor. It follows from this that the lack of effect of ergot alkaloids on 5-HT uptake might be due to a failure of the rigid ergolene moiety to mimic 5-HT in its extended conformation.

Several in vitro studies seem to support this assumption. In suspension of guinea-pig liver and rat fundus BOL-148 failed to affect the penetration of both tryptamine and 5-HT (BARLOW, 1961; HANDSCHUMACHER and VANE, 1963, 1967). The extraneuronal accumulation of 5-HT into the isolated rabbit ear artery was unaltered after 30 min preincubation with 100 μM methysergide (BUCHAN et al., 1974).

Facilitation of the uptake of [^{3}H]5-HT was observed in the isolated cat spleen perfused with methysergide at 0.3–1 μg/min (OWEN et al., 1971a, b; SALZMANN

and KALBERER, 1973) and in the isolated rabbit heart perfused with 1 μg/ml ergotamine (FOZARD and BERRY, 1976; FOZARD and WRIGHT, 1974). Even higher concentrations of ergot alkaloids, such as methysergide, ergotamine, 1-methyl-ergotamine and dihydroergotamine, inhibited the [^{3}H]5-HT uptake into the isolated perfused cat spleen (OWEN et al., 1971a, b; SALZMANN and KALBERER, 1973).

Methysergide has been found to exhibit a dose-dependent protective influence against the 5-HT depleting activity of reserpine in rat blood in vivo (OWEN et al., 1971a, b), but it failed to affect the reserpine-induced reduction of 5-HT content in human blood platelets in vitro (CUMING and HILTON, 1971).

In addition, there is no evidence for an interference of ergot alkaloids with the spontaneous release of 5-HT from blood platelets in vitro. Up to 10 μM, neither D-LSD (CARLSSON et al., 1957) nor the peptide alkaloids ergotamine and dihydroergotamine (LINGJAERDE, 1970) developed any effect on spontaneous efflux of 5-HT from blood platelets.

In conclusion, at concentrations which cause pharmacologic effects ergot alkaloids will not interfere with either uptake or release of 5-HT in peripheral tissues.

b) Effects of Ergot Alkaloids on 5-HT Metabolism in the Central Nervous System

Investigations on the influence of ergot alkaloids on the metabolism of 5-HT in the brain showed that D-LSD produced a small but reproducible increase in the level of 5-HT in the rat brain. About 30 to 120 min following the administration of D-LSD into rats the 5-HT concentration of the brain was elevated (BOGGAN and FREEDMAN, 1973; DIAZ and HUTTUNEN, 1971; DIAZ et al., 1967, 1968; FREEDMAN, 1960, 1961, 1963, 1966; FREEDMAN and AGHAJANIAN, 1967; FREEDMAN and BOGGAN, 1974; FREEDMAN and COQUET, 1965; FREEDMAN and GIARMAN, 1962; FREEDMAN et al., 1970; KING et al., 1974; LOVELL et al., 1967; MATIN and VIJAYVARGIYA, 1967; PETERS, 1974a; RANDIC and PADJEN, 1971; SCHANBERG and GIARMAN, 1962; TONGE and LEONARD, 1969). Only within the first few minutes following the injection of D-LSD could a small decrease of the 5-HT level be observed (LOVELL et al., 1967; TORRE et al., 1974a, b). When assayed 2–4 h after the administration of D-LSD the 5-HT concentration in the brain was usually unchanged (ANDÉN et al., 1968; BOGGAN and FREEDMAN, 1973; FREEDMAN and BOGGAN, 1974; PAASONEN and GIARMAN, 1958; SCHANBERG and GIARMAN, 1962; SCHILDKRAUT et al., 1969; TONGE and LEONARD, 1969).

These observations have been confirmed in mice (CARLSSON and LINDQVIST, 1972; GLOWINSKI et al., 1973; RUCKEBUSCH et al., 1965; SZARA et al., 1967) and in rabbits (BRODIE, 1954; BRODIE et al., 1956; FREEDMAN, 1963; SANKAR et al., 1961, 1962, 1964).

Additional studies demonstrated that after administration of D-LSD the concentration of 5-HIAA in the brain was decreased (AGHAJANIAN and WEISS, 1968; BOGGAN and FREEDMAN, 1973; CARLSSON and LINDQVIST, 1972; DIAZ et al., 1967, 1968; FREEDMAN and AGHAJANIAN, 1967; FREEDMAN and BOGGAN, 1974; FREEDMAN et al., 1970; LOVELL et al., 1967; PETERS, 1974a; RANDIC and PADJEN, 1971; ROSECRANS et al., 1967; SCHILDKRAUT et al., 1969).

Both 1-acetyl-LSD (FREEDMAN, 1961, 1963; FREEDMAN and GIARMAN, 1962) and 1-methyl-LSD (FREEDMAN, 1963; FREEDMAN et al., 1970) showed D-LSD-like activity.

BOL-148 at doses about 10 times higher than D-LSD also increased the 5-HT level in rat brain within the first 30 min following its administration (FREEDMAN, 1960, 1961; FREEDMAN and GIARMAN, 1962), but no change of the levels of either 5-HT or 5-HIAA could be detected at a later time (DIAZ et al., 1967, 1968; FREEDMAN, 1963; FREEDMAN et al., 1970; KING et al., 1974).

Neither methysergide (ANSELL et al., 1969; D'AMICO et al., 1976; FREEDMAN, 1961; FREEDMAN and GIARMAN, 1962; FREEDMAN et al., 1970; JACOBY et al., 1975) nor L-LSD (FREEDMAN, 1961; FREEDMAN and GIARMAN, 1962; FREEDMAN et al., 1970) were found to increase the level of 5-HT or change that of 5-HIAA in brains.

Methergoline (FUXE et al., 1975a) and methysergide (ANSELL et al., 1969; SOFIA and VASSAR, 1975) have been found to cause dose-dependent decreases of the 5-HT levels in brains from rats and guinea-pigs (D'AMICO et al., 1976) when used at doses of 1–5 mg/kg. About 10 times higher doses were required to decrease the 5-HT level in rat brains with ergotamine (SOFIA and VASSAR, 1975).

SNIDER et al. (1975) found that high doses of bromocriptine increased the 5-HT level, whereas CORRODI et al. (1975) observed no change of the 5-HT concentrations in rat brains after the administration of bromocriptine, ergocornine or PTR 17-402 (6-methyl-8β-[4-(p-methoxyphenyl)-1-piperazinyl]methyl-9-ergolene). Bromocriptine (SNIDER et al., 1975) and dihydroergotoxine mesylate (LOEW et al., 1976) decreased the 5-HIAA concentrations only when used at extremely high doses.

Although several ergot compounds have been found to increase the 5-HT level in the rat brain, only D-LSD also consistently decreased the concentration of 5-HIAA and at the same time the rate of synthesis of 5-HT, indicating that D-LSD slowed the turnover of 5-HT in the brain. Various mechanisms, e.g., enhanced vesicular binding, inhibition of 5-HT release, interneuronal feedback inhibition and/or inhibition of firing, were suggested to be involved in the effect of D-LSD in slowing down the 5-HT turnover.

In the rat brain the largest single collection of 5-HT-containing neurones is situated in the raphe nuclei of the midbrain. Projections from the dorsal raphe nucleus supply the principal 5-HT input to the forebrain (ANDÉN et al., 1966). Placement of electrolytic lesions in the rat midbrain raphe nuclei led to a selective fall in the level of 5-HT in the forebrain (KUHAR et al., 1971, 1972b). Electrical stimulation of the 5-HT-containing neurones of the midbrain raphe nuclei led to an increase of the 5-HIAA level and a decrease of the level of 5-HT in the forebrain, indicating that 5-HT can be released via specific axons projecting into the forebrain from 5-HT-containing neurones in the midbrain (AGHAJANIAN et al., 1967). An increase in brain 5-HT turnover associated with an increase in the level of 5-HIAA in the brain could also be induced by exposure of rats to elevated ambient temperature. Moreover, it was found that with rising body temperature there was a concomitant increase in the rate of firing of individual raphe neurones (WEISS and AGHAJANIAN, 1971). Both the stimulation-induced changes in 5-HT levels (KOSTOWSKI and GIACALONE, 1969; RANDIC and PADJEN, 1971) as well as the temperature-induced increase in the level of 5-HIAA (AGHAJANIAN and WEISS, 1968; CURZON and MARSDEN, 1976; WEISS and AGHAJANIAN, 1971) could be

prevented by treatment of rats with D-LSD as well as by midbrain raphe lesions (WEISS and AGHAJANIAN, 1971).

There exists a reciprocal relationship between brain 5-HT content and the rate of firing of raphe cells. Elevation of brain 5-HT levels inhibits the firing of raphe neurones (AGHAJANIAN, 1972a, b; AGHAJANIAN et al., 1970b). As described in part 3, a of this section, D-LSD was also found to inhibit the firing of 5-HT-containing neurones. These results suggest, therefore, that the D-LSD-induced decrease in 5-HT turnover could result from an inhibition of firing rate of 5-HT-containing neurones.

α) Synthesis and Biological Inactivation of 5-HT in Neuronal Tissues

The regulation of 5-HT synthesis in serotoninergic neurones involves several processes, such as active transport mechanisms of uptake of tryptophan, its hydroxylation into 5-hydroxytryptophan (5-HTP) by the action of the highly specific enzyme tryptophan hydroxylase, and the decarboxylation of 5-HTP into 5-HT by the 5-hydroxytryptophan decarboxylase. Although there is good evidence for the existence of a negative feedback which controls the synthesis of 5-HT in serotoninergic neurones via intraneuronal levels of 5-HT, little is known about the factors which control the active transport into serotoninergic neurones or about the regulation of tryptophan hydroxylation which may be affected by various factors of environmental conditions and possibly by interneuronal feedback regulations (CARLSSON et al., 1972a, b; GLOWINSKI et al., 1973; HAMON and GLOWINSKI, 1974).

Treatment of animals with low doses of D-LSD was found to increase endogenous tryptophan levels in the mouse (GLOWINSKI et al., 1973) and rat brain (DIAZ and HUTTUNEN, 1971; FREEDMAN and BOGGAN, 1974; HAMON et al., 1974; HALARIS et al., 1975; TONGE and LEONARD, 1970), while both methysergide (JACOBY et al., 1975) and bromocriptine (SNIDER et al., 1975) failed to alter the tryptophan level in rat brains.

Chronic treatment of rats with low doses of D-LSD (20 μg/kg/day) for 1 month increased the rate of [^{3}H]5-HT derived from intracisternally injected [^{3}H]tryptophan (DIAZ and HUTTUNEN, 1971) as well as that derived from i.v. injected [^{3}H]-tryptophan in most brain areas, with the exception of forebrain (PETERS, 1974b). On the other hand, injection of a single dose of D-LSD decreased the conversion of labeled tryptophan into 5-HT in rat (DIAZ and HUTTUNEN, 1971; LIN et al., 1969; SHIELDS and ECCLESTON, 1973) and mouse brains (GLOWINSKI et al., 1973). A decreased synthesis of [^{3}H]5-HT from [^{3}H]tryptophan could also be observed in rat striatal slices even 60 min after the i.p. injection of a single high dose (1 mg/kg) of D-LSD (HAMON et al., 1974).

In contrast to these findings with D-LSD, BOL-148 did not change the rate of conversion of tryptophan into 5-HT in brains from either rats (LIN et al., 1969) or mice (SCHUBERT et al., 1970), and methysergide also failed to change the rise in 5-HT level following the administration of 5-HTP in guinea-pig brains (KLAWANS et al., 1973, 1975).

D-LSD was found to prevent the activation of tryptophan hydroxylase induced by methiothepin in rat brainstem slices. Administration of methiothepin, a potent 5-HT receptor blocking drug (MONACHON et al., 1972), into rats in vivo or to

the incubating medium of rat brainstem slices in vitro resulted in a stimulation of the rates of formation of [^{3}H]5-HT and [^{3}H]5-hydroxyindole acetic acid ([^{3}H]5-HIAA) as compared to those in control tissues. This effect was related partly to an enhanced accumulation of [^{3}H]tryptophan in slices; however, it was also due to an activation of the rate of tryptophan hydroxylation, as estimated from the elevated conversion index of tryptophan into 5-hydroxyindoles ([^{3}H]5-hydroxyindoles/tryptophan specific activity). This methiothepin-induced activation of tryptophan hydroxylation could be prevented when brainstem slices were incubated in the presence of both methiothepin (30 μM) and D-LSD (10 μM) (HAMON et al., 1976a, b).

Treatment of mice with l-tryptophan approximately doubled the 5-HTP accumulation in the brain induced by decarboxylase inhibition with Ro 4-4602 (N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl)hydrazine). This 5-HTP accumulation could be retarded by hydroxylase inhibitors but also by D-LSD (1–6 mg/kg) administered 60 min before death. Since additional experiments on mouse brain slices gave no support for a direct inhibition of tryptophan hydroxylase by D-LSD, it was suggested that synthesis and turnover of 5-HT is regulated by a feedback mechanism operating via changes in the intraneuronal 5-HT levels and/or in the activity of postsynaptic receptors (CARLSSON and LINDQVIST, 1972; CARLSSON et al., 1972a, b). In contrast to these findings with D-LSD, no change of the 5-HTP accumulation in rat brains following decarboxylase inhibition could be induced with bromocriptine (SNIDER et al., 1975).

The active uptake of 5-HTP by rat brain slices was unchanged after pretreatment of the animals with D-LSD (SCHANBERG and GIARMAN, 1960). Following the i.p. administration of labeled 5-HTP into mice, D-LSD, but not BOL-148, increased the levels of radioactive metabolites of 5-HTP in most brain areas (SZARA et al., 1967).

As observed with peripheral tissues, D-LSD had no influence on the biological inactivation of 5-HT. Neither in vitro nor in vivo was D-LSD found to change the destruction of 5-HT in the rat brain when used at pharmacologically active doses (FREEDMAN, 1961; FREEDMAN and AGHAJANIAN, 1967; FREEDMAN and GIARMAN, 1962). Only when used at concentrations higher than 10 μg/ml did D-LSD enhance the enzymatic inactivation of 5-HT in rat brain slices (HAMON et al., 1974).

β) Uptake of Exogenous 5-HT by Neuronal Tissues

5-HT is suggested to function as the main neurotransmitter in several invertebrates. The uptake of [^{3}H]5-HT by subesophageal ganglia of the snail *Helix pomatia* was not affected by D-LSD at concentrations of 10–200 μM (OSBORNE et al., 1975) and in the parasites *Schistosoma mansoni* and *Mesocestoides corti* ergot compounds, such as D-LSD, BOL-148, methysergide and 1-methyl-LSD, also failed to change the uptake of 5-HT (BENNETT and BUEDING, 1973; HARIRI, 1975).

Similar results have been obtained with brain slices and hypothalamic synaptosomes from vertebrates. Up to 10 μM D-LSD failed to affect the uptake of [^{3}H]5-HT into brain slices from mice (ROSS and RENYI, 1967) and rats (ZIEGLER et al., 1973) as well as that by rat hypothalamic synaptosomes (TUOMISTO, 1974).

The uptake of [^{3}H]5-HT into rat brain slices was found to be reduced to 50% by 500 μM methysergide (SHASKAN and SNYDER, 1970), 10 μM methergoline (FUXE et al., 1975a) and 1.6 μM PTR 17–402 (CORRODI et al., 1975). Used at 10 μM, bromocriptine caused 20% inhibition, while ergocornine failed to change the uptake of [^{3}H]5-HT by rat brain slices (CORRODI et al., 1975). In rat hypothalamic synaptosomes, 10 μM ergotamine reduced the accumulation of [^{3}H]5-HT by 50% (TUOMISTO, 1974).

There is evidence for the existence of at least two kinetically distinct 5-HT uptake mechanisms in the rat brain, and it was supposed that 5-HT—even in low doses—may also enter catecholaminergic neurones in significant proportions (SHASKAN and SNYDER, 1970).

γ) Release of 5-HT From Neuronal Tissues

Release of 5-HT From Extragranular Storage Sites

It seems possible that in the rat brain 5-HT is stored in at least two pools receiving amine synthesized by separate pathways. As has been mentioned, the strongest inhibition of [^{3}H]5-HT accumulation into rat brain slices was obtained with the ergolene derivative PTR 17-402 having an ED_{50} of 1.6 μM. This effect, however, seemed to be due to a PTR 17-402-induced 5-HT release from extragranular stores. It has been found that PTR 17-402 increased the spontaneous [^{3}H]5-HT release from cortical slices from nialamide-pretreated rats already in a concentration of 0.1 μM, while there was no releasing effect on slices of untreated animals. Based upon these observations, it was concluded that PTR 17-402 depleted only extragranular 5-HT stores, and that the large granular pool, where in slices of untreated animals most of the [^{3}H]5-HT is probably localized, may not be affected by PTR 17-402 (CORRODI et al., 1975).

Release of 5-HT From Granular Storage Sites

As has been mentioned, there is considerable evidence that 5-HT is formed and stored in presynaptic neuronal structures of special neurones and serves as neurotransmitter in the central nervous system (ANDÉN et al., 1969). In response to stimulation of 5-HT-containing neurones, the amine is released into the extracellular space, where it is partly deaminated by monoamine oxidase and partly taken up again by the nerve terminal. The existence of an inhibitory feedback loop from 5-HT-sensitive units to 5-HT-containing neurones and consequently presynaptic 5-HT-release inhibition as a mode of action of ergot alkaloids, seems therefore plausible.

Using a cerebroventricular perfusion technique to investigate neurochemical changes in the cerebrospinal fluid in rats, D-LSD at doses as low as 75 μg/kg intraperitoneally decreased significantly the efflux of [^{3}H]5-HT formed in vivo from [^{3}H]tryptophan paralleled with a total inhibition of raphe cell firing (GALLAGER and AGHAJANIAN, 1974, 1975). At higher doses, D-LSD inhibited the 5-HT overflow induced by electrical stimulation of midbrain raphe nuclei in rats (RANDIC and PADJEN, 1971) and decreased the overall output of [^{14}C]activity following

a 30-min intraventricular infusion of [^{14}C]5-HT, having no discernible action on catecholaminergic pools (SPARBER, 1975; TILSON and SPARBER, 1972). These findings were supported by the observation that the retention of intraventricularly injected [^{3}H]5-HT in the rat brain was increased 60 min after i.p. treatment of the animals with D-LSD (ZIEGLER et al., 1973).

In vitro D-LSD at concentrations of 1–200 μM was found to inhibit 5-HT release from brain slices from guinea-pigs (KAWAI, 1970) and rats induced by electrical stimulation (CHASE et al., 1967, 1969; FARNEBO and HAMBERGER, 1971b; KATZ and KOPIN, 1969; KOPIN, 1970).

Reduction of the 5-HT overflow during electrical stimulation of brain slices has also been found with ergocornine (1 μM) and bromocriptine (10 μM) (CORRODI et al., 1975; FARNEBO and HAMBERGER, 1974) and with 1-acetyl-LSD (200 μM), whereas BOL-148 and L-LSD failed to inhibit the stimulation-evoked 5-HT release (KATZ and KOPIN, 1969; KOPIN, 1970).

In addition, D-LSD reduced the 5-HT overflow in response to depolarization induced by potassium. In rat striatal slices the release of [^{3}H]5-HT, synthesized from [^{3}H]tryptamine or taken up by tissue, was increased when concentrations of potassium in the incubation medium reached 30 or 50 mM. D-LSD administered in vivo (1 mg/kg) or in vitro (1 to 10 μM) effectively prevented the potassium-induced 5-HT release. The inhibitory effect of D-LSD on 5-HT release could be seen as soon as 10 min after the administration in vivo, when [^{3}H]5-HT synthesis was not affected by D-LSD. These observations suggested, therefore, that the inhibitory effect of D-LSD on 5-HT release could be mediated by a local feedback process linked to the stimulating action of the ergot compound on presynaptic 5-HT receptors (HAMON et al., 1974, 1976a).

While several ergot alkaloids reduced stimulation-induced 5-HT overflow, methiothepin, a potent 5-HT receptor blocking agent (MONACHON et al., 1972), significantly increased the 5-HT overflow induced by electrical stimulation of rat brain slices without inhibiting its uptake (FARNEBO and HAMBERGER, 1974).

These observation strongly suggest that 5-HT release can be modified by 5-HT acting on presynaptic 5-HT receptors, and that several ergot compounds may inhibit 5-HT release by stimulating these presynaptic 5-HT receptors.

Effects of Ergot Alkaloids on Drug-Induced Depletion of Neuronal 5-HT Stores

In the rat brain and spinal cord D-LSD markedly reduced the rate of 5-HT depletion due to tryptophan hydroxylase inhibition with either H 22/54 (α-propyl-dopacetamide) or PCPA (p-chlorophenylalanine) (ANDÉN, 1968; ANDÉN et al., 1968; TONGE and LEONARD, 1969) and stimulated the endogenous repletion of 5-HT stores after the administration of reserpine (FREEDMAN, 1960, 1961, 1963; FREEDMAN and GIARMAN, 1962; HALARIS and LOVELL, 1973).

In reserpinized rats 1-acetyl-LSD and BOL-148 showed also a certain activity, while methysergide failed to elevate the brain 5-HT levels (FREEDMAN, 1960; FREEDMAN and GIARMAN, 1962).

It has been suggested that D-LSD acted by either enhanced binding of 5-HT

to storage sites (FREEDMAN, 1961, 1963, 1975; HALARIS and LOVELL, 1973; LOVELL et al., 1967; SCHANBERG and GIARMAN, 1962) or by an inhibitory feedback mechanism to presynaptic 5-HT neurones via stimulation of postsynaptic 5-HT receptors (ANDÉN, 1968; ANDÉN et al., 1968).

When the tryptophan hydroxylase was inhibited by H 22/54, only ergocornine and PTR 17-402, in addition to D-LSD, were found to reduce the 5-HT depletion in the rat brain, while bromocriptine (CORRODI et al., 1975), BOL-148 and methysergide (ANDÉN et al., 1968) failed to change the H 22/54-induced 5-HT depletion. On the other hand, methergoline enhanced the H 22/54-induced 5-HT depletion of the whole brain and counteracted the reduction of H 22/54-induced 5-HT depletion caused by D-LSD. The enhancement of the H 22/54-induced 5-HT depletion by methergoline was suggested to be partly due to a 5-HT receptor blocking action of methergoline, which may lead to a compensatory activity of central 5-HT neurones. However, an additional presynaptic action was also assumed (FUXE et al., 1975a).

3. Effects of Ergot Alkaloids on Neuronal 5-HT Receptors

Based upon the observation that D-LSD provided powerful and specific antagonism against 5-HT in smooth muscle preparations, GADDUM (1953, 1954) and WOLLEY and SHAW (1954a, b) already assumed that D-LSD might produce its central actions by interfering with the function of 5-HT in the brain. The subsequent research on the possible interactions of ergot alkaloids with the serotoninergic system in the brain led to conflicting results. Though several reports suggested that ergot alkaloids, e.g., D-LSD, ergometrine, BOL-148 or 1-methyl lysergic acid diethylamide, can antagonize the effects of 5-HT on spontaneous or evoked electrical activity in cat brains recorded via macro-electrodes (BOND and GUTH, 1964; GADDUM and VOGT, 1956; GUTH and SPIRTES, 1958; VOGT, 1954; VOGT et al., 1957), many reports showed either no antagonism or even synergism between different ergot compounds and 5-HT (BRADLEY, 1958; BRADLEY and HANCE, 1956a, b; GADDUM and VOGT, 1956; MARRAZZI, 1957; MARAZZI and HART, 1955a, b; SCHWARZ et al., 1956; VOGT, 1954; VOGT et al., 1957).

Since systemically applied 5-HT is not supposed to cross the blood brain barrier, most of these findings probably resulted from an action of 5-HT on peripheral, e.g., vascular, 5-HT receptors. Much interesting information came from the use of 5-HT precursors and/or monoamine oxidase inhibitors to bypass the blood brain barrier and elevate the endogenous 5-HT levels. In rabbits, methysergide effectively prevented EEG changes due to i.v. injection of 5-HTP but failed to change responses to i.v. injections of 5-HT (NAREBSKI et al., 1963).

In addition, the use of tryptophan hydroxylase inhibitors or amine-releasing agents to deplete endogenous 5-HT stores proved a useful method to study the interaction of drugs with neuronal 5-HT receptors.

The best available method for directly evaluating the qualitative effects of drugs on single neurones is by microiontophoresis. This method permits the application of relatively small amounts of substances directly into the immediate spatial environment of a living neurone, while neuronal responses can be recorded by

microelectrodes. The microiontophoresis thus eliminates several of the interpretive uncertainties associated with parenteral or topical methods of pharmacologic analysis.

It has been demonstrated that brain 5-HT is contained primarily within specific neuronal elements located in raphe nuclei of the brainstem (DAHLSTRÖM and FUXE, 1964, 1965). Projections from the dorsal raphe nucleus supply the principal 5-HT input to the forebrain (ANDÉN et al., 1966). 5-HT-containing cell bodies in the caudal raphe nuclei of the brainstem give rise to axons which descend the spinal cord to contact motoneurones (FUXE, 1965). Other postsynaptic areas that receive a dense and uniform 5-HT input are the ventral lateral geniculate, amygdala, optic tectum and subiculum (AGHAJANIAN et al., 1973), the hippocampus and superior colliculus (BLOOM et al., 1972, 1973).

On both the 5-HT-containing raphe neurones as well as on neurones receiving 5-HT input, microiontophoretically applied 5-HT produces inhibition. Neurones receiving little or no 5-HT input, e.g., cells in the reticular formation or neurones of the cerebral cortex, may be either excited or inhibited by 5-HT.

a) Effects of Ergot Alkaloids on 5-HT-Containing Neurones

The histochemical identification and mapping of the location of 5-HT-containing neurones in the rat brain (DAHLSTRÖM and FUXE, 1965) provided the possibility to study the effects of drugs on the activity of single 5-HT-containing neurones directly by means of microelectrode recording. Raphe neurones produce a characteristic spontaneous activity of regular rhythm. Both 5-HT and D-LSD inhibited the firing of raphe neurones when applied microiontophoretically (AGHAJANIAN and HAIGLER, 1974; AGHAJANIAN et al., 1972; BRAMWELL and GONYE, 1973; HAIGLER and AGHAJANIAN, 1973a, b, 1974b), the latter being much more potent than 5-HT (AGHAJANIAN and HAIGLER, 1974). When submaximal amounts of D-LSD and 5-HT were ejected simultaneously, their combined inhibitory effects were additive (AGHAJANIAN et al., 1972). Microiontophoretically applied methysergide and methergoline also mimicked the inhibitory activity of 5-HT (HAIGLER and AGHAJANIAN, 1974a), while BOL-148 was found to have less than 1% of the activity of D-LSD in depressing raphe neurones (AGHAJANIAN and HAIGLER, 1974; AGHAJANIAN et al., 1972). Systemically administered D-LSD produced also a reversible inhibition of raphe cell firing. When injected i.v., D-LSD was active at a dose range of 3–20 μg/kg (AGHAJANIAN et al., 1968, 1970a; BENNETT and AGHAJANIAN, 1976; FOOTE et al., 1969; GALLAGER and AGHAJANIAN, 1974, 1975, 1976, HAIGLER and AGHAJANIAN, 1973a, b, 1974a; MOSKO and JACOBS, 1974; SVENSSON et al., 1974), while BOL-148 at doses about 10 times higher than D-LSD induced only partial inhibition of raphe firing (AGHAJANIAN et al., 1970a).

The failure of both PCPA (p-chlorophenylalanine) (AGHAJANIAN et al., 1970b) and Ro 4-4602 (GALLAGER and AGHAJANIAN, 1976) to alter D-LSD-induced inhibition of raphe firing indicated that these D-LSD effects were not dependent on 5-HT synthesis.

BENNETT and AGHAJANIAN (1976) found that the response of single raphe neurones to i.v. D-LSD was correlated with binding of the drug in the brain. Raphe firing was rapidly decreased by a dose of 3 μg/kg D-LSD i.v., which corresponded

to the high-affinity binding of the drug in vitro. Studies on identified neurones within the serotoninergic system showed that presynaptic (5-HT-containing) neurones are more sensitive to the inhibitory activity of D-LSD than are postsynaptic (cells receiving 5-HT input) neurones (Fig. 13). The primary effect of D-LSD at low doses may thus be to inhibit raphe neurones by blocking 5-HT release via stimulation of presynaptic 5-HT receptors (AGHAJANIAN and HAIGLER, 1974).

b) Effects of Ergot Alkaloids on Neurones Receiving Inhibitory 5-HT Input

Neurones receiving a dense 5-HT input are relatively insensitive to D-LSD at ejection currents that are highly effective in the raphe (HAIGLER and AGHAJANIAN, 1973b, 1974b). When administered systemically at low doses, D-LSD has its primary action upon the presynaptic (i.e., raphe) neurones. The postsynaptic (i.e., ventral lateral geniculate nucleus) neurones tend to accelerate at these low doses perhaps due to a release from a tonic inhibitory influence of raphe on postsynaptic cells (AGHAJANIAN, 1972a; AGHAJANIAN and HAIGLER, 1974; HAIGLER and AGHAJANIAN, 1973b) (Fig. 13). No acceleration, but rather depression, of postsynaptic neuronal firing was observed when methysergide or methergoline was administered intravenously (HAIGLER and AGHAJANIAN, 1974a).

The spontaneous discharge of neurones in the lateral geniculate nucleus (LGN) is supposed to depend on the amount of tonic inhibition excerted by 5-HT neurones upon reticular "generator cells." Reduction of brain 5-HT by substances which inhibit storage or synthesis of 5-HT induces the occurrence of ponto-geniculo-occipital (PGO) waves. Drugs increasing the synaptic concentration of 5-HT by inhibiting neuronal uptake or directly stimulating 5-HT receptors reduce or abolish the PGO-waves. PGO-waves are thus a suitable parameter for detecting the possible effect of a drug on central 5-HT receptors. Using this method, evidence has been provided that D-LSD, methysergide and BOL-148 (FROMENT et al., 1971; HAEFELY et al., 1976; JALFRE et al., 1970, 1972, 1974; MONACHON et al., 1972; RUCH-MONACHON et al., 1976a) as well as the peptide alkaloid dihydroergotamine (RUCH-MONACHON et al., 1976b) effectively reduced drug-induced PGO-waves in the cat lateral geniculate body by directly stimulating 5-HT receptors when administered systemically (Fig. 14).

CURTIS and DAVIS (1961, 1962) first applied the technique of microiontophoresis to the study of neuronal responses of the cat LGN. Both 5-HT and D-LSD were found to diminish or block spontaneous activity and orthodromic firing evoked by nerve stimulation. Ergometrine and methylergometrine were two to three times more potent than D-LSD. BOL-148, methysergide and 12-hydroxy-methylergometrine were very weak, and ergotamine was not active in depressing the activity of cat LGN neurones. Thus, only ergot compounds of the amide type were found to mimic the inhibitory activity of 5-HT. Moreover, neither worker found antagonism of 5-HT effects by ergot alkaloids (CURTIS and DAVIS, 1961, 1962; PHILLIS et al., 1967; TEBÉCIS and DIMARIA, 1972).

These findings have been confirmed on neurones in the rat LGN. In these postsynaptic neurones, microiontophoretically applied ergot compounds, such as D-LSD, methysergide and methergoline had inhibitory activity and never antagonized the depression of firing induced by ejection of 5-HT. Moreover, the effects

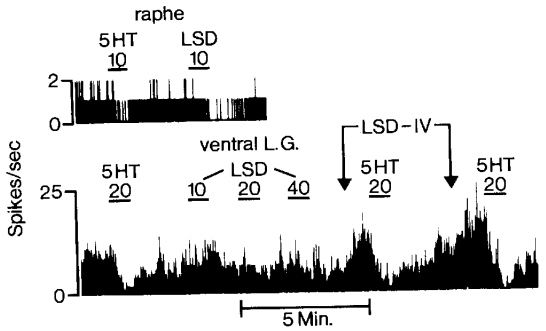


Fig. 13. Effect of 5-HT and D-LSD on the activity of a dorsal raphe neurone and a neurone in the ventral lateral geniculate nucleus (LGN) of the rat. Upper trace: The raphe neurone is inhibited by the microiontophoretic ejection of 5-HT and D-LSD. Lower Trace: The LGN neurone is also inhibited by microiontophoretic 5-HT but is relatively insensitive to D-LSD applied microiontophoretically. D-LSD intravenously (*arrows*) caused acceleration of firing but no 5-HT antagonism. [From Figure 2, AGHAJANIAN, G.K., HAIGLER, H.J.: Adv. Biochem. Psychopharmacol. **10**, 169 (1974)]

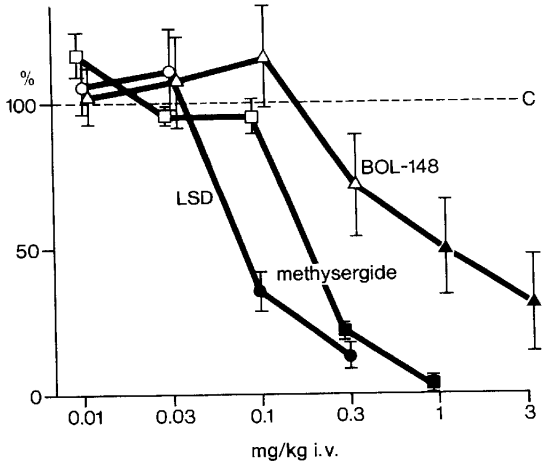


Fig. 14. Reduction of the density of Ro 4-1284-induced PGO-waves in the cat lateral geniculate body by D-LSD, methysergide and BOL-148. [From Figure 4, RUCH-MONACHON, M.A. (et al.): Arch. int. Pharmacodyn. **219**, 274 (1976)]

of combined administration of 5-HT and ergot compounds were often additive and sometimes produced an inhibition lasting much longer than the inhibition produced by 5-HT alone (AGHAJANIAN and HAIGLER, 1974; HAIGLER and AGHAJANIAN, 1973b, 1974a).

Investigating the actions of 5-HT and D-LSD in more detail, two types of dose-dependent depressant actions in the cat LGN have been observed. The depression of orthodromic firing at low concentrations of 5-HT or D-LSD was suggested

to be mediated by block of the release or effect of an excitatory transmitter from optic nerve terminals, whereas the depression of chemically and sometimes also of antidromic-evoked firing at higher concentrations of 5-HT or D-LSD was suggested to indicate a direct action on postsynaptic 5-HT receptors of LGN neurones (TEBÉCIS and DIMARIA, 1972). These findings support the notion that D-LSD might have a higher affinity to presynaptic than to postsynaptic 5-HT receptor sites.

In cats, reserpine-induced PGO-like activity could be reduced by injecting both 5-HT and D-LSD into the locus ceruleus, while methysergide increased the frequency of the PGO waves, indicating 5-HT blocking activity (KOSTOWSKI et al., 1975).

5-HT is supposed to act as inhibitory neurotransmitter of the raphe-hippocampal pathway. Stimulation of raphe nuclei as well as iontophoretically applied 5-HT generated a long-lasting inhibition of spontaneous discharges of the hippocampal pyramidal neurones. Responses to 5-HT could be antagonized by iontophoretically administered ergot alkaloids, such as D-LSD, BOL 148 and methysergide (SEGAL and BLOOM, 1974). While methysergide also antagonized responses to raphe stimulation, D-LSD failed to alter these effects (SEGAL, 1975).

Guinea-pig brain slices containing the superior colliculus and incoming optic tract maintained electrical activity and were used for recording of postsynaptic field potentials evoked by optic tract stimulation. In this preparation 5-HT (0.1–1 μM) suppressed the evoked potentials without changing spontaneous activity. Similarly, D-LSD, used at 1000 times lower concentrations, caused a decrease of the postsynaptic field potentials which, however, was less than that induced by 5-HT. When tested against 5-HT both D-LSD and lysergic acid ethylamide (LAE) enhanced the 5-HT-induced suppression at low concentrations (1–10 nM) but antagonized the 5-HT effects when used at higher concentrations. In contrast, BOL-148 and morphine were found to be devoid of antagonistic activity against 5-HT (KAWAI and YAMAMOTO, 1968, 1969).

c) Effects of Ergot Alkaloids on Areas With Neurones Which are Either Excited or Inhibited by 5-HT

Cells in areas which receive little or no 5-HT input, e.g., neurones in the cerebral cortex or reticular formation, may be either excited or inhibited by 5-HT. Microiontophoretical studies provided evidence that in cat cortical neurones two separate receptors for 5-HT might exist: One for excitation and one for depression, showing marked pharmacologic differences in their responses to 5-HT antagonists. While several 5-HT antagonists effectively inhibited 5-HT-induced excitation, the same 5-HT antagonists failed to block 5-HT-induced depression. In the cat's cerebral cortex various kinds of neuronal discharge, including spontaneous firing, responses evoked by afferent nervous stimulation and excitation produced by local application of glutamate, were depressed by 5-HT. A similar but much more prolonged depression could be obtained with ergot compounds, such as D-LSD, methysergide BOL-148, ergometrine or 12-hydroxy-ergometrine (KRNJEVIC and PHILLIS, 1963a, b; LEGGE et al., 1966; ROBERTS and STRAUGHAN, 1967), while methylergometrine had

a predominantly excitant activity (KRNJEVIC and PHILLIS, 1963a). D-LSD, methysergide, and BOL-148 failed to antagonize the depressant effect of 5-HT but selectively prevented 5-HT-induced excitation (BEVAN et al., 1974a, b; BRADSHAW et al., 1971; KRNJEVIC and PHILLIS, 1963a; LEGGE et al., 1966; ROBERTS and STRAUGHAN, 1967; SZABADI and BRADSHAW, 1974). Recently, potentiation of responses to 5-HT by low concentrations of methysergide has been reported, and it has been suggested that a selective blockade of masked inhibitory receptors may be the basis for this dose-dependent phenomenon (BEVAN et al., 1974a, b; SZABADI and BRADSHAW, 1974). Low concentrations of methysergide may block the more sensitive masked inhibitory receptors only, causing potentiation of the response, whereas higher concentrations of the same antagonist may block the less sensitive dominant receptors as well, causing antagonism of the observed response to 5-HT (SZABADI and BRADSHAW, 1974).

In rats, microiontophoretic application of 5-HT to cells of the reticular formation (BRIGGS, 1976; HAIGLER and AGHAJANIAN, 1974a) or to pontine raphe neurones originating in the nucleus paragigantocellularis lateralis (COUCH, 1974) induced both inhibition and excitation. D-LSD, methysergide and methergoline antagonized the 5-HT-induced excitation, leaving the inhibitory activity unaffected. Similar results have been obtained with postsynaptic neurones in the cat. In studies where microiontophoretic application of 5-HT to cells in the cat brainstem induced both inhibitory and excitatory responses, D-LSD had only inhibitory activity (BRADLEY and WOLSTENCROFT, 1964, 1965). When tested against 5-HT, D-LSD selectively antagonized the excitatory response to 5-HT but never the inhibitory effect. Methysergide was less potent than D-LSD, and BOL-148 only rarely antagonized responses to 5-HT (BOAKES et al., 1969, 1970a, b).

Stimulation of the reticular formation in the cat depressed some neurones and excited others within the thalamus. When 5-HT was administered microiontophoretically to single thalamic neurones, it depressed the majority of cells in the superficial group but excited a greater proportion of deeper cells. Both D-LSD and methysergide depressed most of the cells on which they were tested. These included neurones which were also depressed by 5-HT and some which were not affected by the latter (PHILLIS et al., 1967).

Serotoninergic neurones in the spinal cord originating in the raphe nuclei in the brainstem are supposed to influence motoneurone excitability by either facilitating or inhibiting transmission. In rabbits and rats, all the 5-HT in the spinal cord is associated with such descending fibers. In cats, high values of 5-HT in the areas of motor outflow to the limbs suggest the existence of additional segmental 5-HT-containing neurones (ANDERSON, 1972).

In the acutely spinalized rat elevation of endogenous 5-HT levels with nialamide plus 5-HTP causes athetoid movements and hyperextension in the hindlegs, tremor in the forelimbs and movements of the head. Similar symptoms could be provoked with D-LSD (ANDÉN, 1968; ANDÉN et al., 1968) and ergocornine (CORRODI et al., 1975) in a dose-dependent manner. D-LSD and ergocornine produced these changes even after depletion of 5-HT stores, suggesting that both ergot compounds directly stimulated 5-HT receptors of postsynaptic neurones.

PTR 17-402 also produced a dose-dependent increase in extensor reflex activity which, however, was abolished by combined reserpine-H 22/54 treatment and in-

creased by prior treatment with the MAO inhibitor nialamide, indicating that this ergolene derivative acted indirectly by releasing 5-HT (CORRODI et al., 1975). Methergoline blocked head twitches and facilitation of reflex activity induced by 5-HTP in both mice (FERRINI and GLASSER, 1965) and rats (CLINESCHMIDT and LOTTI, 1974). Moreover, it caused a dose-dependent reduction of D-LSD-induced increase in extensor reflex activity without having any intrinsic activity (FUXE et al., 1975a). The peptide alkaloid bromocriptine antagonized the enhancement of the extensor reflex by the 5-HT receptor stimulating drug 5-methoxydimethyltryptamine also without showing any intrinsic activity (CORRODI et al., 1975). Neither antagonism of the effects of 5-HTP or D-LSD nor any functional action could be found with BOL-148 and methysergide (ANDÉN et al., 1968).

In both spinal dogs (MARTIN and EADES, 1970) and cats (BELL and MARTIN, 1974) D-LSD, like tryptamine, facilitated the excitability of motoneurones. Both effects could be inhibited by cyproheptadine, indicating the involvement of serotoninergic mechanisms. While in the dog methysergide also induced facilitation of the flexor reflex which could be inhibited by cyproheptadine (MARTIN and EADES, 1970), it induced initial depression of C-fiber reflexes in the cat. Thereafter, methysergide also facilitated the C-fiber reflex in the cat, and this effect again could be inhibited by cyproheptadine (BELL and MARTIN, 1974). In the cat, methysergide also antagonized the effects of tryptamine on the flexor reflex, while phenoxybenzamine and cocaine failed to block these tryptamine effects (MARLEY and VANE, 1967).

These results suggest that ergot compounds, such as D-LSD, methysergide and ergocornine, might increase motoneurone activity by directly stimulating postsynaptic 5-HT receptors. On the other hand, the same ergot compounds, D-LSD and methysergide as well as BOL-148 developed antagonistic properties when the spinal neuronal activity was either increased or inhibited by elevating the endogenous 5-HT level. These latter effects might reflect stimulation of presynaptic 5-HT receptors by ergot compounds, thus leading to inhibition of 5-HT release.

Elevation of the spinal cord level of 5-HT by MAO inhibitors (ANDERSON et al., 1967) or by injection of the 5-HT precursor 5-HTP into a spinal cat produced a number of neuronal potentials and increased the monosynaptic spike amplitudes. The administration of methysergide, D-LSD, BOL-148 as well as of cyproheptadine during the height of action resulted in a reversal of all excitatory effects (ANDERSON et al., 1967; BANNA and ANDERSON, 1968; SHIBUYA and ANDERSON, 1968).

Intact guinea-pigs developed myoclonus within 1 hr after injection of the 5-HT precursor 5-HTP. At this time the whole brain 5-HT level was unchanged. The 5-HTP-induced myoclonus was acutely prevented by methysergide, while chronically pretreatment with methysergide intensified 5-HTP-induced myoclonus again without changing brain 5-HT levels. It was assumed that prolonged methysergide administration can result in pharmacologically induced denervation hypersensitivity of central 5-HT receptors (GOETZ and KLAWANS, 1974; KLAWANS et al., 1973, 1975).

Another function of the descending serotoninergic system—the inhibitory influence on motoneurone excitability, which could be induced by treatment of the acute spinal cat with 5-HTP or reserpine—was found to be antagonized by both methysergide and BOL-148, while phenoxybenzamine failed to reverse the

5-HTP-induced reflex depression (ENGBERG et al., 1966, 1968a, b; PROUDFIT and ANDERSON, 1973).

Activation of the bulbospinal system in the cat by stimulation of the caudal raphe nuclei via implanted electrodes either facilitated or inhibited segmentally monosynaptic reflexes, dependent on the interval between the conditioning brainstem volley and the test stimulus to the dorsal root. Methysergide shifted the brainstem conditioning curve in a facilitatory direction with no change in the shape of the curve (PROUDFIT and ANDERSON, 1972, 1973). An increased facilitation of raphe-evoked monosynaptic reflexes might have been the reason for the previously stated reduction of inhibition of spinal reflexes in response to methysergide, D-LSD and BOL-148 in the same experimental model (CLINESCHMIDT and ANDERSON, 1969, 1970). In rats, electrical stimulation of the nucleus raphe medianus increased the lumbosacral motoneurone excitability. This effect was potentiated by the administration of l-tryptophan, indicating the involvement of serotoninergic neurones. Intravenous injection of both D-LSD (5–15 μg/kg) and methysergide (0.75–1 mg/kg) reduced the effectiveness of nucleus raphe stimulation. Raphe stimulation as well as microiontophoretical application of 5-HT to cells from which potentials were recorded increased the amplitude of extracellular field potential responses. Both effects could be antagonized by microiontophoretically applied methysergide as well as by cinanserine.

The similarity of the responses of lumbar motoneurones to applied 5-HT and the activity within the raphe-spinal pathway suggested that lumbar motoneurone excitability in the rat could be increased by raphe-spinal pathway via release of 5-HT in the ventral horn of the spinal cord, and that both effects could be antagonized by ergot compounds, such as D-LSD and methysergide (BARASI and ROBERTS, 1973, 1974). Further evidence for this was provided by the finding that symptoms such as abduction of the hindpaws and muscular rigidity following the injection of 5-HTP into the lateral ventricle could be prevented by BOL-148 (2 mg/kg), methysergide and D-LSD (1 mg/kg) given i.p. immediately before the 5-HTP administration (REICHENBERG et al., 1975).

In the rabbit olfactory bulb, both D-LSD and BOL-148 appeared to interact with 5-HT as well as with α-adrenergic receptor sites. Electrophoretic administration of both 5-HT and noradrenaline always resulted in slowing of the spontaneous discharge of olfactory neurones. D-LSD and BOL-148 occasionally also slowed the spontaneous rate of discharge by themselves and blocked responses to both 5-HT and noradrenaline being rather more effective against noradrenaline than against 5-HT. On the other hand, phentolamine and dibenamine selectively antagonized responses to noradrenaline without changing those to 5-HT (BLOOM et al., 1964; SALMOIRAGHI et al., 1964).

d) Effects of Ergot Alkaloids on 5-HT Receptors Which Modify Ganglionic Transmission

Studies on the ganglionic transmission in the isolated cat superior cervical ganglion demonstrated that there exist at least two independent receptors for 5-HT mediating opposite physiological effects. In a medium and high dose range (threshold dose

3–10 nmol 5-HT), a short-lasting stimulation and depolarization with facilitation of ganglionic transmission occurred, which was unchanged by low doses of ergot compounds, such as D-LSD or methysergide. Only when doses of 100 nmol and more were used did D-LSD depress the stimulant action of 5-HT.

With extremely low doses (threshold dose approximately 30–100 picomol 5-HT) up to the highest ones there occurred a long-lasting inhibition of ganglionic transmission which seemed to involve both pre- and postsynaptic sites of action. D-LSD and methysergide again showed no blocking activity against 5-HT effects, but both ergot compounds inhibited ganglionic transmission, as did 5-HT. Inhibition of ganglionic transmission with D-LSD occurred at doses of 0.3–1 nmol while 1 μmol induced complete blockade of the ganglionic transmission. A characteristic property of 5-HT, which has been already described for smooth muscle stimulation, was a very marked desensitization of the excitatory but not of the inhibitory 5-HT receptors (HAEFELY, 1971, 1974).

In addition, enhancement of the postsynaptic nerve activity by stimulant doses of 5-HT has been observed in the cat inferior mesenteric ganglion. In this preparation the 5-HT effect again could be prevented only by high doses of ergot compounds, such as BOL-148 (40–200 μg) and D-LSD (200–400 μg), but also by similar high doses of cocaine, atropine or morphine (BINDLER and GYERMEK, 1961; GYERMEK and BINDLER, 1962), indicating the involvement of some indirect actions.

In vitro investigations on the isolated rat superior cervical ganglion demonstrated inhibition of ganglionic transmission by methysergide (5–10 μg/ml) (KALBERMATTEN, 1962) but no antagonism of the stimulant activity of 5-HT by methysergide (WATSON, 1970).

Responses to submaximal preganglionic stimulation in the isolated rat stellate ganglion were increased by 5-HT and BOL-148 as well as by methysergide when used at μg/ml concentrations (HERTZLER, 1961).

To summarize: The effects of ergot compounds, such as D-LSD, methysergide and BOL-148, on 5-HT receptors modifying ganglionic transmission generally resemble those induced by 5-HT. Depending on the concentrations used, both inhibitory and stimulatory effects may be observed, suggesting the involvement of two types of 5-HT receptors. Antagonism of 5-HT effects by ergot alkaloids occurred only when they were used at extremely high concentrations.

The chemoreceptor discharges in the cat carotid body increased in response to both 5-HT (5 μg i.a.) and D-LSD (10 μg i.a.) but were unchanged after methysergide. Moreover, methysergide and D-LSD up to 100 μg/kg failed to change the chemoreceptor stimulant action of 5-HT in cats (NISHI, 1975), as BOL-148 and ergotamine did not prevent the chemoreceptor stimulant action of 5-HT in dogs (SALMOIRAGHI et al., 1957). These observations support the notion that cat's coronary chemoreflex in response to 5-HT was not antagonized but rather increased by D-LSD (ZAKUSOV, 1962). They are further in line with the finding that 5-HT-induced spikes in some afferent fibers of the cat vagus nerve were enhanced by D-LSD (100 μg/kg) (GYERMEK and SUMI, 1963).

In vitro D-LSD, like 5-HT, enhanced spontaneous and light-evoked activity of ganglion cells of the rabbit retina while methysergide caused depression of the activity (AMES and POLLEN, 1969).

e) Effects of Ergot Alkaloids on 5-HT Receptors Which Modify Release of Acetylcholine

The first pharmacologic data on nervous 5-HT receptors distinguishable from those obtained on smooth muscle came from studies of ROCHA E SILVA et al. (1953) and GADDUM and PICARELLI (1957) on the isolated guinea-pig ileum. These authors described nervous receptors in the guinea-pig ileum which could be activated by 5-HT and were markedly influenced by drugs, such as cocaine, atropine and morphine but not by ergot alkaloids.

The classical "M-receptors," described by GADDUM and PICARELLI (1957), are supposed to be localized at the varicose cell processes from which acetylcholine is released towards the muscle. Spike activity in such processes, which can be recorded by extracellular techniques, is increased by 5-HT, and this effect is prevented by morphine (DINGLEDINE et al., 1974).

In contrast, intracellular recordings from single myenteric plexus neurones demonstrated that 5-HT at concentrations of 25 nM to 1 μM reversibly depressed EPSP (excitatory postsynaptic potentials) evoked by single focal stimulation but failed to change responses to acetylcholine. This action of 5-HT could be antagonized by methysergide, D-LSD, and cyproheptadine but was unaffected by morphine. Besides preventing the action of 5-HT, methysergide (1.7 μM) also slightly depressed the EPSP amplitude, indicating some 5-HT-like activity. These findings suggested that 5-HT reduces EPSP in guinea-pig ileum by inhibiting the release of acetylcholine from presynaptic nerve terminals within the myenteric plexus (HENDERSON and NORTH, 1975; NORTH and HENDERSON, 1975).

Using muscle twitch reflexes and intravenous 5-HT, facilitation of flexor reflexes and inhibition of extensor reflexes in the spinal cat have been observed. D-LSD usually augmented the stimulatory effect of 5-HT and prevented the depressor effect of 5-HT (LITTLE et al., 1957; SLATER et al., 1955; WEIDMANN, 1957; WEIDMANN and CERLETTI, 1957).

Since 5-HT is not supposed to cross the blood-brain barrier, the effects probably resulted from an action of 5-HT on peripheral receptors or sensory nerve endings as has been suggested by DEFFENU and MANTEGAZZINI (1966). These authors found that 5-HT was about 10 times more potent when injected intra arterially as compared to intra venous administration. Methysergide and also dibenamine and chlorpromazine prevented the inhibitory effect of 5-HT. These findings were supported by the finding that in the rat nerve-muscle preparation methysergide, like cyproheptadine and chlorpromazine, prevented 5-HT-induced muscle weakness (PATTEN et al., 1974).

DRETCHEN et al. (1972) showed that 5-HT reversed the effects of neuromuscular blocking agents, and that this 5-HT effect could be reduced by methysergide, whereas α-adrenergic blocking agents or M-receptor blockers did not affect the anticurare action of 5-HT. It was suggested that 5-HT acts presynaptically at the neuromuscular junction by increasing the amount of acetylcholine liberated on nerve stimulation.

Bilateral microinjections of 5-HT into the rabbit nucleus amygdalae caused an increase of motor activity as well as arousal of the electroencephalographic

activity in the cortex, while i.p. administration of methysergide (5 mg/kg) induced a slight reduction of the electrogenesis. While atropine effectively prevented the changes of electrogenesis evoked by 5-HT, both methysergide and cyproheptadine only slightly reduced the responses to 5-HT which was administered 60 min later. These results suggested that the stimulation induced by injecting 5-HT into the rabbit nucleus amygdalae was mediated mainly through the release of acetylcholine (PRZEWLOCKI, 1975).

To conclude, both facilitation and inhibition of acetylcholine release may be induced by 5-HT. Ergot compounds such as D-LSD and methysergide usually antagonized the effects in response to decreased acetylcholine release. Both ergot alkaloids, however, failed to inhibit 5-HT effects induced by enhanced acetylcholine release, which could be blocked by drugs, such as cocaine, atropine and morphine.

f) Effects of Ergot Alkaloids on Neuronal 5-HT Receptors in Invertebrates

Many neurones of molluscs are accessible, large, well identifiable and highly sensitive to 5-HT, thus being more suitable to study the interaction of drugs with neuronal receptor sites than are neurones of vertebrate species. Moreover, there seem to exist many common properties between the 5-HT receptors of molluscan neurones and those in vertebrates. Both are easily desensitized by high 5-HT concentrations and both may mediate physiologically opposite effects in response to 5-HT, e.g., excitation and inhibition or facilitation and depression of responses to other stimuli. The effects of ergot alkaloids are often mixed agonistic-antagonistic, depending on the concentrations employed. In some molluscs, e.g., *Helix aspersa* and *Aplysia californica,* at least six different types of neuronal responses to 5-HT in terms of their pharmacologic and physiologic properties have been distinguished. Some of these responses to 5-HT were found to be blocked by high concentrations (10 μM) of D-LSD (GERSCHENFELD, 1971; GERSCHENFELD and PAUPARDIN, 1972; GERSCHENFELD and PAUPARDIN-TRITSCH, 1974a, b, c). Cells with inhibition of long duration, the so-called CILDA neurones (GERSCHENFELD and TAUC, 1964), are highly sensitive to both acetylcholine and 5-HT. Depolarization of 2–4 mV could be obtained with 1 nM 5-HT at the receptor level. These 5-HT receptors are blocked by BOL-148 in a selective and competitive way ($pA_2 = 8.0$) (GERSCHENFELD and STEFANI, 1965), whereas for antagonism of 5-HT by D-LSD much higher concentrations (100 μg/ml) were necessary (GERSCHENFELD and STEFANI, 1965, 1966, 1967, 1968; GERSCHENFELD and TAUC, 1964; SHIMAHARA and TAUC, 1975).

The ciliary activity of an isolated gill-nerve-ganglion preparation from the mussel *Mytilus edulis* is activated by 2–10 Hz electro stimulation of the brachial nerve. This effect was suggested to be mediated by the release of 5-HT. Evidence for this was provided by the observation that reserpine treatment of the mussel significantly diminished the 5-HT content in the gill and also reduced the response to electrical stimulation (AIELLO and GUIDERI, 1966). Responses to electrical stimulation, but not those to exogenous 5-HT, were also significantly decreased by cocaine (AIELLO and GUIDERI, 1964). Moreover, BOL-148 reversibly diminished the effects of both nerve stimulation and exogenous 5-HT. In this preparation BOL-148 itself caused slight stimulation at concentrations about 10 times lower

than those required for 5-HT antagonism (AIELLO and GUIDERI, 1966; AIELLO and PAPARO, 1974).

5-HT is also suggested to function as neurotransmitter of the relaxing nerve fibers supplying the anterior byssus retractor muscle of *M. edulis* (WELSH, 1954a; TWAROG, 1954). When contraction of the anterior byssus retractor muscle was induced by nerve stimulation, the following relaxation was much slower in the presence of BOL-148 (10 μg/ml). This action of BOL-148 on tension delay could be partly reversed by 5-HT (BULLARD, 1967).

Antagonism by methysergide of 5-HT-induced increase in spontaneous activity in giant neurones has been found in the subesophageal ganglion of the snail *Achatina fulica* (TAKEUCHI et al., 1974). Responses of the heart of the snail *Helix pomatia* to stimulation of the intestinal nerve were also antagonized by BOL-148 (0.1 μg/ml), while D-LSD at the same concentration enhanced the effects (RÓZSA and GRAUL, 1964).

In *Helix pomatia* 5-HT is suggested to be the transmitter in synaptic connections between giant 5-HT-containing cells and non-amine-containing neurones. Iontophoretic application of 5-HT to the non-amine-containing cells produced a depolarizing potential change. D-LSD (30–300 μM) also elicited depolarization and reduced the responsiveness to 5-HT of these neurones. Methysergide and BOL-148 used at the same concentration ranges evoked less depolarization but similar antagonism of 5-HT effects. Lower concentrations of these ergot alkaloids failed to antagonize responses to 5-HT. Neither D-LSD nor methysergide produced reduction of EPSP resulting from giant 5-HT cell stimulation when used at 1–30 μM. On the contrary, 1 μM D-LSD was found to enhance the EPSP effects, suggesting the involvement of a presynaptic action of D-LSD (COTTRELL, 1970b). Concentrations of D-LSD required to abolish EPSP elicited by giant 5-HT cells resulted in a considerable depolarization and activation of the non-amine-containing cells (COTTRELL, 1970a, b; COTTRELL and MACON, 1974; COTTRELL et al., 1974).

4. Effects of Ergot Alkaloids on 5-HT-Sensitive Enzyme Systems

Various invertebrate systems have proved of value in studying the interaction of drugs with 5-HT receptor sites as well as the intermediate steps following activation of the 5-HT receptor. Some effects in response to stimulation of 5-HT receptor sites are mediated by an increase in the formation of cyclic AMP (3′,5′-adenosine monophosphate).

In salivary glands from the blow-fly *Calliphora erythrocephala,* besides inducing fluid secretion, 5-HT has been shown to cause 2–4 fold increase in cyclic AMP concentrations (PRINCE et al., 1972). A similar stimulation of both fluid secretion and cyclic AMP formation was produced with D-LSD. After 10 min incubation of salivary glands with either 10 nM 5-HT or 10 nM D-LSD, the level of cyclic AMP was increased by about 30% (BERRIDGE and PRINCE, 1974).

The liver fluke *Fasciola hepatica* responds to 5-HT with increased rhythmical movements paralleled with striking increase in the formation of cyclic AMP mainly in the oral end of the fluke. D-LSD at 1 nM, although enhancing the motility, failed to increase the cyclic AMP formation. On the contrary, with 5 nM D-LSD

a 50% inhibition of the 5-HT effect on adenylate cyclase was obtained. Only when used at 10 μM did D-LSD slightly increase the formation of cyclic AMP. Based upon the observation that it took about four times more to reverse the D-LSD effect by washout as compared to the 5-HT effect, it was assumed that for activation of the adenylate cyclase system in the liver fluke a certain degree of reversibility of the effector-receptor complex may be required (ABRAHAMS, 1974; ABRAHAMS et al., 1976; MANSOUR et al., 1960).

In the mollusc *Macrocallista nimbosa* the 5-HT-induced increase in myocardial cyclic AMP could be blocked by 1 μM methysergide (HIGGINS, 1974).

Adenylate cyclase sensitive to 5-HT has also been found on homogenates from cockroach thoracic ganglia. In this preparation a selective inhibition of 50% of the 5-HT-induced activation of adenylate cyclase could be obtained with BOL-148 and D-LSD at concentrations of 10 and 20 nM, respectively, while for a 50% inhibition by cyproheptadine 200 nM were required. Both D-LSD and BOL-148 stimulated the adenylate cyclase when used at concentrations of 1 μM and higher (NATHANSON and GREENGARD, 1974).

As far as known a 5-HT sensitive adenylate cyclase system in nervous tissues from vertebrates has been found only in brains from young rats. In cell-free preparations from superior and inferior colliculi of 1 to 3 days old rats half maximal stimulation of the adenylate cyclase was produced with 1 μM 5-HT. D-LSD inhibited more than 50% of the 5-HT effect when used at the relatively high concentration of 10 μM, and the 5-HT antagonism induced by BOL-148, methysergide and MCE (1-methyl-8β-carbobenzyloxy-aminomethyl-10 α-ergoline) was still weaker than that caused by D-LSD (VON HUNGEN et al., 1974a, 1975). In this preparation, 10–100 μM D-LSD were necessary to produce a slight stimulation of adenylate cyclase activity, and BOL-148, methysergide or MCE were devoid of any stimulating activity (HAMON et al., 1976a; VON HUNGEN et al., 1975).

These findings were supported by experiments on rat brain stem slices where D-LSD at 100 μM raised the concentration of cyclic AMP, but 5-HT failed to change the level of cyclic AMP (UZUNOV and WEISS, 1972).

In rat heart slices 5-HT was found to increase cyclic AMP accumulation indirectly by releasing endogenous catecholamines. This effect could be inhibited by high (15 μM) concentrations of dihydroergotamine but not by phenoxybenzamine (BENFEY et al., 1974).

Studies on the effects of receptor stimulation on the lipid metabolism have shown that in the isolated guinea-pig ileum stimulation of D-receptors by 5-HT (125 μM) elicited an increase in phosphatidylinositol turnover. This effect could be abolished by 10 μg/ml methysergide (JAFFERJI and MICHELL, 1976).

A stereospecific inhibition of an enzymatic activity by ergot compounds in vitro has been demonstrated using a de-acetylase (aryl acylamidase) isolated from rat brains. This enzymatic activity could be inhibited in vitro by 5-HT as well as by pharmacologically active ergot compounds, such as D-LSD, BOL-148 and methysergide at concentrations of 10–100 μM, while L-LSD was inactive as inhibitor of the enzymatic activity (PAUL and HALARIS, 1976; PAUL et al., 1976).

C. Actions of Ergot Alkaloids at Dopamine Receptors

1. Actions of Ergot Alkaloids at Extraneuronal Dopamine Receptors

a) General Description of "Specific Dopamine Receptors"

Until a few years ago, dopamine was known only as the precursor of noradrenaline. However, its unusual distribution as well as the discovery of specific dopaminergic pathways suggested that this amine had also physiological roles. The structure of dopamine is consistent with a multireceptor potential and fits in adrenergic as well as in serotoninergic receptors, both of which also represent binding sites for ergot compounds (Fig. 15). It follows from this that antagonists, especially those containing the ergoline moiety, will often have a narrow range of selectivity.

In vascular smooth muscles both contraction and relaxation in response to dopamine has been demonstrated in arteries and veins. In canine renal arteries (KELLY, 1972; STRANDHOY et al., 1972; ZAROLINSKI and BROWNE, 1971) and in aortic strips from rats (COHEN and BERKOWITZ, 1975) and rabbits (KOHLI, 1969) the dopamine-induced contractions appear to be due, at least in part, to stimulation of α-adrenoceptors. Alpha-adrenergic blocking agents, such as phentolamine and phenoxybenzamine, antagonized responses to both dopamine and noradrenaline in similar concentrations. In canine femoral and carotid arteries, however, the dopamine receptor appears to be related to 5-HT- or tryptamine receptors but not to α-adrenoceptors. In canine femoral and carotid arterial strips the 5-HT receptor blocking agent cyproheptadine produced nearly identical pA_2 values (7.5, 7.6 and 7.4) when tested against dopamine, 5-HT and tryptamine. Moreover, dopamine and 5-HT exerted cross protection on dopamine, 5-HT and tryptamine receptors against blockade by both cyproheptadine as well as by phenoxybenzamine, while noradrenaline failed to protect any of these receptors in canine arteries (GILBERT and GOLDBERG, 1975). When isolated canine renal, mesenteric, coronary, intracerebral or small (< 1 mm, outside diameter) femoral arteries were exposed to phenoxybenzamine and contracted with potassium or prostaglandin $F_{2\alpha}$, dopamine caused dose-dependent relaxation (GOLDBERG, 1975; GOLDBERG and TODA,

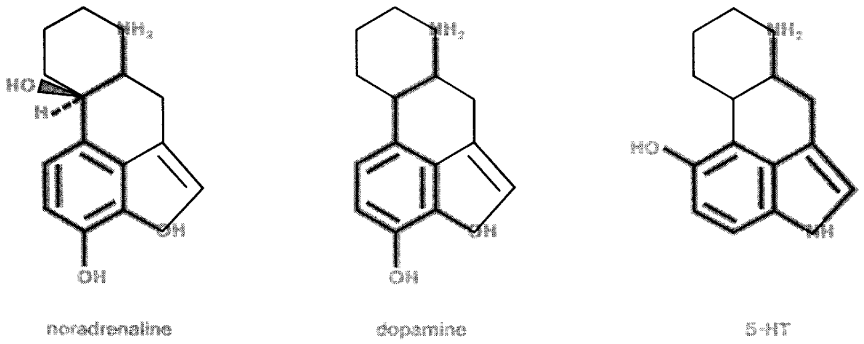


Fig. 15. Common structural conformations of noradrenaline, dopamine and 5-HT with the ergoline moiety

1975; GOLDBERG et al., 1973; TODA and GOLDBERG, 1973, 1975; TODA et al., 1973). Studies of potential dopamine antagonists have demonstrated only partial antagonism of dopamine-induced relaxation, since all the selective dopamine antagonists active in vivo, e.g., haloperidol, chlorpromazine, apomorphine and bulbocapnine, in estimated effective concentrations caused marked relaxation of the isolated canine arteries (GOLDBERG et al., 1973). Attempts to antagonize dopamine-induced relaxation in canine renal and mesenteric arteries with ergometrine have been without success (MÜLLER-SCHWEINITZER, 1975b). Thus, the definite characterization of a peripheral dopamine receptor has not yet been accomplished.

b) Effects of Ergot Alkaloids on Peripheral Dopamine Receptors

Dopamine receptors in the longitudinal musculature of the worm *Schistosoma mansoni* mediate lengthening of the worms in response to dopamine, noradrenaline, adrenaline and apomorphine. The relaxation of the longitudinal musculature induced by these agonists could be antagonized more effectively by dopamine blockers, such as haloperidol, spiroperidol and pimozide, than by α- or β-adrenergic blocking agents, indicating that the lengthening of the worms was mediated by stimulation of dopamine receptors. Responses to the three agonists could also be antagonized by ergot alkaloids, such as ergometrine, dihydroergocristine and dihydroergotamine, suggesting that these ergot compounds combined with the dopamine receptor (TOMOSKY et al., 1974).

2. Interaction of Ergot Alkaloids With Indirect Dopamine Effects

Dopamine in a concentration of 0.1 μM produced contraction of the rat stomach fundus preparation. Repeated exposure to dopamine resulted in tachyphylaxis, but the sensitivity to dopamine could be restored by incubating the tissue with 5-HT. This action of dopamine, which thus might be caused indirectly by release of 5-HT, could be blocked by methysergide (0.1 μM). It remains to be demonstrated, however, whether methysergide antagonized the 5-HT-releasing activity of dopamine or whether it competed with the released amine at the 5-HT receptor site (SONNEVILLE, 1968).

3. Actions of Ergot Alkaloids at Neuronal Dopamine Receptors

a) Effects of Ergot Alkaloids on Neuronal Dopamine Receptors in Invertebrates

Interaction of ergot alkaloids with neuronal dopamine receptors was first investigated on neurones of invertebrates. Although there may be similarities between the dopamine receptors and the 5-HT receptors—which are also binding sites for most ergot compounds—evidence for the existence of separate receptors for dopamine on the one hand and for 5-HT on the other has been provided. WOODRUFF et al. (1971) found that the snail neurones used in their study were all hyperpolarized

by dopamine but depolarized by 5-HT. The effects of both agonists could be blocked by ergot compounds, such as D-LSD and methysergide.

It can be further assumed that distinct dopamine receptors and adrenoceptors exist. Structure activity studies suggested that the structural requirements for dopamine-like activity are more specific than those for activity on adrenergic receptors (WOODRUFF and WALKER, 1969).

More detailed studies showed the existence of two types of dopamine receptors mediating physiologically opposite effects in the brain of *Helix aspersa* (STRUYKER BOUDIER and VAN ROSSUM, 1974). Dopamine receptors mediating neuronal excitation (DA_e receptors) are selectively activated by apomorphine and selectively inhibited by neuroleptics, such as haloperidol (STRUYKER BOUDIER et al., 1974), whereas the dopamine receptors mediating neuronal inhibition (DA_i receptors) are selectively activated by (3,4-dihydroxy-phenylamino)-2-imidazoline (DPI) and selectively inhibited by ergot compounds, such as ergometrine (STRUYKER BOUDIER et al., 1975; COOLS and VAN ROSSUM, 1976).

Ergometrine, which has little or no α-adrenergic blocking activity, was the first ergot compound to be described as a potent antagonist of the inhibitory action of dopamine on neurones of the snail *H. aspersa* (WALKER et al., 1968; WOODRUFF et al., 1970). In addition to these findings, long-lasting antagonism of the inhibitory action of dopamine on *Helix* neurones has been found with D-LSD, methysergide (WOODRUFF et al., 1971), and also with the peptide alkaloids ergotoxine, ergotamine and their dihydrogenated derivatives dihydroergotoxine mesylate and dihydroergotamine. As compared to the dopamine blocking activity of ergometrine, the natural ergopeptins were found to be about 10 times less potent, and their dihydrogenated derivatives were at least 100 times less potent in antagonizing the dopamine-induced inhibition of *Helix* neurones (WALKER et al., 1968; STRUYKER BOUDIER et al., 1974).

As observed with *H. aspersa* neurones, the addition of dopamine to identified neurones in ganglia of *Aplysia californica* induced both excitatory and inhibitory postsynaptic responses, but only the latter effect could be antagonized with D-LSD (SATO and SAWADA, 1975), ergometrine, methylergometrine or ergotamine (ASCHER, 1972). The blocking action of both ergometrine and methylergometrine was preceded by a small hyperpolarization, indicating some agonistic activity.

BERRY and COTTRELL (1975), studying the effects of iontophoretically applied dopamine on central neurones of the water snail *Planorbis corneus*, also observed excitatory and inhibitory responses. In this preparation ergometrine again specifically antagonized the inhibitory postsynaptic potentials in response to stimulation of dopamine-containing neurones as well as the inhibitory response to applied dopamine. As observed with *Aplysia* neurones, ergometrine developed some agonistic activity. The addition of ergometrine resulted in a hyperpolarization and reduction or abolition of spontaneous firing in the follower cells (BERRY and COTTRELL, 1975; COTTRELL et al., 1974).

Dopamine receptors sensitive to ergot compounds have been found to mediate inhibition of lateral ciliary activity in the bivalve mollusc *Modiolus demissus*. This effect was antagonized by ergometrine, methysergide and BOL-148 (MALANGA, 1973). A further type of dopamine receptor seems to mediate stimulation of the

frontal ciliary activity in bivalve molluscs. This effect was antagonized by ergometrine and BOL-148 but unchanged by methysergide (MALANGA, 1973, 1974).

In addition, ergometrine was found to antagonize the inhibitory action of dopamine in the intestine of the mollusc *Tapes watlingi* (DOUGAN and MCLEAN, 1970).

There was no change of the dopamine uptake into subesophageal ganglia of the snail *Helix pomatia* by D-LSD up to 10–200 μM (OSBORNE et al., 1975).

b) Effects of Ergot Alkaloids on Neuronal Dopamine Receptors in Vertebrates

Investigations on the electrical properties and responses to transmural stimulation in neurones of the submucous plexus of the guinea-pig ileum showed that most neurones received excitatory synaptic input, but an appreciable proportion of neurones also received a single inhibitory input – both being activated by transmural stimulation. BOL-148 (0.1–1 μg/ml) was found to antagonize the inhibitory synaptic potentials in a selective and reversible way (HIRST and MCKIRDY, 1975). Using the technique of iontophoretic application of drugs to neurones of the submucous plexus of guinea-pig small intestine, it could be demonstrated that both dopamine and noradrenaline caused responses which closely resembled those inhibitory synaptic potentials evoked by transmural stimulation, while 5-HT caused excitation of the neurones. Moreover, it was found that methysergide, like BOL-148, antagonized both the inhibitory synaptic potentials and the inhibitory effects of dopamine and noradrenaline but had only little activity when tested against 5-HT potentials (HIRST and SILINSKY, 1975). These findings support the notion that ergometrine at concentrations of 0.03–1 μM reversed the inhibitory action of low concentrations of both dopamine and noradrenaline in the isolated rabbit jejunum (WOODRUFF et al., 1969).

Studies on the canine cardiac sympathetic ganglion demonstrated inhibition of the ganglionic transmission by catecholamines, such as noradrenaline, adrenaline and dopamine, injected into the right subclavian artery during preganglionic nerve stimulation. Dihydroergotamine antagonized responses to both adrenaline and dopamine. Apomorphine and haloperidol selectively antagonized the effects of dopamine, while phentolamine did not significantly affect responses to dopamine. These results suggest that the receptors for dopamine may differ from those for noradrenaline and adrenaline (ICHIMASA et al., 1975).

It has been proposed to use *Helix aspersa* dopamine-sensitive neurones as model for the design of drugs selectively interfering with dopamine-sensitive structures in mammalian brains. Two distinct types of dopamine receptors having electrophysiologic and pharmacologic properties comparable to those of DA_e and DA_i receptors within the snail have been found within the feline caudate nucleus. As observed with *Helix* neurones, evidence has been provided that only DA_i receptors are selectively antagonized by ergot compounds, such as ergometrine, while DA_e receptors can be blocked by neuroleptics, such as haloperidol (COOLS, 1975; COOLS and VAN ROSSUM, 1976; COOLS et al., 1976; VAN ROSSUM et al., 1975). Microiontophoretic studies on the effectiveness of these antagonists within the caudate nucleus of cats are, however, required to prove this hypothesis.

In rats, apparently the dopamine-loaded structures within the brain contain two anatomically-histochemically distinct areas, which are each characterized by their own pharmacologic features: The neostriatum, which is more sensitive to apomorphine than to ergometrine, and the nucleus accumbens, which is more sensitive to ergot alkaloids such as ergometrine than to apomorphine. Administration of ergometrine directly into the nucleus accumbens of rats produced a pattern of enhanced locomotor activity similar to that seen after dopamine injection (PIJNENBURG and VAN ROSSUM, 1973; PIJNENBURG et al., 1973). The locomotor stimulation after ergometrine was blocked by low doses of haloperidol and pimozide, suggesting that dopamine receptors are involved in the action of ergometrine. Depletion of dopamine and noradrenaline in the brain by pretreatment of the rats with α-methyl-p-tyrosine had no influence on the activity of ergometrine, indicating that a presynaptic action is unlikely. Methysergide was ineffective in producing locomotor stimulation (PIJNENBURG et al., 1973). Bromocriptine (2-bromo-α-ergokryptine, CB 154, Parlodel) antagonized the dopamine-induced hyperactivity only at doses considered very large in behavioural terms (COSTALL and NAYLOR, 1976). Moreover, in contrast to that observed with ergometrine, bromocriptine appeared to have affinity to presynaptic dopamine receptors as well. The stimulation-induced release of [^{3}H]dopamine from superfused striatal synaptosomes was significantly inhibited by 0.1 μM bromocriptine (MULDER et al., 1975).

Biochemical studies provided first evidence for the possible existence of dopaminergic neurones in the rat cortex (THIERRY et al., 1973a, b). Using the technique of microiontophoresis on cortical neurones from rats, it was found that the majority of cells tested responded in the same manner to dopamine and ergometrine (CROSSMAN et al., 1973) as well as to agroclavine (STONE, 1974). Moreover, chlorpromazine, an antagonist at central dopamine receptors (YORK, 1972), selectively antagonized responses to both dopamine and agroclavine, leaving those to noradrenaline and 5-HT unchanged. From these results it was suggested that agroclavine and possibly other ergot alkaloids may have an agonistic action at central dopamine receptors (STONE, 1974).

c) Effects of Ergot Alkaloids on Neuronal Dopamine Turnover

Although the levels of dopamine in rat brain were not affected by ergot alkaloids, such as D-LSD (DA PRADA et al., 1975b), methergoline (FUXE et al., 1975a), ergocornine and bromocriptine (CORRODI et al., 1973), these ergot alkaloids caused a clearcut decrease in dopamine turnover as indicated by the retardation of the disappearance of dopamine in the brain following the administration of α-methyl-p-tyrosine (CORRODI et al., 1973; FUXE et al., 1974; HÖKFELT and FUXE, 1972; DA PRADA et al., 1975a, b; SNIDER et al., 1976). Further experiments demonstrated that ergot alkaloids, such as ergocornine, bromocriptine (CORRODI et al., 1973; HÖKFELT and FUXE, 1972) and PTR 17-402 (6-methyl-8β-[4-(p-methoxyphenyl)-1-piperazinyl]methyl-9-ergolene) (FUXE et al., 1975b) mainly reduced dopamine turnover in the subcortical limbic areas and in the neostriatum. The action on dopamine metabolism by these ergot compounds might probably be due to dopamine receptor stimulating activity of these agents. It has been shown that γ-hydroxybutyric acid inhibits neuronal firing in dopaminergic neurones, thus causing several alterations

in dopamine metabolism, e.g., increase in dopamine concentration (WALTERS et al., 1973). As observed with various dopamine agonists, both ergocornine and bromocriptine inhibited the rise in dopamine after γ-hydroxybutyric acid, thus providing evidence for the concept of local receptor feedback on dopamine synthesis. Haloperidol, which effectively antagonized the inhibition by apomorphine, failed to block that induced by ergocornine or bromocriptine. These results support the notion that there are at least two types of dopamine receptors (HANDFORTH and SOURKES, 1975).

4. Effects of Ergot Alkaloids on Dopamine-Sensitive Enzyme Systems

Recent evidence has been accumulating which suggests that specific dopamine receptors are involved in the elevation of cyclic AMP (3′,5′-adenosine monophosphate) occurring after addition of dopamine to mammalian brain and retina in vitro. Reports indicating that a number of ergot derivatives exert dopamine-like actions on central neurones in the rat gave rise to investigations of the interaction of ergot alkaloids with dopamine-sensitive adenylate cyclase systems in the rat brain. UZUNOV and WEISS (1972) found that incubation of rat brain stem slices with D-LSD increased the concentration of cyclic AMP, and that this activity of D-LSD was not shared by BOL-148. The inhibition of the D-LSD-induced accumulation of cyclic AMP by the neuroleptic trifluoperazine suggested the involvement of dopamine receptors. Further studies demonstrated that D-LSD may act both as agonist and as antagonist on the dopamine-sensitive adenylate cyclase systems within the rat brain. A significant stimulation of the adenylate cyclase in rat striatal tissue could be obtained with concentrations of D-LSD as low as 0.1 μM and was increased about 30% by 10–20 μM D-LSD (DA PRADA et al., 1975a, b; SPANO et al., 1975a, b; VON HUNGEN et al., 1974b). This was about one-half the activation produced by an equimolar concentration of dopamine. Responses to both dopamine and D-LSD could be abolished by equimolar concentrations of haloperidol, chlorpromazine, BOL-148 and MLD (1-methyl-d-lysergic acid diethylamide), while propranolol failed to antagonize the stimulation of striatal adenylate cyclase by either dopamine or D-LSD. On the other hand, 1 μM D-LSD antagonized the stimulation of cerebral adenylate cyclase activity by dopamine (Fig. 16) (DA PRADA et al., 1975a, b; VON HUNGEN et al., 1974a, b).

Stimulation of striatal adenylate cyclase could also be elicited with ergometrine (ELKHAWAD and WOODRUFF, 1975; ELKHAWAD et al., 1975; MUNDAY et al., 1976), while both MLD (1-methyl-d-lysergic acid diethylamide) and BOL-148 (SPANO et al., 1975a, b; VON HUNGEN et al., 1974a) were devoid of any intrinsic activity. The injection of bromocriptine (0.5–2 mg/kg i.p.) into rats produced a dose-dependent increase of striatal cyclic AMP concentration. In vitro, however, bromocriptine up to 100 μM was inactive in stimulating dopamine sensitive adenylate cyclase in rat striatal homogenates, though it inhibited the dopamine-induced stimulation of the enzyme activity even at concentrations as low as 1 μM (TRABUCCHI et al., 1976). This dopamine antagonism by bromocriptine, however, appears not to be selective. It has been found that bromocriptine is less potent in antagoniz-

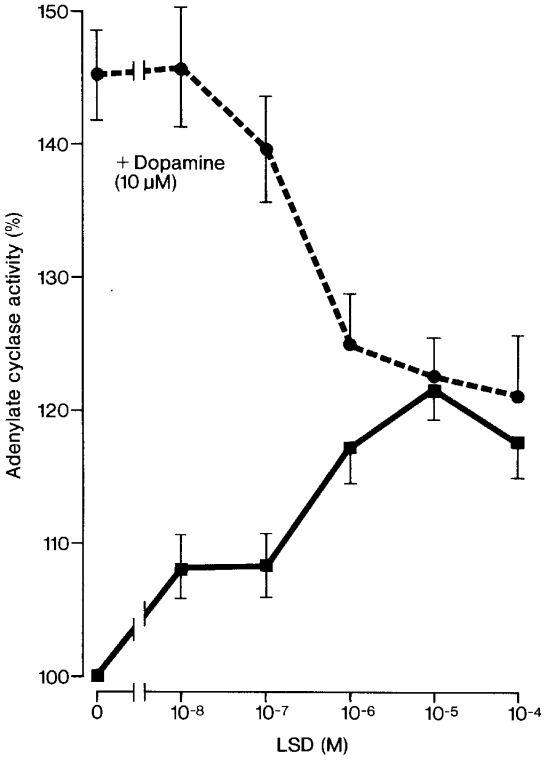


Fig. 16. Effect of D-LSD on the adenylate cyclase activity in homogenates of rat striatum without (■——■) and in the presence of 10 μM dopamine (●---●). Each point indicates a mean value with SEM from 7 experiments. [From Figure 3, DA PRADA, M. (et al.): Brain Res. **94**, 70 (1975)]

ing the activation of striatal adenylate cyclase by dopamine (pA_2 value 5.9) than that induced by noradrenaline (pA_2 value 6.3) (MARKSTEIN et al., unpublished).

The dopamine-sensitive adenylate cyclase in retinae of different animal species could also be activated by D-LSD at a concentration of 1 μM (SPANO et al., 1975a, b). In the isolated rabbit retina significant increases in cyclic AMP concentration were found after incubation with ergometrine, agroclavine or bromocriptine. The increases in cyclic AMP elicited by the three ergot compounds were detectable at 1 μM and comparable to those seen after dopamine or apomorphine when concentrations of 100 μM were used. Moreover, the responses to the ergot alkaloids could be blocked by the dopamine antagonist fluphenazin, suggesting that the three ergot alkaloids stimulated dopamine receptors in the rabbit retina (SCHORDERET, 1976; SCHORDERET and FRANGAKI, 1976).

5. Effects of Ergot Alkaloids on Dopamine Receptors Mediating Hormone Secretion

There is good evidence that dopamine receptors control prolactin secretion from the pituitary gland. Both dopamine and apomorphine were found to inhibit the

release of prolactin from the isolated pituitary, while neuroleptics, such as haloperidol and perphenazine, antagonized responses to both agonists (MACLEOD and LEHMEYER, 1972, 1974). Incubation of pituitary glands from female rats with 0.2 μM α-ergokryptine caused a 50% inhibition of prolactin secretion. Responses to both α-ergokryptine and apomorphine could be blocked by the in vitro presence of 0.1 μM haloperidol or perphenazine (HILL-SAMLI and MACLEOD, 1975; MACLEOD and LEHMEYER, 1974). These results suggest that dopamine inhibits prolactin secretion by stimulating dopamine receptors in the pituitary gland, and that this effect can be mimicked by α-ergokryptine.

D. Actions of Ergot Alkaloids at Adrenoceptors

R. SALZMANN and TH. BUCHER

1. Effects of Ergot Alkaloids Mediated by Peripheral α-Adrenoceptors

It is now clear that ergot alkaloids, by virtue of their own complex chemical structure, which includes the lysergic acid group, interact in a complex manner with drug receptors. In earlier times the pharmacologic effects of ergot alkaloids were attributed to a "direct" action on smooth muscle without reference to receptors; this notion was applied particularly to their stimulant effects, since blocking effects of ergot alkaloids on specific receptor sites, such as adrenergic or 5-HT receptors, had been known for a long time. More recently there has been increasing evidence that some, or perhaps all, of the stimulant effects of ergot alkaloids are also exerted at specific receptor sites on which they may act as partial agonists. Ergot alkaloids may also interfere in other ways with neurotransmission processes either peripheral or central, e.g., by promoting or inhibiting transmitter release or by blocking uptake sites.

a) Ergot Alkaloids as α-Adrenoceptor Blocking Agents

DALE's early work on ergot (DALE, 1906) has been the source of most subsequent developments in receptor pharmacology of both ergot and catecholamines (SCHILD, 1976). In his discussion of adrenaline reversal (SOLLMANN and BROWN, 1905; DALE, 1906), DALE does not use the word *receptor* (although he was aware of LANGLEY's postulated *receptive substances*), referring only to *motor* and *inhibitor myoneural junctions* of the sympathetic.

Nevertheless, his work was the first to show clearly that ergot alkaloids could block adrenergic receptors. He also showed that the block by ergot spared the inhibitory effects of adrenaline on smooth muscle as well as its stimulant effect on the heart, thus anticipating AHLQUIST's (1948) subdivision into α- and β-"adrenotropic" receptors.

A number of investigations dealing with α-adrenoceptor block by ergot alkaloids is summarized in Table 3. Certain important test systems on which the antagonism between catecholamines and ergot alkaloids has been investigated are discussed in more detail below.

Table 3. Alpha-adrenoceptor blocking activity of ergot alkaloids in isolated preparations in vitro and in situ
(Abbreviations for agonists: A = adrenaline, NA = noradrenaline, PH = phenylephrine)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds				Ref-er-ences
BOL-148 (2-Bromo-D-LSD)	Brain slices (hypothalamus, brain stem), rat	10^{-5} M. Antagonism of elevation in cAMP due to NA				1
	Isolated ear, *rabbit*	100 µg/l: Reduction of the effects of A and NA				2
	Heart, rabbit	10^{-6} M. Reduction of positive inotropic effects of NA				1
	Aorta, rabbit	Agonist	$pA_{2(10\,min)}$	$pA_{10(10\,min)}$ normal strips	reser-pinized strips	3
		NA	6.4	5.6	5.7	
		PH	–	5.8	–	
		Methoxamine	–	5.7	–	
		Nordefrine	–	5.3	–	
		Ephedrine	–	5.0	5.0	
		d-Amphetamine	–	4.6	4.4	
	Aorta, rat	Agonist	$pA_{2(15\,min)}$ normal	reser-pinized	$pA_{10(15\,min)}$ normal	reser-pinized	4
		NA	7.8	7.9	6.5	6.5
		Methoxamine	7.7		6.7	
		Nordefrine	7.8		6.6	
	Mesenteric arteries, dog	1×10^{-7} M to 1×10^{-5} M: Reduction of vasoconstrictor responses to NA				1
	Umbilical artery, man	15 µg/0.3 ml: No alteration of the contractions to tyramine or NA				5
	Uterus (primed by isoprenaline), rat	100 ng/ml: Prevention of motor responses to A, NA and PH				6
Dihydro-ergo-cornine	Seminal vesicle, guinea-pig	2 to 60×10^{-5}: Inhibition of A-reaction. Relative effectiveness: Ergotamine = 1, dihydro-ergocornine = 25				7, 8, 9, 10, 11
	Uterus (isolated), rabbit	2 to 3×10^{-5}: Inhibition of excitatory A-effect. Relative effectiveness: Ergotamine = 1, dihydro-ergocornine = 2.5				8, 9, 10, 11
	Uterus (in situ), rabbit	Inhibition of A-effect by 0.125–0.15 mg/kg i.v.				8
Dihydro-ergo-cristine	Aorta thoracalis, rabbit	ED_{50} (Inhibition of NA-effect): 1.2×10^{-7}				12
	Vena palmaris metacarpalis profunda, bovine	ED_{50} (Inhibition of NA-effect): 8.5×10^{-9}				12
	Seminal vesicle, guinea-pig	2 to 60×10^{-5}: Inhibition of A-reaction. Relative effectiveness: Ergotamine = 1, dihydro-ergocristine = 35				7, 8, 9, 10, 11

Table 3 (continued)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds	References
	Uterus (isolated) rabbit	2 to 30×10^{-5}: Inhibition of excitatory A-effects. Relative effectiveness: Ergotamine = 1, dihydroergocristine = 3.5	8, 9, 10, 11
	Uterus (in situ) rabbit	0.15 mg/kg i.v.: Inhibition of A-effect	8
	Hind limb (innervated, perfused), dog	Inhibition of increase in vascular resistance to NA. Intermediate activity between ergotamine and 1-methyl-ergotamine	13, 14, 15
Dihydroergokryptine	Seminal vesicle, guinea-pig	2 to 60×10^{-5}: Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, dihydroergokryptine = 35. Inhibition of A-effect by dihydro-α-ergokryptine and dihydro-β-ergokryptine (0.5–5 µg/l). Relative activity: Dihydro-α-ergokryptine 100%, dihydro-β-ergokryptine 130%	7, 8, 9, 10, 11, 16
	Uterus (isolated) rabbit	2 to 30×10^{-5}: Inhibition of excitatory A-effect. Relative effectiveness: Ergotamine = 1, dihydroergokryptine = 5	8, 9, 10, 11
	Uterus (in situ) rabbit	Inhibition of A-effect. 0.15–0.2 mg/kg i.v.	8
Dihydroergosine	Seminal vesicle, guinea-pig	Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, dihydroergosine = 6	8, 9
	Uterus (isolated), rabbit	Inhibition of excitatory A-effect. Relative effectiveness: Ergotamine = 1, dihydroergosine = 2	8, 9
	Uterus (in situ), rabbit	Inhibition of A-effect. 0.15–0.2 mg/kg i.v.	8
Dihydroergostine	Hind limb (innervated, perfused), dog	Inhibition of increase in vascular resistance to NA. Intermediate activity between that of ergotamine and 1-methylergotamine	13, 14, 15
Dihydroergotamine (DHE-45, Dihydergot)	Superior cervical ganglion, rabbit	10^{-5} M. Inhibition of depressant action of A	17
	Isolated perfused ear, rabbit	20 µg/l: Greatly diminished response to A	18
	Papillary muscle, cat	$3.7–7.4 \times 10^{-5}$ M. Competitive antagonism against A and NA	19
	Blood vessels		
	a) Arteries		
	Aorta, rabbit	Inhibition of A and NA. Apparent K_I in Mols/Liter: 2×10^{-8} (30 min), 10^{-8} (60 min), 5×10^{-9} (240 min)	20
	Auricular artery, rabbit	pA_2 against NA: 8.0	21
	Saphenous arteries, dog	$pA_{2(15\,min)}$ against NA: 8.4	22
	Umbilical artery, man	9.2 to 23.1 µg/0.3 ml. Total block of constrictor and dilator responses to A and NA	23
		23 µg/0.3 ml. Abolition of contractions to tyramine and NA	5

Table 3 (continued)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds	References
Dihydroergotamine (continued)	*b) Veins*		
	Femoral veins, dog	$pA_{10(15\,min)}$ against NA: 8.4	24, 25
	Saphenous veins, man (normal, varicous), dog	$pA_{10(15\,min)}$ against NA: 5.6 (man), 7.2 (dog)	24, 25
	Intestinal tract		
	Intestinum, dog	0.1–1 mg/kg i.v.: Reduction of inhibitory response to PH	26
	Jejunum, rabbit	5–200 µg/50 ml: Order of decreasing susceptibility to blockade by DHE was methoxamine ~PH > A > NA > isoproterenol	27
	Ileum, cat	2 mg/kg i.v.: Antagonism of the inhibitory effects of A and NA	28
	rabbit	Stronger inhibition of the A-effect than ergotamine	29
	Taenia caecum, guinea-pig	10 µg/ml: Abolition of relaxation to NA	30
	Genital organs		
	Seminal vesicle, guinea-pig	2 to 60×10^{-5}: Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, dihydroergotamine = 7	7, 8, 9, 10, 11
		Inhibition of A-effect. ED_{50}: 2 ng/ml	31
	Vas deferens, guinea-pig	$pA_{2(30\,min)}$ against NA: 8.3	32
	Retractor penis, dog	0.5 mg/kg i.v.: Reduction of the contraction to A and PH	26
	Uterus, dog	Blockade of A-stimulation and reversal to inhibition	33
	guinea-pig	Blockade of A-stimulation	33
	rabbit	2 to 30×10^{-5}. Blockade of A-stimulation. Relative effectiveness: Ergotamine = 1, dihydroergotamine = 2.25	8, 9, 10, 11, 33,
		2×10^{-5}. Antagonism of A-contraction	34
		0.02–0.05 mg/kg i.v.: Inhibition of A-effect	8
	rat	0.01–20 ng/l: Reduction of inhibitory effect to A	35
		10 µg/ml: Prevention of inhibitory responses to A and PH	36
		Blockade of A-inhibition	37, 38
		100 ng/ml: Inhibition of the motor responses to A, NA and PH (in two of five instances)	6
	man	Blockade of stimulation, occasional reversal to inhibition	39
		1:3 Mill. to 1:80 Mill.: Inhibition of the excitatory effect of A and NA	40
	Other preparations		
	Hind limb (innervated, perfused), dog	Inhibition of increase in vascular resistance to NA. 5 times less active than ergotamine (for a 40% NA-inhibition). Intermediate activity between ergotamine and 1-methylergotamine	13, 14, 15, 41

Table 3 (continued)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds	References
	Melanophores, lizard (Anolis carolinensis)	Only partial inhibition of MSH-reaction. Dihydroergotamine inhibits α-adrenergic receptor activity of concentrations which do not antagonize MSH-darkening	42
Dihydroergotoxine mesylate (Hydergine)	Seminal vesicle, guinea-pig	ED_{50} (inhibition of A): 0.66 ng/ml	31
	Uterus (in situ), rabbit	1 mg/kg i.v.: Antagonism against A, NA and ergometrine	43
	rat	200 ng/ml: Inhibition of motor effect of A, NA and PH	6
	man	1:3 Mill. to 1:80 Mill.: Inhibition of excitatory effect of A and NA	40
	Jejunum, man	Block of PH-effect; response to isoprenaline only reduced	44
	Taenia coli, man	5 µg/ml: Abolition of NA relaxation 1 µg/ml: Complete block of A-relaxation	45
Ergocornine	Seminal vesicle, guinea-pig	2 to 60×10^{-5}. Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergocornine = 2	7, 8, 9, 10, 11,
	Uterus (isolated), rabbit	2 to 30×10^{-5}. Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergocornine = 0.5	10, 11
	Uterus (in situ), rabbit	0.025–0.2 mg/kg i.v.: Inhibition of A-effect	8
Ergocristine	Seminal vesicle, guinea-pig	2 to 60×10^{-5}. Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergocristine = 4	7, 8, 9, 10, 11
	Uterus (isolated), rabbit	2 to 30×10^{-5}. Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergocristine = 1	8, 9, 10, 11
	Uterus (in situ), rabbit	0.1–0.2 mg/kg i.v.: Inhibition of A-effect	8
Ergokryptine	Seminal vesicle, guinea-pig	2 to 60×10^{-5}. Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergokryptine = 4 Inhibition of A-effect by α-ergokryptine and β-ergokryptine (1–10 µg/l). Relative activity: α 100%, β 160%	7, 8, 9, 10, 11, 16
	Uterus (isolated), rabbit	2 to 30×10^{-5}. Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergokryptine = 1.5	8, 9, 10, 11
	Uterus (in situ), rabbit	0.15–0.2 mg/kg i.v.: Inhibition of A-effect	8
Ergometrine (Ergotocine, Ergobasine)	Ear, rabbit	100 to 1000 µg/l: No definite effect on A and NA. 100 µg/l: No significant effect on the response to A	2 18
	Ventricle, rat	5×10^{-7} and 2×10^{-6} g/ml: Significant reduction of positive inotropic action of tyramine	46
	Ventricle (electrically stimulated), rat	5×10^{-7} g/ml: Potentiation of A 2×10^{-6} g/ml: No significant change of NA	47
	Uterus, rabbit	1:500,000: No inhibition of A-reaction	48

Table 3 (continued)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds	References
Ergosine	Seminal vesicle, guinea-pig	Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergosine = 1	8, 9
	Uterus (isolated), rabbit	Inhibition of A-effect. Relative effectiveness: Ergotamine = 1, ergosine = 1	8, 9
	Uterus (in situ), rabbit	0.15–0.2 mg/kg i.v.: Inhibition of A-effect	8
Ergostetrine	Uterus (isolated), rabbit	0.2 to 0.4 mg/50 ml: Inhibition of A to only a relatively slight degree	49
Ergostine	Hind limb, dog	Inhibition of increase in vascular resistance to NA	13, 14, 15
	Seminal vesicle, guinea-pig	Approximately three times more active in inhibiting the A-effect than ergotamine	50
Ergotamine (Gynergene)	Dilator iridis, rabbit	$1:10^5$ to $1:8 \times 10^5$: Antagonism against A (reversal of A-effect)	51
	Isolated perfused ear, rabbit	Suppression or reversal of A-constriction M/10 Mill.: Inhibition of A-effect 40 µg/l: Abolition of A-effect	52 53 18
	Nictitating membrane, cat, dog	Fairly regular inversion of A-effect after high doses	54, 55, 56
	Circulatory system		
	Ventricle, rat	1.5×10^{-6} g/ml: Significant reduction of positive inotropic action of tyramine	46
	Papillary muscle, cat	10^{-6} M: Total abolition of the contractile force of methoxamine. Reduction by at least half the contractile force of PH	57
	Blood vessels		
	a) Arteries		
	Basilar artery, dog, man	No change of response to NA	58
	External carotid artery, dog	No inhibition of NA-reaction. Dose response curves for NA were shifted to the left	59
	Arteria coronaris cordis, bovine	Inhibition of dilating action of A	52
	Mesenteric artery, bovine	Inhibition of A-contraction	52
	Saphenous artery, dog	$pA_{2(60\,min)}$ against NA: 8.7	59
	b) Veins		
	Lateral saphenous vein, dog	pA_2 against A and NA: 8.2	60

Table 3 (continued)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds	References
Ergotamine (continued)	Femoral vein, dog	pA_2 against NA (competitive antagonism): 9.0 pD'_2 against NA (non-competitive antagonism): 7.6	61
		$pA_{2(15\,min)}$ against NA: 8.8	62
	Pulmonary vessels, cat	$>10^{-5}$. Reversal of the action of A and NA	63
	Intestinal tract		
	Stomach, guinea-pig	Preparations with previously increased tone: $2\times10^{-8}-2\times10^{-6}$ M: Enhancement of the inhibitory action of PH 5×10^{-6} M: Antagonism of the effects produced by A, NA and PH Preparations with low (spontaneous) tone: $pA_{2(20\,min)}$ against PH: 8.0. pA_2 against A, NA were not determined because responses were too small and variable that quantitative evaluation was not feasible	64
	Jejunum, rabbit	Weaker inhibition of the A-effect than DHE	29
	Genital organs		
	Vas deferens, guinea-pig	1 mg/200 ml: Inhibition or slight inversion of A-contraction	65
	Seminal vesicle, guinea-pig	2 to 60×10^{-5}. Inhibition of A-contraction	7, 8, 9, 10, 11, 52
		A-inhibitory action approx. 50 times stronger than that of LSD	66
		Approximately three times less active in inhibiting the A-effect than ergostine	50
		$pA_{2(20\,min)}$ against A, NA and PH: 8.1	67
		ED_{50} (inhibition of A-effect): 14 ng/ml	31
	Uterus, guinea-pig	Blockade of A-stimulation and reversal to inhibition. No effect on A-inhibition	68
		Inhibition of A-decrease of tone	52
	rabbit	Inversion or inhibition of A-contraction	52
		1:2 Mill. to 1:4 Mill. Diminution, removal or reversal of the contracting A-reactions	69
		Inhibition of excitatory A-reaction	8, 10, 11
	rat	No effect on A-inhibition	68
	Other preparations		
	Hind limb, dog	Dose-dependent inhibition of the increase in vascular resistance to NA	13,14, 15, 41
	Extremity, frog	Suppression or reversal of A-constriction	52
	Melanophores, lizard (Anolis carolinensis)	10^{-5} M. Prevention from catecholamine (A, NA) lightening of MSH-darkened skins. Increased darkening of skins in response to catecholamines after the skins have been treated with ergotamine	70, 71, 72
	Spleen, cat	ED_{50} (Inhibition of A-effect): 0.02 µg/ml	73
Ergotaminine	Nictitating membrane, cat	No action on A-contraction after high concentrations	55

Table 3 (continued)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds	References
Ergotoxine	Isolated, perfused ear, rabbit	0.02 µg/ml: Same constriction with a dose of A 10 times greater than initial test dose	53
	Nictitating membrane, cat	Up to 9 mg/kg: Relaxation of A-contraction Relaxation of A- and NA-contraction Relaxation after A and NA in the ergotoxine-treated animal	74 75 56
	Seminal vesicle, guinea-pig	1 in 4×10^6: Reduction of A-contraction by 75% 1 in 1.5×10^6: Almost complete annulment of the A-action	76
	Bladder, rabbit	Abolition of A-excitation. No change of A-inhibition	77
	Uterus, rabbit	Inhibition or abolition of stimulative activity of A and ergostetrine 1:10 Mill.: Inhibition of A-reaction	49 48
	Spleen, dog, rabbit, cat, buffalo, man	1:100,000: Abolition of A-effect on dog's, rabbit's, cat's or buffalo's splenic capsule 1:25,000: Abolition of A-effect in human splenic capsule 0.25–2 µg/50 ml: Inhibition of A-reaction	78 79
	Hind limb, cat	0.5 mg: Reversal of A-effect	76
D-LSD	Brain slices (hypothalamus, brain stem), rat	10^{-5} M: Antagonism against NA-induced elevation in cyclic AMP	1
	Isolated, perfused ear, rabbit	100 µg/l: Increase of A- and NA effects	2
	Heart, rabbit	10^{-6} M. Reduction of positive inotropic effects of NA	1
	Pulmonary vessels, cat	Little effect on the actions of A and NA	63
	Mesenteric arteries, dog	10^{-6} M. Diminution of NA effect by 25%	1
	Seminal vesicle, guinea-pig	Approximately 50 times weaker than ergotamine (inhibition of A-effect)	66
	Uterus, rat	0.01–20 ng/l: Reduction of inhibitory A-effect	35
	Trachea, guinea-pig, rat	0.3 µg/ml: No NA-antagonism	80
	Hind leg, cat, dog	10^{-6}: Only slight diminution of A-effect	63
1-Methyl-dihydro-ergocristine	Hind limb, dog	Only weak inhibition of increase in vascular resistance to NA	13, 14, 15
5′-Methyl-ergoalanine	Hind limb, dog	Strong α-adrenergic blocking activity of increase in vascular resistance to NA	13, 14, 15
1-Methyl-ergostine	Hind limb, dog	Only weak inhibition of increase in vascular resistance to NA	13, 14, 15

Table 3 (continued)

Ergot compounds	Preparation and species	Pharmacologic effect of ergot compounds	References
1-Methyl-ergotamine	Seminal vesicle, guinea-pig	ED_{50} (Inhibition of A-reaction): 19.6 ng/ml	31
	Hind limb, dog	Only weak inhibition of increase in vascular resistance to NA	13, 14, 15, 41
Methy-sergide (Deseril)	Isolated organs (general)	No adrenolytic effect in contrast to the ergot alkaloids of the peptid group	81
	Aorta, rabbit	pA_2 against NA: 5.3	82
	Saphenous arteries, dog	$pA_{2(15\,min)}$ against NA: 5.5	22
	Vas deferens, rat	$pA_{2(5\,min)}$ against NA: 5.8	83
	Colon, rat	1 µg/ml: No significant alteration of contractile responses to A	84
		300 ng/ml: Contractions induced by A were reduced by 49% (10 ng), 34% (30 ng) and 22% (100 ng) 500, 1000 ng/ml: merely reduced contractile responses to A ('non-specific antagonism against A')	85
	Stomach, guinea-pig	Up to 10^{-6} M. No antagonistic action against A, NA, PH	64
	rat	No effect on contractions to A, NA and PH	86
Nicergo-line (MNE, Sermion)	Ileum, guinea-pig	Reduction of A $ED_{50} = 0.007$ µg/ml	87
Sensi-bamine	Uterus (gravid), rabbit	1:2 to 1:4 Mill.: Diminution, removal or reversal of the contracting A-reaction	69
10-Methoxy-ergoline deriva-tives	Seminal vesicle, guinea-pig	Among the pyridyl carboxylic esters of 1-methyl-10α-methoxydihydrolysergol, the nicotinates, and notably those having an electron-withdrawing group in position 5, are characterized by a strong alpha adrenergic blocking activity (against adrenaline). Relative activity 120 to 7800, ergotamine = 100 For further detail see original paper	88
6-Methyl-8β-amino-methyl-10α-ergo-line (Dihydro-lyserg-amine)	Seminal vesicle, guinea-pig	Structure-activity relationship of carboxylic and carbonic acid derivatives of dihydrolysergamine with regard to α-adrenoceptor-blockade, oxytocic and anti-5-HT-activity is described For details see original paper	89

References: 1. PALMER and BURKS (1971); 2. SAVINI (1956); 3. KOHLI (1968); 4. KRISHNAMURTY (1971); 5. GULATI and KELKAR (1971); 6. TOTHILL (1967); 7. BRÜGGER (1945); 8. ROTHLIN (1946/1947); 9. ROTHLIN and CERLETTI (1949); 10. ROTHLIN and BRÜGGER (1945a); 11. ROTHLIN and BRÜGGER (1945b); 12. FLÜCKIGER and BALTHASAR (1967); 13. AELLIG and

Table 4. Relative values of the adrenaline-antagonistic action of natural and dihydrogenated ergot alkaloids on isolated organs. [From Table 3, ROTHLIN, E.: Bull. Schweiz. Akad. Med. Wissensch. **2**, 262 (1946/47)]

Isolated uterus of rabbit				Isolated seminal vesicle of guinea-pig			
Natural		Hydrogenated		Natural		Hydrogenated	
Ergocornine	0.5	Dihydroergosine	2.0	*Ergotamine*	1	Dihydroergosine	6
Ergotamine	1.0	Dihydroergotamine	2.25	Ergosine	1	Dihydroergotamine	7
Ergosine	1.0	Dihydroergocornine	2.5	Ergocornine	2	Dihydroergocornine	25
Ergocristine	1.0	Dihydroergocristine	3.5	Ergocristine	4	Dihydroergocristine	35
Ergokryptine	1.5	Dihydroergokryptine	5.0	Ergokryptine	4	Dihydroergokryptine	35

Adrenaline-induced contraction of isolated guinea-pig seminal vesicle. In this preparation (BRÜGGER, 1945) ergot alkaloids antagonize adrenaline-induced contractions without exerting a contractile effect of their own. Adrenaline produces a slow rise in tone of the isolated preparation followed by a series of intermittent contractions. The objective of this procedure is to find the dose of ergot which after 20 min incubation reduces adrenaline responses by 50%. The block by ergot alkaloids is reversible so that two alkaloids may be compared in the same preparation by a cross-over procedure. The relative activities of two ergot alkaloids as α-blockers may be compared quantitatively by this method; the data in Table 4 represent average activity ratios, relative to ergotamine, obtained from about 100 determinations each. The dihydrogenated ergot alkaloids were consistently more active by this test than the corresponding natural alkaloids; among the latter ergocristine and ergokryptine were most active.

BERDE (1969); 14. BERDE (1971); 15. BERDE (1972); 16. SCHLIENTZ et al. (1968); 17. CHRIST and NISHI (1971); 18. GADDUM and HAMEED (1954); 19. KIMURA et al. (1970); 20. FURCHGOTT (1955); 21. FOZARD (1973b); 22. MÜLLER-SCHWEINITZER (1975a); 23. GOKHALE et al. (1966); 24. MÜLLER-SCHWEINITZER (1973); 25. MÜLLER-SCHWEINITZER (1974c); 26. LEVY and AHLQUIST (1961); 27. LUM et al. (1966); 28. TÜRKER et al. (1965); 29. ROTHLIN (1946); 30. ÅBERG et al. (1969); 31. PACHA and SALZMANN (1970); 32. BIRMINGHAM and SZOLCSÁNYI (1965); 33. GREEFF and HOLTZ (1951); 34. SCHILD (1960); 35. HOLZBAUER and VOGT (1955); 36. LEVY and TOZZI (1963); 37. WIQVIST (1959); 38. RUDZIK and MILLER (1962); 39. GARRETT (1955); 40. ROTHLIN and BERDE (1954); 41. AELLIG (1967); 42. GOLDMAN and HADLEY (1972); 43. FREGNAN and GLÄSSER (1964); 44. WHITNEY (1965); 45. BUCKNELL and WHITNEY (1964); 46. WENZEL and SU (1966a); 47. WENZEL and SU (1966b); 48. DAVIS et al. (1935); 49. THOMPSON (1935); 50. CERLETTI (1963); 51. SACHS and YONKMAN (1942); 52. ROTHLIN (1925); 53. FLECKENSTEIN (1952); 54. BACQ (1934a); 55. BACQ (1934b); 56. SMITH (1963); 57. PARMLEY et al. (1974); 58. MÜLLER-SCHWEINITZER (1976c); 59. MÜLLER-SCHWEINITZER and STÜRMER (1975); 60. GUIMARÃES and OSSWALD (1969); 61. MÜLLER-SCHWEINITZER and STÜRMER (1972); 62. MÜLLER-SCHWEINITZER and STÜRMER (1974a); 63. GINZEL and KOTTEGODA (1953); 64. GUIMARÃES (1969b); 65. BACQ (1934c); 66. ROTHLIN (1957c); 67. GUIMARÃES (1969a); 68. MENDEZ (1928); 69. RÖSSLER and UNNA (1935); 70. GOLDMAN and HADLEY (1969); 71. GOLDMAN and HADLEY (1970a); 72. GOLDMAN and HADLEY (1970b); 73. BICKERTON et al. (1962); 74. ROSENBLUETH (1932); 75. ACHESON (1940); 76. BROWN and DALE (1935); 77. STREULI (1916); 78. SAAD (1935); 79. GYÖRGY et al. (1958b); 80. FLEISCH et al. (1970); 81. FANCHAMPS et al. (1960); 82. APPERLEY et al. (1974); 83. GÖRLITZ and FREY (1973); 84. BELISLE and GAGNON (1971); 85. GAGNON (1972); 86. OGLE and WONG (1971); 87. ARCARI et al. (1968); 88. ARCARI et al. (1972); 89. FREGNAN and GLÄSSER (1968).

Instead of guinea-pig seminal vesicle, the rat's seminal vesicle may be used (LEITCH et al., 1954).

Adrenaline contraction of isolated rabbit uterus. BROOM and CLARK (1923) introduced a method in which the abolition of the motor action of adrenaline on the rabbit uterus provides a basis for the standardization of ergot. The BROOM-CLARK method is of historical interest, having been the starting point for studies of the antagonism between adrenaline and ergotamine from which some of the early ideas of receptor theory arose (GADDUM, 1926; CLARK's Appendix to MENDEZ, 1928), but it has serious disadvantages as a test method: An unsharp endpoint (complete abolition of the adrenaline response); insufficiently long contact with ergot (5 min followed by washout before adding adrenaline); a frequent stimulant effect of ergot on rabbit uterus; and a frequent relaxant effect of adrenaline preceding its contractile action. ROTHLIN and BRÜGGER (1945a, b) modified the method, obtaining the results of Table 4, which again show greater blocking activity of dihydrogenated compared to natural alkaloids, although the discrepancy is less than in seminal vesicles.

GADDUM (1926) employed the isolated rabbit uterus for a graded response assay. He proved that plotting the adrenaline response on a logarithmic scale in the absence and presence of ergotamine results in two parallel lines (Fig. 17). This was an early demonstration of competitive drug antagonism (although GADDUM did not interpret it thus). The degree of displacement of the parallel lines can be considered as measuring the affinity of ergotamine for catecholamine receptors; the displacement would no doubt have been greater if more than 5 min had been allowed for equilibration with ergotamine.

Adrenaline inhibition of rabbit intestine. It has been shown repeatedly that ergotamine antagonizes the inhibitory effect of adrenaline on the isolated rabbit intestine (NANDA, 1931). Pendulum movements are particularly affected. Hydrated ergot alkaloids are also effective (Fig. 18).

The antagonism by ergot alkaloids is specific for catecholamines; papaverine relaxation of the intestine is not antagonized (ROTHLIN et al., 1954).

This effect of ergot alkaloids seems to contradict DALE's view that only the stimulant actions of adrenaline are antagonized, but it fits readily into the wider hypothesis that ergot alkaloids block α-adrenoceptors, since there is evidence from various species that both α- and β-adrenoceptors contribute to intestinal relaxation (AHLQUIST and LEVY, 1959; FURCHGOTT, 1960). JENKINSON and MORTON (1967a, b, c) analyzed the dual mechanism of catecholamines in producing relaxation in the isolated guinea-pig tenia coli. They showed that two mechanisms are involved: (1) An α-adrenoceptor-mediated ionic mechanism causing increased potassium permeability and hyperpolarization which is antagonized by typical α-adrenoceptor blocking agents such as phentolamine; (2) A β-adrenergic mechanism which can function in the absence of a polarized cell membrane, bringing about relaxation by catecholamines in completely depolarized intestinal muscle (EVANS et al., 1958). This mechanism is antagonized by β-adrenoceptor blocking agents.

Noradrenaline contraction of isolated veins. MÜLLER-SCHWEINITZER (1974c) studied the effect of dihydroergotamine (DHE) on the noradrenaline-induced contraction of isolated veins, recording isometric tension in spiral strips of dog saphenous and femoral veins and human varicose veins. Cumulative log dose-response

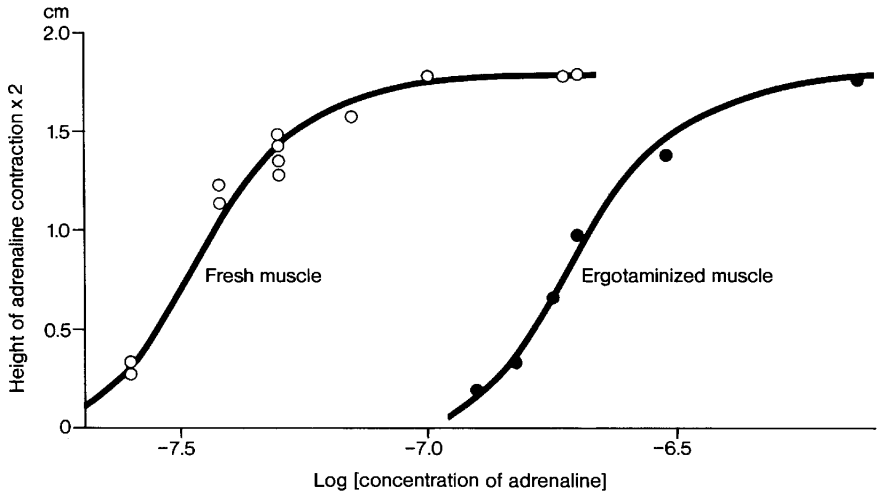


Fig. 17. Contraction of isolated rabbit uterus. Antagonism of adrenaline responses by ergotamine. [From Figure 4, GADDUM, J.H.: J. Physiol. (Lond.) **61**, 144 (1926)]

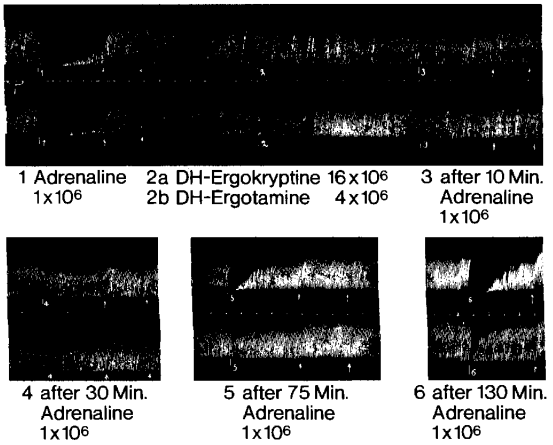


Fig. 18. Record of the isolated small intestine of the rabbit. Inhibition of adrenaline by dihydroergokryptine and dihydroergotamine. [From Figure 10, ROTHLIN, E.: Bull. Schweiz. Akad. Med. Wissensch. **2**, 266 (1946/47)]

curves of noradrenaline exhibited a parallel shift in the presence of dihydroergotamine in all three vein preparations. As shown in Figures 19, 20 and 21, their displacement corresponded approximately to that expected in a simple competitive antagonism (Fig. 22).

Contrary to a simple competitive relationship, however, dihydroergotamine also produced a slight rise in baseline, due to a partial agonist effect, and, with higher concentrations, some reduction of maximum responses. These results are summarized in Table 5, which shows: (1) the $pA_2 - pA_{10}$ differences for dihydroergotamine approximate to the theoretical value of 0.95 expected for competitive

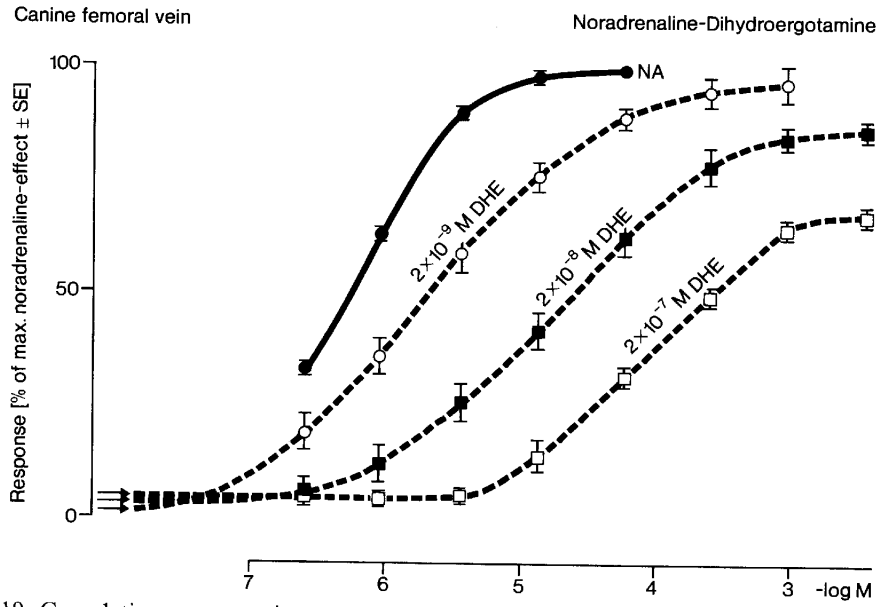


Fig. 19. Cumulative concentration-response curves for noradrenaline without (●) and 15 min after dihydroergotamine in the final concentrations of 2×10^{-9} (○), 2×10^{-8} (■) and 2×10^{-7} M (□) on spiral strips from canine femoral veins. [From Figure 1, MÜLLER-SCHWEINITZER, E.: Europ. J. Pharmacol. **27**, 232 (1974)]

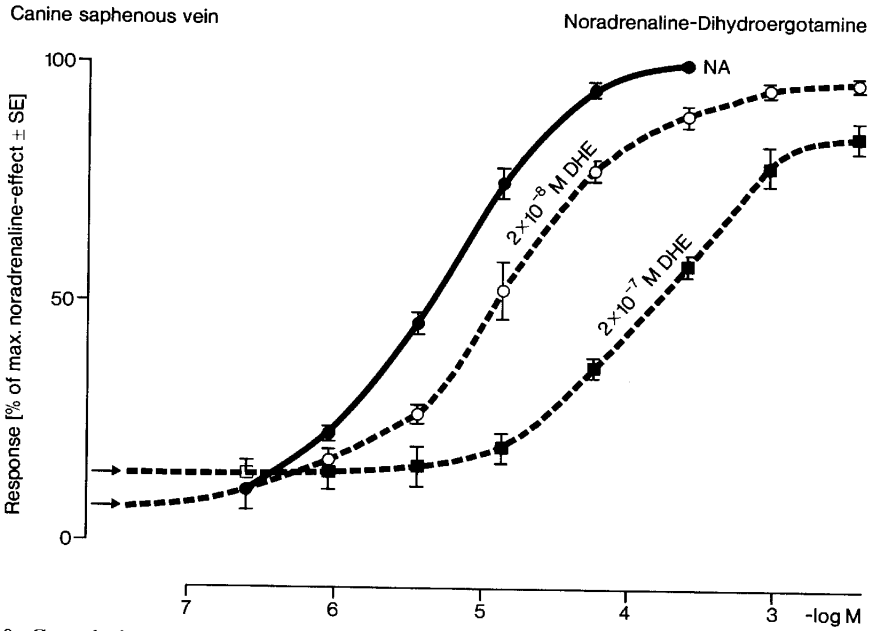


Fig. 20. Cumulative concentration-response curves for noradrenaline without (●) and 15 min after dihydroergotamine in the final concentrations of 2×10^{-8} (○) and 2×10^{-7} M (■) on spiral strips from canine saphenous veins. [From Figure 2, MÜLLER-SCHWEINITZER, E.: Europ. J. Pharmacol. **27**, 232 (1974)]

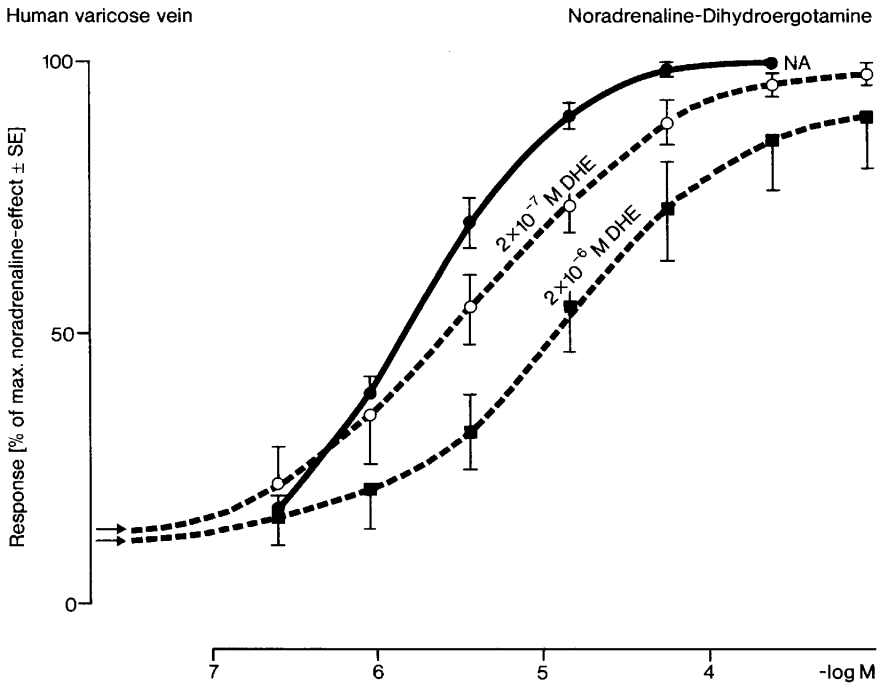


Fig. 21. Cumulative concentration-response curves for noradrenaline without (●) and 15 min after dihydroergotamine in the final concentrations of 2×10^{-7} (○) and 2×10^{-6} M (■) on spiral strips from human varicose veins. [From Figure 3, MÜLLER-SCHWEINITZER, E.: Europ. J. Pharmacol. **27**, 233 (1974)]

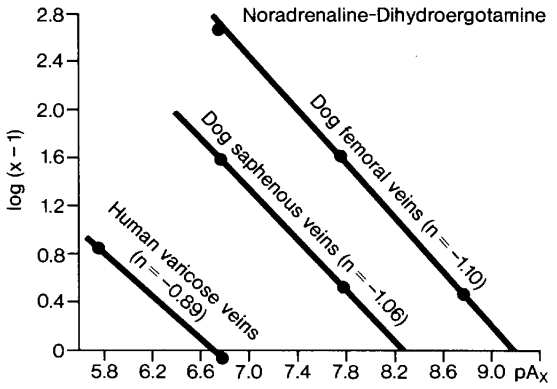


Fig. 22. Plots of the data from Figures 19, 20 and 21 according to ARUNLAKSHANA and SCHILD (1959). The slopes are slightly atypical in terms of a simple competitive antagonism. [From Figure 4, MÜLLER-SCHWEINITZER, E.: Europ. J. Pharmacol. **27**, 233 (1974)]

antagonism; (2) Intrinsic (stimulant) activity or efficacy of dihydroergotamine in terms of the noradrenaline maximum is relatively low; (3) The receptor affinities of dihydroergotamine as expressed by pA_2 values show marked differences in the three vein preparations, although the agonist activities of dihydroergotamine as expressed by pD_2 values appear to be similar. The differences in pA_2 values

Table 5. Antagonist and partial agonist effects of dihydroergotamine on isolated vein strips. [From Table 1, MÜLLER-SCHWEINITZER, E.: Europ. J. Pharmacol. **27**, 234 (1974)]

	pA values against noradrenaline		pD_2 value	Intrinsic activity
	pA_{10}	pA_2		
Human varicose veins	5.6	6.7	7.5	0.3
Dog saphenous veins	7.2	8.0	8.3	0.1
Dog femoral veins	8.4	9.2	8.0	0.16

Table 6. Antagonism of noradrenaline by various ergot alkaloids. pA_2 values were calculated after an incubation time of 15 min on spiral strips from canine femoral veins (MÜLLER-SCHWEINITZER, unpublished)

Ergot type: "peptide"		"amide"	
Ergotamine	8.8	Ergometrine	< 5.5
1-Methylergotamine	8.3	Methylergometrine	< 5.5
α-Ergokryptine	9.0	Methysergide	5.5
Bromocriptine[a]	8.9	BOL-148	7.1
Ergocornine	8.8		
Dihydroergovaline	8.5		
Dihydroergotamine	9.2		
Dihydro-α-ergokryptine	9.1		

[a] 2-bromo-α-ergokryptine, CB-154, Parlodel.

are puzzling, since they seem to indicate differences in α-adrenoceptors in these preparations; they can possibly be explained by technical considerations, e.g., insufficient time for attainment of full equilibrium of receptors with dihydroergotamine.

Table 6 summarizes pA_2 values obtained by MÜLLER-SCHWEINITZER (1975b) on canine femoral veins, with various ergot alkaloids of the "peptide" and "amide" types, using noradrenaline as agonist. The pA_2 values for various peptides are closely similar; the difference between ergotamine and dihydroergotamine is only 0.4 (log units). Among the amide alkaloids tested only BOL-148 (2-bromo-d-lysergic acid diethylamide, 2-bromo-LSD) had appreciable, if relatively low, activity; ergometrine (ergobasine, ergonovine, ergotocine), methylergometrine (d-lysergic acid L-2-butanolamide, Methergine) and methysergide (1-methyl-lysergic acid-L-2-butanolamide, Deseril) showing little or no α-adrenoceptor blocking activity.

Noradrenaline stimulation of cyclic AMP (cAMP) formation in rat brain slices. PALMER and BURKS (1971) have shown that D-LSD (d-lysergic acid diethylamide, Delyside) and BOL-148 antagonize the stimulant effect of noradrenaline on cAMP formation in rat brain stem and hypothalamus. MARKSTEIN and WAGNER (1975) have shown that dihydroergotoxine mesylate (Hydergine) antagonizes the stimulant effect of noradrenaline in rat brain cortex. Figure 23 shows recent results obtained by these authors in rat brain cortex slices. Dihydroergotoxine mesylate antagonizes

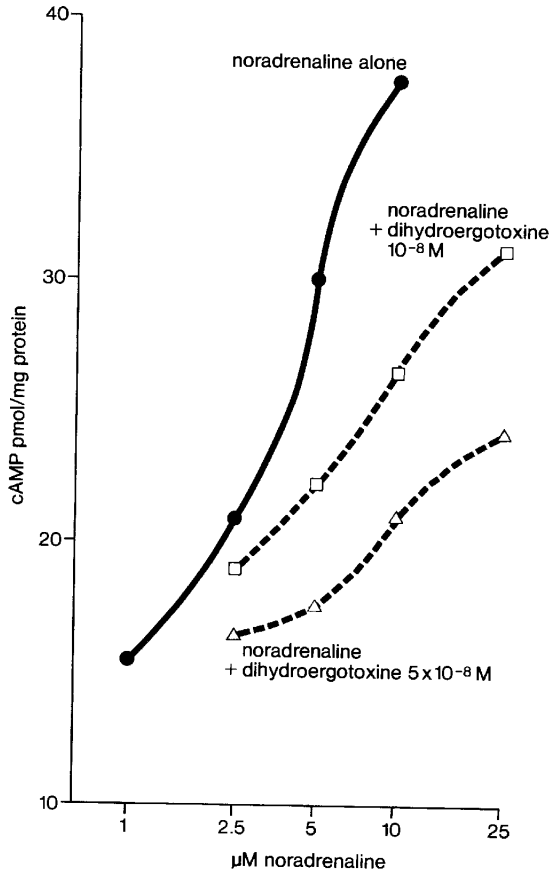


Fig. 23. Cyclic AMP (cAMP) production in rat cerebral cortex slices. Tissue incubated in Ringer (45 min, 37° C) followed by dihydroergotoxine mesylate (15 min) followed by noradrenaline (8 min). Means of two experiments. cAMP was measured by a protein-binding assay using sepharose-bound cAMP-binding protein. [From Figure 5, MARKSTEIN, R., WAGNER, H.: Gerontology **24** (Suppl. I), 101 (1978)]

the effect of noradrenaline on cAMP formation, shifting the response curve to the right. A clear shift of the noradrenaline curve occurs with low concentrations of dihydroergotoxine mesylate (10^{-8}M), indicating a high affinity for catecholamine receptors in the brain. The shift becomes more pronounced with 5×10^{-8}M. The antagonism is of the "noncompetitive" type with progressive depression of maxima. Their evidence suggested that dihydroergotoxine mesylate blocks exclusively α-adrenoceptors; the α-blocker phentolamine produced similar effects. On the other hand, stimulation of cAMP formation by isoprenaline was not antagonized by dihydroergotoxine mesylate, although it was antagonized by β-adrenoceptor blockers. Figure 24 shows evidence that effective concentrations of dihydroergotoxine mesylate accumulate in rat brain if it is fed orally (3 mg/kg/day) over a period of weeks. It was found from the reduction in the noradrenaline effect that the accumulation of dihydroergotoxine mesylate was only marginal after 1 week but obvious after

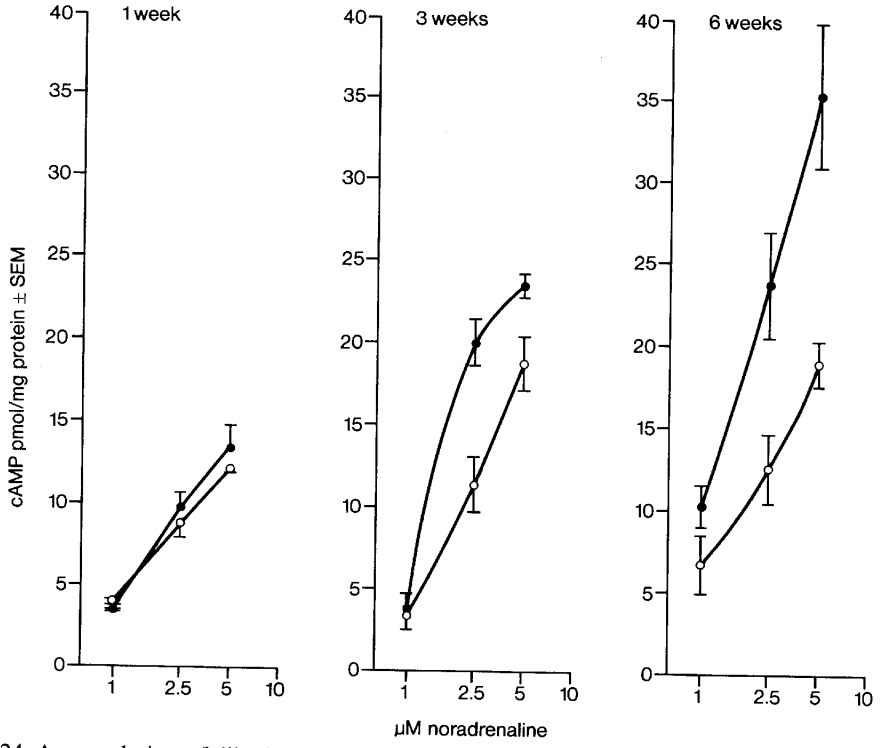


Fig. 24. Accumulation of dihydroergotoxine mesylate in rat brain following oral administration of 3 mg/kg/day for 1, 3 and 6 weeks (○—○). Dihydroergotoxine mesylate content was inferred from inhibition of noradrenaline stimulated cAMP production compared to controls (●—●). Means of four experiments. [From Figure 7, MARKSTEIN, R., WAGNER, H.: Gerontology **24** (Suppl. I), 103 (1978)]

3 and 6 weeks, when the log dose-response curves indicated a concentration of the order of 5×10^{-8}M dihydroergotoxine mesylate present in brain tissue (Fig. 24).

Catecholamine-promoted platelet aggregation. Adrenaline and noradrenaline promote the aggregation of blood platelets in man, rabbit and various other species (MILLS and ROBERTS, 1967; BARTHEL and MARKWARDT, 1974) which effect is antagonized by dihydroergotamine. Both the first and the second phase of aggregation are affected. Similar antagonistic effects are produced by phentolamine, suggesting that α-adrenoceptors are involved. Curiously, dibenamine has been found inactive in blocking adrenaline-promoted platelet aggregation.

b) Ergot Alkaloids as α-Adrenoceptor Stimulating Agents

The mechanism of action of ergot alkaloids in causing smooth muscle contraction is complex and not fully understood; it appears to be different in different types of smooth muscle. As has been mentioned, the older textbook notion (e.g., SOLLMANN, 1948) of a "direct" stimulant effect on smooth muscle has been superseded by the notion that ergot alkaloids activate certain standard drug receptors, such

as α-adrenoceptors and receptors for 5-HT and dopamine, the abundance of any particular receptor type varying in different tissues. The section that follows is concerned with evidence of α-adrenoceptor stimulation by ergot alkaloids.

Stimulant effects on α-adrenoceptors. The notion that ergot alkaloids stimulate adrenaline receptors has been around for a long time. BACQ suggested in 1934 that ergotamine augments the tonus of tissues stimulated by adrenaline, observing a close correspondence between the stimulant effects of ergotamine and adrenaline in various tissues (BACQ, 1934a). MALORNY and ORZECHOWSKI (1940) considered that ergotamine and ergometrine had sympathomimetic activity. They suggested that they act on sympathetic receptors, exhibiting stimulation, tachyphylaxis and antagonism. INNES (1962a) carried out receptor protection experiments (FURCHGOTT, 1954) which showed that receptors for ergotamine and ergometrine were "protected" by adrenaline.

Experiments with α-adrenoceptor blockers have demonstrated their antagonism of ergot alkaloids in a variety of preparations. GYÖRGY et al. (1958a) found that dibenamine antagonizes ergotoxine, reducing its pressor effect in the decapitated cat and abolishing its stimulant effect on the nictitating membrane. KONZETT (1960) showed that dibenamine antagonizes ergometrine stimulation of the rabbit uterus in situ. Phenoxybenzamine has been found to antagonize the vasoconstrictor action of ergotamine in the rabbit hindlimb (WEIDMANN and TAESCHLER, 1966) and the action of dihydroergotamine in constricting capacitance vessels in the anesthetized cat (CHU and STÜRMER, 1973; CHU et al., 1976). Phentolamine antagonizes the vasoconstrictor action of dihydroergotamine in human hand veins (AELLIG, 1974) and the effects of ergotamine in decreasing volume and increasing vascular resistance in the perfused cat spleen (SALZMANN et al., 1968).

Although this evidence is suggestive of an action of ergot alkaloids on α-adrenoceptors, it is inconclusive in view of the known unspecific effects of α-blockers, particularly their anti-5-HT-effects. More quantitative evidence is provided by the following experiments.

Dual effect of ergotamine on α-adrenoceptors. MÜLLER-SCHWEINITZER and STÜRMER (1974a, b) have shown that ergotamine acts as both partial agonist and antagonist on α-adrenoceptors in dog femoral and saphenous veins. Their principal findings were as follows: (1) Ergotamine stimulates canine isolated veins, functioning as a slow-acting partial agonist of about one-third the efficacy (intrinsic activity) of noradrenaline (Fig. 4); (2) Phentolamine antagonizes the stimulant effects of both noradrenaline and ergotamine, producing parallel log dose-response curves in both cases. However, whereas the effect of phentolamine on noradrenaline curves was a simple shift to the right, its effect on ergotamine was a shift to the right coupled with a theoretically unexpected progressive increase of the maxima of the curves (Fig. 25). Measurement by the method of ARUNLAKSHANA and SCHILD (1959), based on the degree of parallel shift of the cumulative log dose-response curves, gave the pA_2 values shown in Table 7.

The authors considered that the pA_2 values of phentolamine with noradrenaline and ergotamine as agonists probably indicate that they act on the same receptor, on the theory that agonists acting on the same receptor give similar pA_2 values when tested with the same competitive antagonist (ARUNLAKSHANA and SCHILD, 1959). They considered that irregularities in the ergotamine response may be due

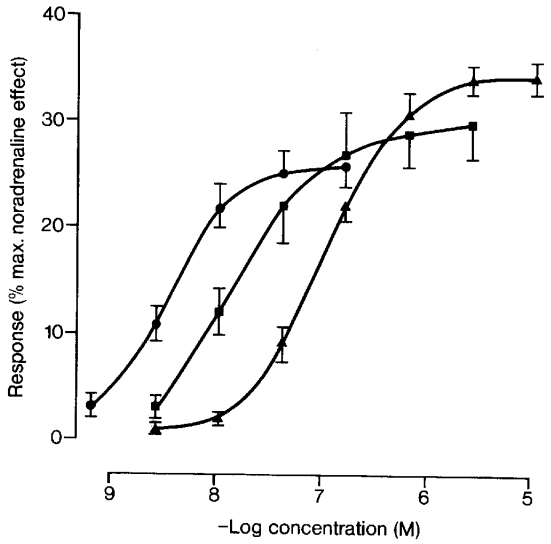


Fig. 25. Cumulative concentration-response curves for ergotamine without (●) and 15 min after phentolamine in the final concentrations of 3.6×10^{-7} (■) and 3.6×10^{-6} M (▲) on spiral strips from canine femoral veins. The bars represent ±SEM. [From Figure 3, MÜLLER-SCHWEINITZER, E., STÜRMER, E.: Brit. J. Pharmacol. **51**, 444 (1974)]

Table 7. Antagonism by phentolamine of responses to ergotamine and noradrenaline of dog saphenous and femoral vein strips. pA_2 values were calculated after an incubation time of 15 min; n refers to slope of ARUNLAKSHANA and SCHILD plot. [From MÜLLER-SCHWEINITZER, E., STÜRMER, E.: Blood Vessels **11**, 183–190 (1974) and Brit. J. Pharmacol. **51**, 441–446 (1974)]

	Ergotamine	Noradrenaline
Saphenous vein	6.9 (n = −0.97)	7.0 (n = −0.83)
Femoral vein	6.8 (n = −0.83)	7.5 (n = −0.95)

to a second action of ergotamine, such as stimulation of 5-HT receptors (cf. Section B, part 1,b), stimulation of prostaglandin synthesis (cf. Section H) as well as the long-lasting and relatively stable drug-receptor bond produced by ergotamine; (3) Ergotamine antagonizes noradrenaline, producing a series of log dose-response curves with progressively increasing base-lines and with parallelism in the upper reaches (Fig. 5), characteristic of the interaction of a partial and full agonist (VAN ROSSUM, 1963). These findings provide evidence that in isolated canine veins ergotamine in low concentrations stimulates α-adrenoceptors while acting as a competitive antagonist of catecholamines in higher concentrations.

Dual effect of ergotamine on melanophores. BACQ (1933) noted that injections of ergotamine in the catfish resulted in melanosome dispersion within innervated melanophores of normal skin but caused melanosome aggregation within denervated melanophores. PARKER (1941) obtained similar results with innervated pigment cells but not on denervated melanophores. GOLDMAN and HADLEY (1970a), working on the noninnervated melanophores of the lizard, found that ergotamine

acts both as α-adrenergic agonist and antagonist on the noninnervated melanophores of the lizard: It lightens the skin, which is a characteristic α-adrenergic agonist effect, while subsequently blocking (or reversing) the effects of other α-adrenoceptor stimulants.

2. Depletion of Noradrenaline From Tissues by Ergot Alkaloids

a) Depletion of Noradrenaline From Peripheral Tissues

With but one or two minor exceptions, there is no evidence that ergot alkaloids exert an "indirect" sympathomimetic effect (i.e., release of transmitter substance from sympathetic nerve terminals).

In experiments on the isolated perfused spleen of the cat, no evidence of noradrenaline release into perfusion fluid by ergotamine was seen, in spite of very strong contractions produced by ergotamine (SALZMANN et al., 1967, 1968) (Fig. 26). In the femoral vascular bed of anesthetized dogs, ergotamine caused a marked, long-lasting vasoconstriction when given in μg doses either intravenously or intraarterially, the response being measured as a decrease in femoral artery flow or an increase of the perfusion pressure. This response was antagonized by phentolamine but unaffected by guanethidine or by pretreatment of the animals with reserpine, indicating that ergotamine did not act by releasing noradrenaline (OSSWALD

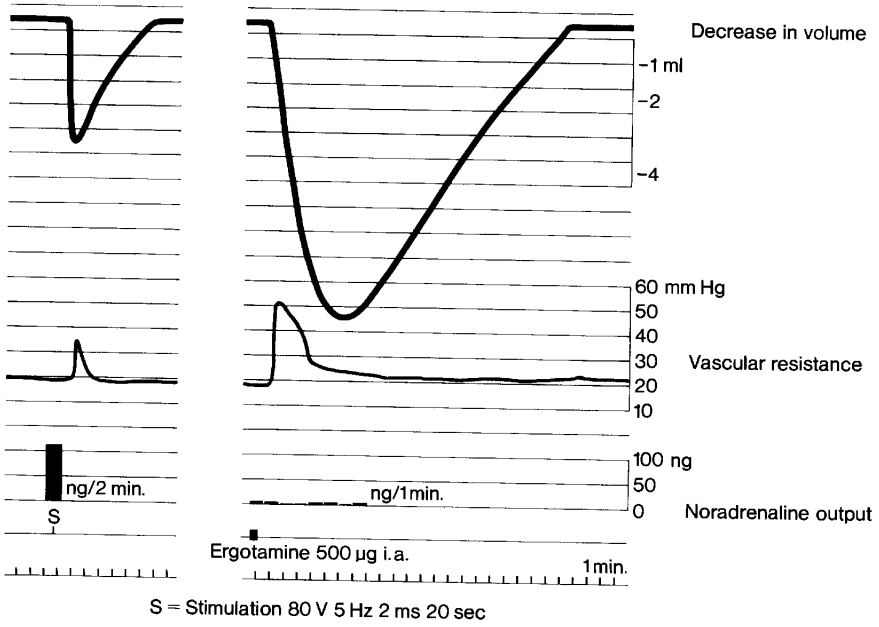


Fig. 26. The effect of ergotamine on the isolated perfused spleen of the cat. Ergotamine, 500 μg i.a., causes strong contraction of the trabecular muscles (volume reduction of the spleen) and vasoconstriction (increase of vascular resistance in the organ). This effect is more pronounced with ergotamine than with supramaximal sympathetic nerve stimulation. In contrast to nerve stimulation, ergotamine causes no noradrenaline release. [From Figure 4, SALZMANN, R. (et al.): Naunyn Schmiedebergs Arch. Pharmacol. **261**, 366 (1968)]

et al., 1970). Likewise, there was no evidence that the vasoconstrictor activity of methysergide in the isolated perfused auricular artery of the rabbit was accompanied by catecholamine release, because here too reserpine pretreatment failed to antagonize the responses (FOZARD, 1973b). In dog saphenous vein strips, 3×10^{-5}M cocaine caused a 6-fold potentiation of the responses to noradrenaline and a ca. 20-fold inhibition of responses to tyramine, whereas dose-response curves for ergotamine were unaffected, thus providing further evidence against noradrenaline release by ergotamine (MÜLLER-SCHWEINITZER, 1974a).

Dihydroergotamine increased plasma concentrations of free fatty acids in normal and adrenalectomized dogs. Pretreatment of dogs with reserpine did not reduce this response to dihydroergotamine (SCRIABINE et al., 1968). Dihydroergotamine had no significant effect on the outflow of [^{3}H]noradrenaline from canine subcutaneous adipose tissue (FREDHOLM and ROSELL, 1970).

There is some indirect evidence that D-LSD can release noradrenaline from sympathetic nerve endings: GILLESPIE and MCGRATH (1974, 1975) showed that contractions of isolated rat anococcygeus muscle and rat vas deferens in response to tyramine, guanethidine and D-LSD were abolished by 6-hydroxydopamine, which destroys sympathetic nerve terminals, while responses to noradrenaline were enhanced. On the other hand, AMBACHE et al. (1975) reported that reserpine pretreatment failed to antagonize D-LSD responses in the rat anococcygeus.

In rabbits some decrease of noradrenaline concentration was found after 150–175 µg/kg i.v. D-LSD in liver, lung, kidney and heart, but not in spleen (SANKAR et al., 1964).

b) Depletion of Noradrenaline From Brain

Effects on the release of central neurotransmitters have been reported for several psychotropic drugs; it is suggested that the release may contribute to the influence of these compounds on behavior. Several authors have described a release of noradrenaline from the brain by D-LSD and related compounds (ANDÉN et al., 1968; FREEDMAN, 1963; LEONARD and LISKA, 1971; SANKAR et al., 1964, 1969; STOLK et al., 1974; SUGRUE, 1969).

Experiments by FREEDMAN (1963) have shown that D-LSD (1.3 mg/kg) decreased noradrenaline concentrations in whole rat brain by about 20%. A fall in noradrenaline concentrations was also observed after 1.6 mg/kg of ALD (1-acetyl-lysergic acid diethylamide). Likewise, noradrenaline levels in rat brains were decreased by 0.2 mg/kg i.p. D-LSD (LEONARD and LISKA, 1971) and 1.3 mg/kg D-LSD (STOLK et al., 1974). After tyrosine hydroxylase inhibition, D-LSD increased the rate of depletion of intraneuronal noradrenaline in the brain of rats (ANDÉN et al., 1968). According to investigations of SUGRUE (1969), administration of 1 mg/kg i.p. D-LSD did not significantly lower the noradrenaline content of the hypothalamus in rats; a significant fall was observed, however, after 2 mg/kg D-LSD. SANKAR et al. (1964) found that D-LSD decreased the noradrenaline concentration in brain tissues of rabbits (cerebrum, cerebellum, stem, rest of brain).

No correlation was demonstrated between the changes in the noradrenaline content of the rat hypothalamus and the alterations in behavior induced by D-LSD (SUGRUE, 1969). According to SUGRUE, excitation induced by D-LSD is not mediated

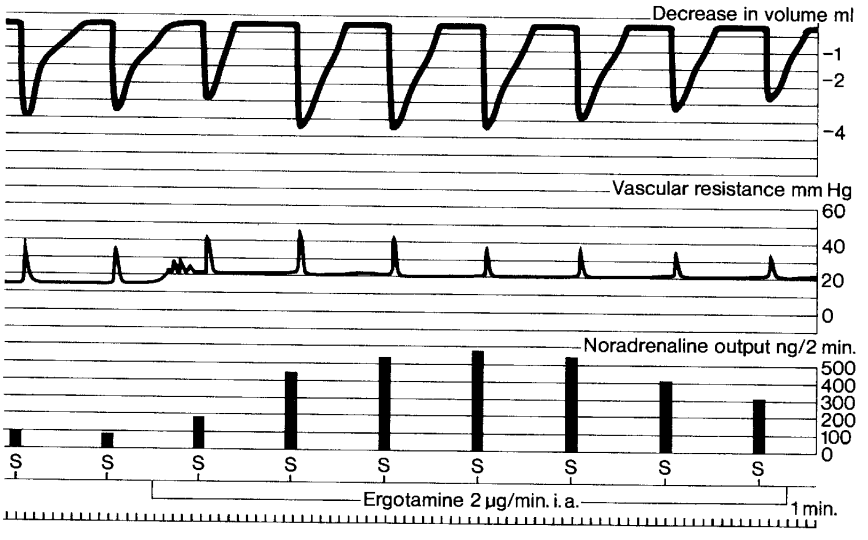
through the release of noradrenaline and may be due to a direct stimulation of central α-adrenoceptors by D-LSD.

No evidence of a noradrenaline depleting action of D-LSD in the central nervous system is provided by findings of NG et al. (1970). D-LSD (10^{-4}M) failed to produce any change in release of [^{3}H]noradrenaline in vitro in rat brain slices. Likewise, BOL-148 was without effect on noradrenaline concentrations in rat brain (FREEDMAN, 1963) and rat hypothalamus (SUGRUE, 1969).

3. Effects of Ergot Alkaloids on Noradrenaline Release and Theories on the Mechanism of Noradrenaline "Overflow"

Many authors have shown that the outflow of neuronally released noradrenaline is increased by α-adrenoceptor blocking agents, including ergot alkaloids.

Spleen. Most investigations of the effect of ergot compounds on the release of noradrenaline from sympathetic nerve terminals were carried out on the cat spleen in situ or the isolated perfused cat spleen. The early observation by BROWN and GILLESPIE (1957) that phenoxybenzamine elevated the output of transmitter was extended to dihydroergotoxine mesylate and other α-blocking agents by BROWN et al. (1961). An increased noradrenaline content in the cat spleen perfusate after nerve stimulation was also described for ergotamine (BERDE, 1971, 1972; PACHA and SALZMANN, 1970; SALZMANN et al., 1967, 1968; SALZMANN and PACHA, 1968, 1976) (Fig. 27), dihydroergotamine (BERDE, 1971, 1972; PACHA and SALZMANN, 1970; SALZMANN and PACHA, 1968, 1976), 1-methyl-ergotamine (BERDE, 1971, 1972;



S = Stimulation 80 V 5 Hz 2 ms 20 sec

Fig. 27. The effect of ergotamine on the response of the isolated perfused spleen of the cat to sympathetic nerve stimulation. Ergotamine (2 µg/min), reinforces volume contraction and vasoconstriction of the spleen and distinctly increases noradrenaline release in the venous output consequent to sympathetic nerve stimulation. [From Figure 6, SALZMANN, R. (et al.): Naunyn Schmiedebergs Arch. Pharmacol. **261**, 370 (1968)]

PACHA and SALZMANN, 1970; SALZMANN and PACHA, 1976), methysergide (SALZMANN and PACHA, 1976) and dihydroergotoxine mesylate (BERDE, 1971, 1972; BLAKELEY et al., 1963; BROWN, 1965; CRIPPS and DEARNALEY, 1971, 1972; PACHA and SALZMANN, 1970). The most pronounced increases were found with drug infusion rates between 0.5 and 10 μg/min. Quantitatively, dihydroergotamine, 1-methylergotamine and dihydroergotoxine mesylate caused a larger increase of noradrenaline release than ergotamine (BERDE, 1971, 1972; SALZMANN and PACHA, 1968; PACHA and SALZMANN, 1970).

The individual components of dihydroergotoxine mesylate, namely dihydroergocornine, dihydroergocristine and dihydroergokryptine, show the same effects (increase of noradrenaline outflow and α-adrenoceptor blockade) as dihydroergotoxine mesylate (PACHA and SALZMANN, 1970).

There is also evidence from other isolated organs, such as heart and vas deferens, that an increased outflow of neuronally liberated noradrenaline is brought about by ergot compounds.

Heart. STARKE (1972) found that noradrenaline release from the isolated rabbit heart following sympathetic nerve stimulation was enhanced by dihydroergotamine (2×10^{-7}), although the uptake of exogenous noradrenaline was not affected up to 6×10^{-6} of dihydroergotamine. In experiments with isolated guinea-pig atria the [^{3}H]noradrenaline efflux in response to sympathetic nerve stimulation was increased more than 2-fold by 10^{-5}M dihydroergotamine (MCCULLOCH et al., 1972). According to RAND et al. (1975), this concentration of dihydroergotamine is optimal for increasing stimulation-induced efflux. Dihydroergotamine was, however, less effective than either phenoxybenzamine or phentolamine. It is interesting that dihydroergotoxine mesylate (3×10^{-7}) further enhanced the effect of cocaine and desipramine on nerve stimulation-induced noradrenaline efflux in the isolated rabbit heart (STJÄRNE and WENNMALM, 1971; WENNMALM, 1971a, b).

Vas deferens. Dihydroergotoxine mesylate (10^{-7}) increased the efflux of [^{3}H]-noradrenaline from the electrically stimulated vas deferens of the guinea-pig by 125%. After pharmacologic blockade of neuronal and extraneuronal uptake of noradrenaline, and after inhibition of local prostaglandin formation, dihydroergotoxine mesylate remained effective in increasing outflow of [^{3}H]noradrenaline in response to transmural stimulation (HEDQVIST, 1973, 1974).

Different explanations have been given for the effects of ergot compounds on the release and overflow of noradrenaline.

a) Occupation of α-Adrenoceptors

In 1957, BROWN and GILLESPIE studied the output of noradrenaline resulting from postganglionic sympathetic nerve stimulation in the venous blood of the spleen of anesthetized cats. They showed that at frequencies of stimulation below 10/sec no noradrenaline could be detected; with increasing frequency of stimulation the output per stimulus increased, reaching a maximum at about 30/sec. The amount of transmitter in the venous blood was not affected by substances inhibiting monoamine oxidase, such as iproniazid (isopropylisonicotinyl hydrazine, Marsilid) at either frequency. The noradrenaline overflow in the venous blood could be altered

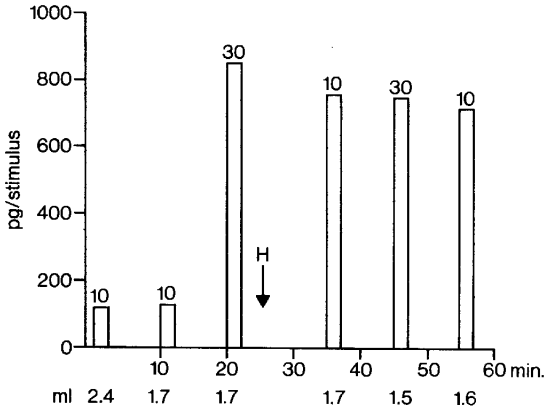


Fig. 28. Output of noradrenaline from the spleen of the cat in response to trains of 200 stimuli to the splenic nerve. The figures at the top of each block indicate the frequency of stimulation. The plasma volume of each sample is given below the abscissa. Between the third and fourth samples dihydroergotoxine mesylate (0.5 mg/kg) was given by intravenous injection. [From Figure 3, BROWN, G.L. (et al.): J. Physiol. (Lond.) **159**, 369 (1961)]

by administering the α-adrenoceptor blocking agents dibenamine and phenoxybenzamine; these drugs greatly increased the output of transmitter.

The authors suggested that noradrenaline liberated from nerve endings is inactivated after combination with α-adrenoceptors. According to this hypothesis, only small quantities of noradrenaline appear in the circulation with low stimulation rates, because the receptor is capable of combining with and/or destroying most of it; at high frequencies of stimulation increasing amounts of noradrenaline overflow into the circulation, because the receptor mechanism is saturated. A similar effect, namely increased noradrenaline release, results from blockade of tissue receptors by α-adrenoceptor blocking agents. The findings of BROWN et al. (1961) that dihydroergotoxine mesylate (0.5 mg/kg i.v.) raised the output of noradrenaline in the venous blood at 10 Hz to that of 30 Hz (Fig. 28) was explained by this theory of receptor occupation, namely that α-adrenoceptors are involved in the inactivation of the neuronally released transmitter from spleen (BROWN and GILLESPIE, 1957; KIRPEKAR and CERVONI, 1963). With dihydroergotoxine mesylate (0.5 mg/kg i.v.), recoveries of infused noradrenaline into the arterial blood supply of the cat spleen increased from 29% (controls) to 61% (GILLESPIE and KIRPEKAR, 1965a, b). The authors assumed that reincorporation of transmitter into the nerve endings might be the most important mechanism removing noradrenaline; they suggest that tissue receptors may play an important part in the reincorporation of transmitter into the nerve endings, acting as a "brake" on the diffusion away from the nerve endings.

Later, THOENEN et al. (1964a, b) found that the ability of the α-adrenoceptor blocking agents phenoxybenzamine, phentolamine and azapetine to increase the noradrenaline outflow after electrical stimulation of the splenic nerves of cats varied considerably from drug to drug. There was no correlation between the intensity of the α-adrenoceptor blocking effect and the increase in noradrenaline output. Likewise, results with ergotamine, dihydroergotamine, 1-methylergotamine

and dihydroergotoxine mesylate on the isolated perfused cat spleen showed that a marked increase of the release of neuronally liberated noradrenaline can be produced by ergot alkaloids, which possess relatively little postsynaptic α-blocking activity (BERDE, 1971, 1972; PACHA and SALZMANN, 1970). These findings are evidence against the view of BROWN and GILLESPIE (1957) that the increased noradrenaline output is caused by blockade of post-synaptic α-adrenergic receptors. THOENEN et al. (1964a, b) postulated a dual site of action of α-adrenergic blocking agents at the peripheral sympathetic synapse of the cat's spleen: Blockade of α-adrenergic receptors and inhibition of re-uptake of neuronally released noradrenaline.

b) Inhibition of Noradrenaline and Adrenaline Uptake

Uptake mechanisms. The major mechanism of physiological inactivation of noradrenaline is an uptake process of noradrenaline either into the postganglionic sympathetic neurones or into extraneuronal sites. The neuronal uptake of noradrenaline has been referred to as uptake$_1$ (IVERSEN, 1965, 1967, 1973). This uptake and inactivation process involves a transport of noradrenaline and related amines from the extracellular space through the axonal membrane of sympathetic nerves and from the axoplasm into storage vesicles. The uptake$_1$ process is saturable and has a very high affinity for noradrenaline. Other amines related to noradrenaline can also act as substrates for this uptake. It is known that 75–80% of the released transmitter noradrenaline is normally removed by the uptake$_1$ mechanism into the sympathetic nerve endings (IVERSEN, 1973).

A second uptake process for catecholamines in the isolated perfused rat heart was discovered by IVERSEN (1965) and was called uptake$_2$. In this process catecholamines are taken up by a different transport system into various extraneuronal peripheral tissues. Uptake$_2$ operates mainly at high perfusion concentrations of noradrenaline, but it can also operate at low concentrations of catecholamines together with uptake$_1$. Physiologically, uptake$_2$ may play some role in terminating the actions of noradrenaline in sympathetically innervated tissues, but it seems to play a minor role compared with uptake$_1$.

Uptake$_1$ is inhibited by structural analogues of noradrenaline and by many other drugs, such as tricyclic antidepressants, local anesthetics, adrenoceptor blocking agents, etc. (IVERSEN, 1967). Inhibitors of uptake$_2$ are in part different from those of uptake$_1$, including for instance steroids, phenoxybenzamine and metanephrine (IVERSEN, 1973). An inhibition of noradrenaline uptake has also been described for ergot alkaloids.

Spleen. In slices of cat spleen incubated with dl-noradrenaline-7[^{3}H], ergotamine (10^{-6}M) inhibited the uptake of noradrenaline by 30% (DENGLER et al., 1961). The increased outflow of neuronally liberated noradrenaline in the perfusate of the isolated cat spleen during infusions of ergotamine, dihydroergotamine, 1-methylergotamine and dihydroergotoxine mesylate (SALZMANN et al., 1967; SALZMANN and PACHA, 1968; SALZMANN et al., 1968; PACHA and SALZMANN, 1970; BERDE, 1971, 1972; SALZMANN and PACHA, 1976) was explained by inhibition of re-uptake of noradrenaline into the nerve endings. The finding that the enzymatic breakdown of noradrenaline was not inhibited by ergotamine (SALZMANN et al.,

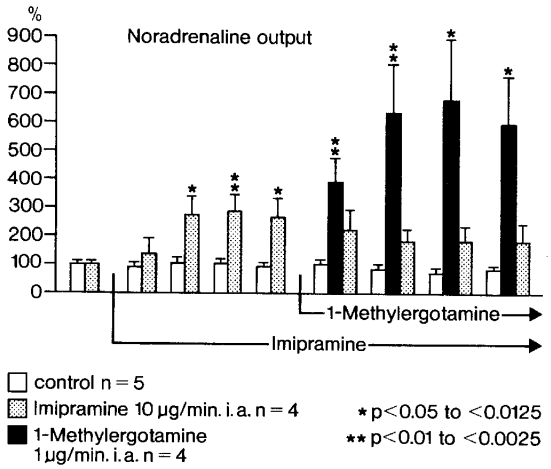


Fig. 29. The effect of imipramine and a combination of imipramine and 1-methylergotamine on noradrenaline output after nerve stimulation in the isolated perfused cat spleen. The heights of the columns indicate the values (mean + SEM) attained by a parameter on nerve stimulation, expressed as a percentage of the response to the first stimulation (first stimulation = 100%). The column groups show the responses of control and test preparations to successive stimulus trains given at 10 min intervals. [From Figure 8, SALZMANN, R., PACHA, W.: Postgrad. Med. J. **52** (Suppl. 1), 30 (1976)]

1968) further supported this interpretation. However, more recent results have shown that inhibition of catecholamine uptake cannot fully explain the action of ergot alkaloids on noradrenaline output from the spleen. When noradrenaline outflow from the spleen was maximally increased by blocking noradrenaline reuptake by imipramine or desmethylimipramine, dihydroergotamine and 1-methylergotamine were able to raise the noradrenaline overflow still further (SALZMANN and PACHA, 1976) (Fig. 29). Thus, a further mechanism may be involved in the increase of noradrenaline outflow by ergot compounds.

During studies in the isolated blood-perfused cat spleen CRIPPS and DEARNALEY (1972) found that dihydroergotoxine mesylate (ca. 10^{-5}M) raised the noradrenaline output in response to electrical stimulation of the splenic nerve. When uptake processes 1 and 2 were blocked in cat spleen with cocaine (2×10^{-5}M) and normetanephrine (10^{-4}M), a further increase in noradrenaline overflow occurred with 10^{-5}M dihydroergotoxine mesylate (CRIPPS and DAERNALEY, 1971, 1972) (Fig. 30). The authors consider it improbable that any of the known uptake mechanisms in the spleen [uptake$_1$ and uptake$_2$, uptake processes into collagen and connective tissue, uptake into endothelial cells (GILLESPIE et al., 1970)] could be responsible for the effect of dihydroergotoxine mesylate. Two possible explanations given of the increased noradrenaline overflow after application of dihydroergotoxine mesylate were that a further site of uptake of noradrenaline which is blocked by dihydroergotoxine mesylate might exist and/or that α-adrenoceptor blocking agents may facilitate the release of transmitter from the nerve endings.

Splenic nerve granules. An interaction of ergot alkaloids with uptake of noradrenaline in bovine splenic nerve granules has been observed by EULER and

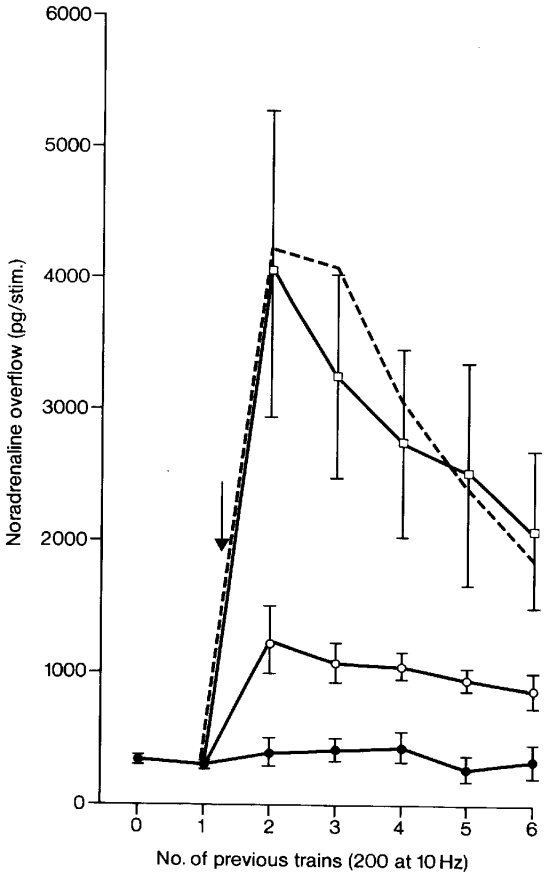


Fig. 30. Effect of blocking α-adrenoceptors and uptake processes. Mean noradrenaline overflow from the isolated spleen at successive trains of 200 stimuli at 10 Hz given at 10 min intervals. ● = no drug; ○ = cocaine (1 mg) + normetanephrine (2 mg); □ = cocaine (1 mg) + normetanephrine (2 mg) + dihydroergotoxine mesylate (0.6 mg); --- = phenoxybenzamine (5 mg). Drugs were given at the arrow. Bars = SEM, n = 4. The SEM after phenoxybenzamine were (in order) ± 737, 137, 156, 326 and 227 pg/stim. (n = 4). [From Figure 7, CRIPPS, H., DAERNALEY, D.P.: J. Physiol. (Lond.) **227**, 656 (1972)]

LISHAJKO (1966, 1968), STJÄRNE and LISHAJKO (1966) and EULER (1970, 1972). Dihydroergotoxine mesylate (2×10^{-5} M) inhibited the uptake of noradrenaline in partially depleted bovine splenic nerve granules in the presence of ATP-Mg (EULER and LISHAJKO, 1966). Dihydroergotoxine mesylate (3×10^{-5} M) and dihydroergotamine (3×10^{-5} M to 3×10^{-4} M) exerted an inhibitory action on the reuptake of [^{3}H]labeled noradrenaline (EULER and LISHAJKO, 1968). The highest activity among several α-blocking agents was shown by dihydroergotamine (EULER and LISHAJKO, 1968; EULER, 1970). STJÄRNE and LISHAJKO (1966) found that dihydroergotoxine mesylate at a concentration sufficient to inhibit strongly the transport mechanism responsible for spontaneous noradrenaline release during incubation

in vitro, blocked noradrenaline uptake only moderately and did not affect the mechanism transporting dopamine to the β-hydroxylation site.

Heart. Dihydroergotamine, in concentrations of up to 6×10^{-5}, did not interfere with the uptake of exogenous noradrenaline in the isolated rabbit heart (STARKE, 1972) but enhanced the output of noradrenaline in response to sympathetic nerve stimulation at a concentration of 2×10^{-7}. The results were explained by an α-adrenoceptor-mediated feedback inhibition of noradrenaline liberation (STARKE, 1972; cf. part 3,c of this section).

Brain. D-LSD (10^{-8} to 10^{-6}M) did not cause inhibition of the uptake of radioactively labeled noradrenaline in slices of cat cortex (DENGLER et al., 1961). D-LSD (10^{-5}M) did not inhibit noradrenaline uptake into rat striatal, cortical, and hypothalamic synaptosomes, whereas ergotamine ($1–2 \times 10^{-5}$M) inhibited the uptake noncompetitively (TUOMISTO, 1974).

Reflex vasodilatation. WELLENS et al. (1970) found no modification of noradrenaline uptake in the dog hind leg after ergotamine and suggested that the inhibition of reflex vasodilatation by ergotamine occurs in the absence of an inhibitory effect on noradrenaline uptake in tissues.

Blood platelets, erythrocytes. BORN (1967) and BORN and SMITH (1970) demonstrated that the immediate uptake of [^{3}H]adrenaline in human blood platelets was partly inhibited by dihydroergotamine. This drug inhibited adrenaline-induced aggregation and the adrenaline potentiating effect on ADP aggregation in human blood platelets (BORN et al., 1967a). In search of a possible correlation between adrenaline-induced aggregation of rabbit blood platelets and uptake of adrenaline by platelets, BARTHEL and MARKWARDT (1975) studied the effects of dihydroergotamine (10^{-11} M) and BOL 148 (3×10^{-6} M) on these reactions. While adrenaline-induced aggregation of blood platelets was completely inhibited by dihydroergotamine and BOL-148 (BARTHEL and MARKWARDT, 1974, 1975) (Fig. 31), there were no significant differences in [^{14}C]adrenaline uptake of the experimental samples compared with nontreated controls. BARTHEL and MARKWARDT (1975) drew the conclusion that the adrenaline-induced aggregation of rabbit blood platelets is not associated with the uptake of this amine.

In human erythrocytes, noradrenaline was taken up at slow rates proportional to the concentration of the amine in the medium up to 1.6×10^{-5}. BOL-148 did not diminish the uptake of noradrenaline (BORN et al., 1967b).

c) Blockade of Prejunctional α-Adrenoceptors

Several authors have postulated the presence of α-adrenoceptors in adrenergic nerve endings, suggesting that noradrenaline released by nerve stimulation acts on these presynaptic or prejunctional α-adrenoceptors to inhibit its own release. These receptors thus mediate an endogenous negative feedback mechanism (FARNEBO and HAMBERGER, 1971a; KIRPEKAR and PUIG, 1971; STARKE, 1972; STARKE and MONTEL, 1973; RAND et al., 1975; LANGER et al., 1975). Alpha-adrenoceptor blocking drugs enhance noradrenaline release from stimulated tissues, because the presynaptic α-adrenoceptors are occupied and the feedback mechanism blocked.

Facilitation of noradrenaline release by blockade of presynaptic α-adrenoceptors was considered for the interpretation of the increased noradrenaline outflow after

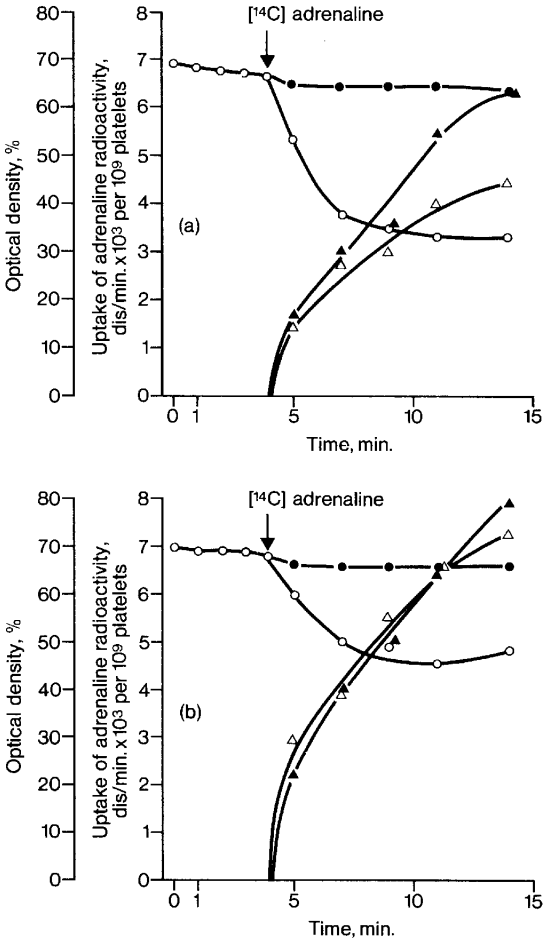


Fig. 31. Aggregation of rabbit blood platelets in TRIS-buffered Tyrode's solution (pH 7.4, 22–24°) by 5×10^{-6} M [^{14}C]adrenaline and its uptake under the influence of (a) 10^{-11} M DHE; (b) 3×10^{-6} M BOL-148. Aggregation and [^{14}C]adrenaline uptake, resp., of the blood platelets in the absence (○, △) and in the presence of inhibitor (●, ▲). Each value represents the mean from five to eight experiments. For the sake of clarity standard deviations of the means have been omitted. [From Figure 1, BARTHEL, W., MARKWARDT, F.: Biochem. Pharmacol. **24**, 1903 (1975)]

the administration of dihydroergotamine in the isolated rabbit heart (STARKE, 1972) and in isolated guinea-pig atria (MCCULLOCH et al., 1972; RAND et al., 1975). Since inhibition of catecholamine uptake is insufficient to explain fully the action of ergot alkaloids on noradrenaline overflow from the isolated cat spleen (as previously explained), it seems likely that a blockade of presynaptic α-adrenoceptors is at least partly responsible for it (CRIPPS and DEARNALEY, 1972; SALZMANN and PACHA, 1976). HEDQVIST (1973, 1974) suggested that blockade of presynaptic α-adrenoceptors by dihydroergotoxine mesylate can remove a feedback mechanism for noradrenaline-release in the isolated guinea-pig vas deferens not mediated by

prostaglandins. This was postulated, since both re-uptake of released noradrenaline and generation of prostaglandin were inhibited by prior administration of desmethylimipramine, normetanephrine, and 5, 8, 11, 14-eicosatetranoic acid.

d) Other Possible Mechanisms of Stimulation of "Overflow" by Ergot Alkaloids

The finding that noradrenaline release is inhibited by prostaglandins of the E series (BRUNDIN, 1968; HEDQVIST, 1969; HEDQVIST and BRUNDIN, 1969; EULER and HEDQVIST, 1969; HEDQVIST et al., 1970; HEDQVIST and EULER, 1972) has led to the speculation that prostaglandins liberated during nerve stimulation play a role in a physiological feedback mechanism which modulates the release of noradrenaline from nerve endings (HEDQVIST and BRUNDIN, 1969; HEDQVIST 1970a, b). Substances which inhibit prostaglandin synthesis can therefore be expected to block the feedback mechanism, leading to increased noradrenaline release.

SALZMANN and PACHA (1976) studied the effects of ergotamine, dihydroergotamine, 1-methylergotamine and methysergide on the responses of the isolated per-

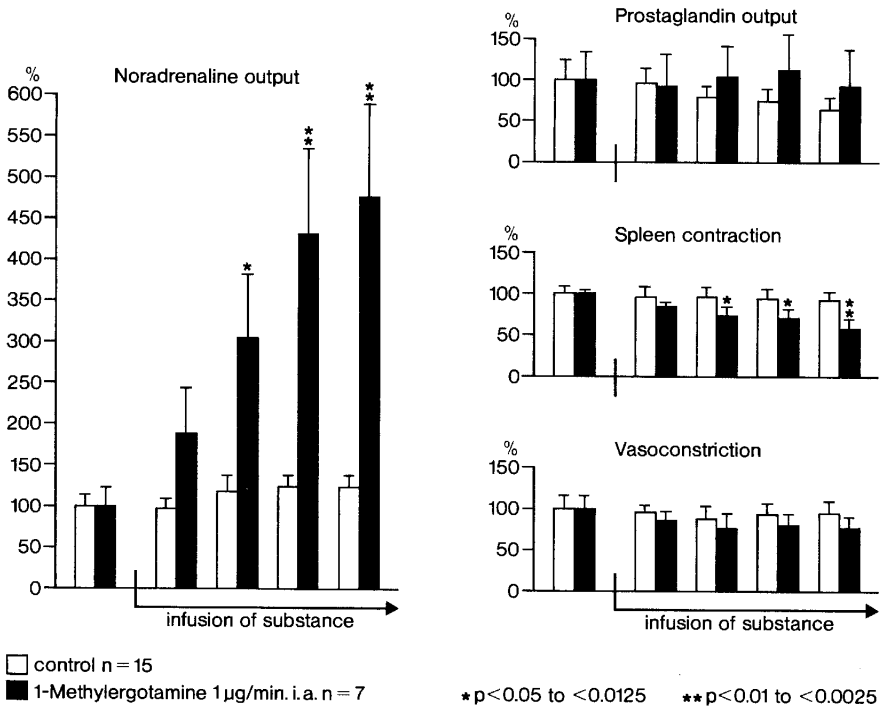


Fig. 32. The effect of 1-methylergotamine on the responses of the isolated perfused spleen of the cat to postganglionic sympathetic stimulation. The heights of the columns indicate the values (mean + SEM) attained by a parameter on nerve stimulation, expressed as a percentage of the response to the first stimulation (first stimulation = 100%). The column pairs show the responses of control and test preparations to successive stimulus trains given at 10 min intervals. [From Figure 3, SALZMANN, R., PACHA, W.: Postgrad. Med. J. **52** (Suppl. 1), 27 (1976)]

fused cat spleen (noradrenaline and prostaglandin efflux, spleen contraction and vasoconstriction) after postganglionic sympathetic nerve stimulation. The ergot alkaloids increased noradrenaline efflux while only slightly affecting prostaglandin outflow (Fig. 32), suggesting that antagonism of prostaglandin-mediated feedback-inhibition of noradrenaline release is probably not involved in the increased noradrenaline overflow brought about by ergot alkaloids.

Anticholinesterase activity. An alternative hypothesis to explain the increase of transmitter release was proposed by BOYD et al. (1960), who described anticholinesterase activity for adrenergic blocking agents. It was suggested that their effect in increasing noradrenaline release might be due to their action upon a cholinergic link in the sympathetic post-ganglionic nerves; but BLAKELEY et al. (1963) considered that the effect of dihydroergotoxine mesylate in increasing transmitter overflow in cat spleen cannot be attributed to an anticholinesterase action.

4. Effects of Ergot Alkaloids on the Responses of Organs to Stimulation of Their Sympathetic Innervation

The critical finding reported by DALE in his classical paper of 1906 was not simply the reversal by ergot alkaloids of the pressor response to adrenaline in the anesthetized cat but the parallelism between the effects of ergot on the responses to injected adrenaline and to stimulation of the sympathetic nerves of a whole variety of organs in situ. These organs comprised mainly a number of different smooth muscle preparations, and DALE's finding was that where the response to sympathetic nerve stimulation was a contraction, adrenaline mimicked these effects, and both responses were abolished or reversed by ergot alkaloids. Conversely, where the response to nerve stimulation was inhibitory, adrenaline also relaxed the smooth muscle, and neither effect was antagonized by ergot. Thus, although it was to be 20 years before the true nature of the events occurring at sympathetic nerve terminals was established, and over 40 years passed before AHLQUIST (1948) proposed the classification of α- and β-adrenoceptors, DALE had seen not only the effects of the blockade of α-adrenoceptors on responses to adrenaline but also on the responses of organs to stimulation of their sympathetic innervation.

To a very large extent, antagonism by ergot alkaloids of responses of organs to stimulation of their sympathetic innervation is adequately explained in terms of α-adrenoceptor blockade. There are however some qualifications of this statement which must be made. A disparity between observations of α-adrenoceptor blockade, as seen when exogenous catecholamines are used to stimulate α-adrenoceptors, and the blockade of responses to sympathetic nerve stimulation, lies in the finding that considerably higher concentrations of the blocking agent may be required to abolish the response to nerve stimulation. This is true as much for other types of α-adrenoceptor blocking drugs as for ergot derivatives. For example, BIRMINGHAM and WILSON (1963) found that in the isolated guinea-pig vas deferens preparation, the concentrations of dihydroergotamine (3×10^{-4}) and phentolamine (2×10^{-4}) necessary to abolish responses to field stimulation of the nervous elements, in addition to abolishing responses to noradrenaline, also reduced those to added acetylcholine and potassium chloride almost to zero. Similar results

were reported for ergotamine by BOYD et al. (1960). In cases such as this it is not justifiable to state categorically that the effect on the response to stimulation was due to blockade of α-adrenoceptors and not to a nonspecific depressive action. This resistance to blockade exhibited by nervously mediated stimuli when compared to exogenously administered neurotransmitters is not an uncommon phenomenon and is possibly accounted for by high local concentrations of the transmitter substance occurring in the junctional cleft between the nerve ending and the effector cell, and overcoming the block.

The historical importance of α-adrenoceptor blockade in the pharmacology of ergot has perhaps obscured some of the more subtle properties of ergot alkaloids and related compounds which have a bearing on adrenergic neuronal transmission. Inhibition by ergot alkaloids of responses to stimulation of adrenergic nerves is conveniently accounted for as being due to "α-block," and the possibility that other mechanisms may be involved in some situations has been understandably ignored. Recent publications have shown that some ergot-related compounds can indeed in certain circumstances inhibit adrenergic transmission by impairing the release of noradrenaline.

Vas deferens. D-LSD, which is practically devoid of α-adrenoceptor blocking activity, inhibits responses to electrical field stimulation of postganglionic nerves in desheathed (i.e., ganglion-free) vas deferens preparations from rats, mice, guinea-pigs, rabbits and gerbils (meriones shawii) without antagonizing motor responses to noradrenaline (AMBACHE et al., 1971, 1973a; HUGHES, 1973; GILLESPIE and MCGRATH, 1975). The effect of D-LSD is dose-dependent up to a maximally effective concentration of 10^{-7} g/ml (Fig. 33), rapid in onset (2–8 min) and slowly reversible on washing out the drug (recovery time > 1 h). The recovery time was prolonged by lengthening the contact time or raising the D-LSD concentration. The possibility that a tryptaminergic motor transmission might be involved was excluded by the findings of AMBACHE and ZAR (1971) that 5-HT failed to contract the guinea-pig vas deferens, and that the inhibitory effect of D-LSD was not shared by BOL-148 or by methysergide, both of which are more potent 5-HT-receptor blocking agents than D-LSD (CERLETTI and DOEPFNER, 1958b). In the guinea-pig and mouse vas deferens, the inhibitory effect of D-LSD was itself antagonized by the α-adrenoceptor blocking agent phentolamine and also by phenoxybenzamine, although the latter was considerably less effective (AMBACHE et al., 1973a; HUGHES, 1973; HUGHES et al., 1975). Both HUGHES (1973) and AMBACHE et al. (1973a) concluded that D-LSD might act by stimulating prejunctional α-adrenoceptors, thereby reducing the output of the sympathetic transmitter. This idea was supported by the demonstration that D-LSD inhibited the overflow of [^{3}H] label from the guinea-pig vas deferens on field stimulation after incubating the tissue with [^{3}H]noradrenaline or [^{3}H]tyrosine, an effect which was also antagonized by phentolamine (HUGHES, 1973) (Fig. 34).

The existence of a D-LSD resistant component of concentrations of the guinea-pig vas deferens evoked by field stimulation was reported by AMBACHE et al. (1973a). These authors found that the inhibitory effect of D-LSD was greater for short train lengths (< 10 pulses), and when the tissue was stimulated with trains of 20 pulses (10 Hz) there was practically no reduction of the response by D-LSD. GILLESPIE and MCGRATH (1975), using the vas deferens of the rat, confirmed

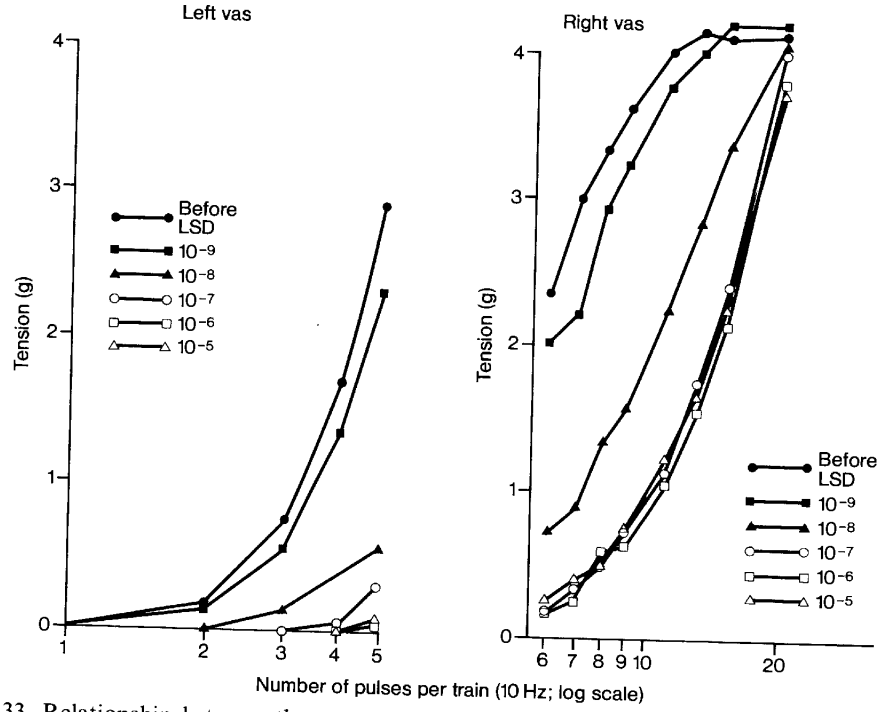


Fig. 33. Relationship between the concentration of D-LSD and the degree of inhibition of the susceptible component in the motor response to field stimulation of intramural nerves. Vasa deferentia from the same guinea-pig stimulated at 1 min intervals with trains of 1 msec pulses. Note increasing inhibition in the concentration range 10^{-9} to 10^{-7}g/ml with no further deepening of inhibition at 10^{-5} g/ml. The contribution of the D-LSD-resistant component to the motor response is insignificant with trains of <5 pulses but grows spectacularly between 5 and 20 pulses. [From Figure 3, AMBACHE, N. (et al.): J. Physiol. (Lond.) **231**, 257 (1973)]

that the motor response to nerve stimulation comprises two components: An initial twitch followed by a slow contraction. The twitch, which occurs at all train lengths—including sometimes even single pulse stimuli, is the component of the response which was inhibited by D-LSD. Longer train lengths (>20 pulses) evoke, in addition, the secondary slow contraction which was not affected by D-LSD in some experiments and in others was slightly potentiated. These effects were also seen in the vas deferens in situ in the pithed rat on i.v. injection of D-LSD.

In addition to D-LSD, ergometrine, methylergometrine, ergotamine, dihydroergotamine and ergocristine have all been reported to inhibit motor responses of the isolated guinea-pig vas deferens to sympathetic nerve stimulation (BOYD et al., 1960; BIRMINGHAM and WILSON, 1963; AMBACHE et al., 1973a). In the isolated vas deferens of the mouse, BENNETT and MIDDLETON (1975) described a significant decrease in the amplitude of the excitatory junction potential after 10^{-5} dihydroergocornine or dihydroergocristine. A comprehensive explanation of these effects in terms of simple α-adrenoceptor blockade is not tenable, since ergometrine and methylergometrine are only weak antagonists at α-adrenoceptors (Table 3). Further-

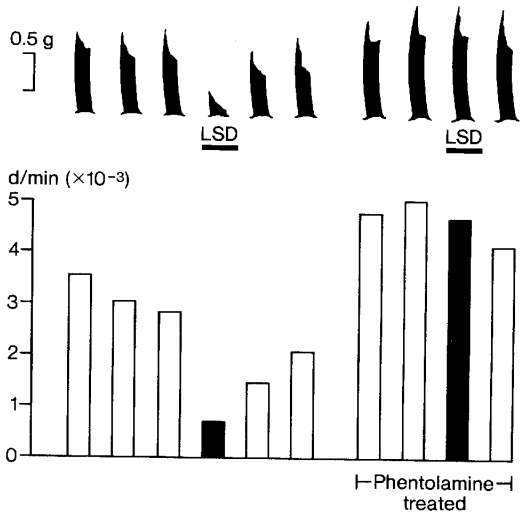


Fig. 34. Antagonism of D-LSD by phentolamine. Guinea-pig vas deferens labeled with [^{3}H]-noradrenaline and field-stimulated. Upper part: tension in the vas deferens during periods of stimulation. Lower part: increased levels of [^{3}H]-labeled material released into the bath during periods of stimulation in the absence (*white columns*) and presence (*black columns*) of D-LSD (50 ng/ml). For the experiments on the right-hand side, phentolamine (2 µg/ml) was present in the bathing solution. [From Figure 1, HUGHES, J.: Brit. J. Pharmacol. **49**, 707 (1973)]

more, AMBACHE et al. (1973a) reported that the inhibitory effect of dihydroergotamine was prevented by phentolamine. Therefore, it may be that dihydroergotamine, and possibly other ergot alkaloids, can inhibit the effects of sympathetic nerve stimulation in two ways, namely by exciting prejunctional α-adrenoceptors as well as by blocking postjunctional α-adrenoceptors.

Anococcygeus muscle. D-LSD inhibits responses to motor sympathetic nerve stimulation in rat and cat anococcygeus muscles without depressing noradrenaline contractions (AMBACHE et al., 1973b, 1975; GILLESPIE and MCGRATH, 1975). As is the case in the vas deferens, the inhibition by D-LSD was maximal with short trains and declined with longer trains of stimuli, indicating the existence of a D-LSD resistant component of the response. The D-LSD effect was dose-dependent and was antagonized by phentolamine. Unlike the guinea-pig vas deferens, the rat anococcygeus was contracted by 5-HT. However, the possible involvement of 5-HT as a transmitter substance would not explain the effect of D-LSD, because methysergide was considerably weaker than D-LSD in inhibiting motor transmission. Methysergide also suppressed contractions evoked by noradrenaline and acetylcholine in doses which did not block motor transmission. BOL-148 slightly inhibited the responses to nerve stimulation but also depressed noradrenaline contractions, indicating that it blocked α-adrenoceptors. Responses to acetylcholine were at the same time potentiated. Raising the concentration of BOL-148 slightly potentiated motor transmission, possibly by blocking prejunctional α-adrenoceptors. These results obtained by AMBACHE et al. (1975) using the rat anococcygeus are similar to those reported for the vas deferens of the guinea-pig (above), so

that the antagonism by D-LSD of motor transmission in both preparations may be due to the same mechanism, namely a reduction in transmitter output brought about by stimulation of prejunctional α-adrenoceptors. The possibility that prostaglandin release might be involved was excluded by experiments using indomethacin, which failed to reduce the effect of D-LSD. GILLESPIE and MCGRATH (1975) compared the action of D-LSD in the anococcygeus muscle of the cat with that of the adrenergic neurone blocking agent guanethidine, both of which not only inhibited motor responses to nerve stimulation but also contracted the muscle. Phentolamine antagonized this contractile response in both instances, but it was also prevented by pretreatment of the tissue with 6-hydroxydopamine, which destroys sympathetic nerve terminals. The contractile response is therefore probably due to release of sympathetic transmitter from the nerve terminals. The authors drew particular attention to the similarities between D-LSD and guanethidine, but it is as yet too early to be able to say whether these two drugs share a common site or mode of action on sympathetic motor nerves.

Other organs. AMBACHE et al. (1975) investigated the effects of D-LSD at a number of autonomic nerve-muscle junctions. Using electrical field stimulation to excite selectively the nervous elements in the tissues studied, they found that inhibition of transmission by an agonist action of D-LSD at prejunctional α-adrenoceptors was confined to the sympathetic junctions (rat anococcygeus, dog retractor penis and dog splenic capsule strips). In four of six experiments using the dog splenic capsule, however, D-LSD antagonized not only the responses to field stimulation but also those to administered noradrenaline, revealing a blocking action at postjunctional α-adrenoceptors in this preparation. The dog splenic capsule also was distinguished from the other two preparations in that it did not respond to high concentrations of D-LSD with outright contractions [an action attributed to release of noradrenaline from sympathetic nerve endings (GILLESPIE and MCGRATH, 1975)]. The absence of this response in the dog splenic capsule would be accounted for by the blocking action of D-LSD at postjunctional α-adrenoceptors in this preparation, although it was not established whether or not noradrenaline release was inhibited. At a parasympathetic nerve-muscle junction (longitudinal muscle of the guinea-pig ileum), no inhibition by D-LSD of responses to electrical field stimulation was observed. On the contrary, D-LSD, especially in high concentrations, potentiated the motor responses to electrical stimulation and to administered acetylcholine. This potentiation was attributed by the authors to blockade of prejunctional α-adrenoceptors. Evidence for the existence of such receptors on parasympathetic nerve endings was obtained using propranolol-treated guinea-pig ileum preparations in which noradrenaline powerfully antagonized responses to field stimulation without inhibiting contractions evoked by administered acetylcholine. Furthermore, this effect was antagonized by D-LSD, thus supporting the idea that both substances act at prejunctional α-adrenoceptors. At another parasympathetic nerve-muscle junction (rabbit rectococcygeus) (AMBACHE et al., 1975), both potentiation by D-LSD and inhibition by noradrenaline of the twitches evoked by field stimulation were observed. However, D-LSD did not antagonize the effect of noradrenaline, which was also obtained in the presence of propranolol. This finding contrasts with that made in the guinea-pig ileum and suggests that potentiation of transmission by D-LSD in the rabbit rectococcygeus might be

mediated by a site other than the prejunctional α-adrenoceptor. Such an alternative might be provided by a 5-HT receptor, in which case the potentiation might be regarded as a purely physical phenomenon (i.e., an increase in muscle tone without visible contraction, due to a partial agonist effect of D-LSD).

Effects on responses to nerve stimulation in whole animals. DREW (1976) recently published a method which allows a comparison of the effects of drugs on pre- and postjunctional α-adrenoceptors in a single preparation. The method is an extension of that described by GILLESPIE and MUIR (1967) and involves selective electrical stimulation of the cardiac sympathetic outflow in the pithed rat. Heart rate was maintained constantly elevated by continuous stimulation, while blood pressure was hardly affected. Agonist effects on postjunctional α-adrenoceptors were measured as elevations of blood pressure and actions on the prejunctional receptors by means of the fall in heart rate. The ratio of doses required to produce given magnitudes of effect on blood pressure and heart rate was determined for each of a number of substances. The results indicated D-LSD to be a highly selective stimulant of prejunctional α-adrenoceptors, more selective in fact than clonidine. The reduction in heart rate induced by D-LSD was antagonized by phentolamine but not by cyproheptadine. While such experiments are possessed of a certain elegance insofar as the comparison is drawn between two independent effects in the same preparation at the same time, the results cannot be regarded as furnishing a general rule; affinities of drugs to both pre- and postjunctional receptors must be expected to vary from one organ to another [cf. the blockade of postjunctional α-adrenoceptors by D-LSD in dog splenic capsule and of the prejunctional α-adrenoceptors in the guinea-pig ileum (AMBACHE et al., 1975)]. Furthermore, it is questionable whether the assumption that vasoconstrictor activity is due solely to postjunctional α-adrenoceptor stimulation is entirely justifiable, even in the pithed animal. In pithed cats an agonist effect of dihydroergotoxine mesylate at prejunctional α-adrenoceptors has been shown by SCHOLTYSIK (1975). Small i.v. doses of dihydroergotoxine mesylate dose-dependently inhibited the increases in heart rate evoked by electrical stimulation of spinal segments C_7 and T_1, and the effect was partly prevented by phenoxybenzamine. The same stimulus simultaneously contracted the nictitating membrane but here dihydroergotoxine mesylate did not affect the responses to stimulation up to a dose of 3.5 μg/kg i.v.

A number of papers not mentioned in this text, in which effects of ergot alkaloids on responses to nerve stimulation have been described are summarized in Table 8.

Table 8. Miscellaneous observations on the effects of ergot alkaloids on responses to nerve stimulation in various organ systems

Preparation, species, nerve stimulated	Observations, references. (The response to stimulation is muscle contraction except where otherwise stated)
Aorta (spiral strips) in vitro – rabbit, field stimulation	Dihydroergotamine (2×10^{-6}): 70% reduction in response. Dihydroergotoxine mesylate (2×10^{-6}): 50% reduction in response. Result complicated in both cases by partial agonist effect (1).

Table 8 (continued)

Preparation, species, nerve stimulated	Observations, references. (The response to stimulation is muscle contraction except where otherwise stated)
Penile artery (spiral strips) in vitro – bull, field stimulation	This preparation commonly possesses high spontaneous tone and relaxes in response to field stimulation. The relaxation is not affected by methysergide (10^{-7} to 5×10^{-6}), which itself induces contractions (2).
Portal vein (longitudinal strips) in vitro – rabbit, field stimulation	Ergotamine (5×10^{-7} to 5×10^{-6}) blocks contractions and raises tone, exposing a relaxant response (3,4). BOL-148 (10^{-7}) affects neither contractile nor relaxant responses (3).
Spleen (perfused) in vitro – cat, splenic nerve	Spleen contractions are only weakly antagonized by ergotamine infusions (> 1 µg/min i.a.) (5,6); more strongly by dihydroergotamine (0.1 to 100 µg/min i.a.) (7). Dihydroergotoxine mesylate (approx. 10^{-5} M) can also block the response (8). Order of potency for inhibition of contractions: dihydroergotamine > dihydroergotoxine mesylate > ergotamine > 1-methylergotamine (9).
Seminal vesicle in vitro – guinea-pig, hypogastric nerve	Dihydroergotoxine mesylate (3×10^{-6}) reduces responses by up to 40%. The same concentration of dihydroergotoxine mesylate abolishes responses to noradrenaline and partially antagonizes responses to ATP (10). A purinergic innervation has been postulated (11).
Retractor penis in vitro – bull, field stimulation	Ergotamine (5×10^{-6}) and methysergide (10^{-7} to 1.3×10^{-6}) evoke contractions, thereby revealing relaxation in response to stimulation (2).
Nictitating membrane in vivo – cat, cervical sympathetic nerve	Small doses of ergotamine (1 µg/kg i.v.) potentiate pre- and postganglionic stimulation; larger doses (> 5 µg/kg i.v.) inhibit (12). Ergotaminine is without effect (13). Ergotoxine antagonizes the response (14).
Submaxillary gland in vivo – rat, cervical sympathetic nerve	Duct constriction is abolished and secretion reduced by dihydroergotamine (0.5 to 1 mg/kg i.v.) (15).
Parotid gland in vivo – cat, cervical sympathetic nerve	Duct constriction is abolished by dihydroergotamine (0.5 to 1.5 mg/kg i.v.) but secretion is only slightly reduced (16).
Esophagus in vitro – chicken, vagus nerve	Contractions are not antagonized by methysergide (10^{-8}) (17).
Rectum in vitro – chicken, Remak nerve	Contractions are not antagonized by methysergide (10^{-8}) (17).
Swim bladder in vitro – cod (gadus morhua), field stimulation	Dihydroergotamine (10^{-5}) blocks contractions of the radial muscle (18).

References: 1. PATERSON (1965); 2. KLINGE and SJÖSTRAND (1974); 3. HUGHES and VANE (1967); 4. HUGHES and VANE (1970); 5. SALZMANN et al. (1967); 6. SALZMANN et al. (1968); 7. SALZMANN and PACHA (1968); 8. CRIPPS and DEARNALEY (1972); 9. PACHA and SALZMANN (1970); 10. NAKANISHI and TAKEDA (1973b); 11. NAKANISHI and TAKEDA (1973a); 12. SALZMANN and WEIDMANN (1966); 13. BACQ (1934b); 14. CANNON and ROSENBLUETH (1937); 15. THULIN (1974); 16. THULIN (1975); 17. BARTLET (1974); 18. NILSSON (1971).

5. Actions of Ergot Alkaloids at β-Adrenoceptors

There is no evidence for either stimulation or block of β-adrenoceptors by ergot compounds. In studies on the vascular bed of the anesthetized dog, ergotamine had no detectable agonistic or antagonistic actions on β-adrenoceptors, as shown by the absence of positive inotropic and chronotropic effects as well as by the failure of ergotamine to block the cardiostimulant, vasodilator and retractor penis-relaxing actions of isoprenaline (GUIMARÃES and OSSWALD, 1969; OSSWALD et al., 1970). These in vivo observations correlate well with those found in vitro, where ergotamine failed to block β-adrenoceptors in canine saphenous veins (GUIMARÃES and OSSWALD, 1969) and in isolated guinea-pig atria (OSSWALD and GUIMARÃES, 1962). Pretreatment of the isolated guinea-pig trachea with 1.5–15 μM dihydroergotamine diminished the maximum relaxation in response to isoprenaline, indicating that the antagonism by dihydroergotamine was noncompetitive and nonspecific (LEVY and WILKENFELD, 1970). In cultured rat astrocytoma cells an increase in the content of cAMP induced by both noradrenaline and isoprenaline can be blocked by β- but not by α-adrenoceptor blocking drugs. Preincubation of confluent cultures with 50 nM dihydroergotamine inhibited the stimulatory effect of noradrenaline on cAMP level, suggesting that in this experimental model dihydroergotamine presumably has some action at β-adrenoceptors (MAURER and GRIEDER, 1975).

The frog erythrocyte adenylate cyclase can also be activated by isoprenaline, adrenaline and noradrenaline in descending order of potency. Propranolol (5 μM) inhibited the isoprenaline effect, indicating the involvement of β-adrenoceptors. When dihydroergotamine was tested as antagonist, extremely high concentrations (50–500 μM) were necessary to inhibit the isoprenaline-induced stimulation of the frog adenylate cyclase. The inhibition by dihydroergotamine was of the noncompetitive type, suggesting an unspecific effect (CHAN and ELLENBOGEN, 1974). These findings are supported by the observation that in rat cerebral cortex slices, dihydroergotoxine mesylate antagonized stimulation of cAMP formation caused by noradrenaline but failed to inhibit that induced by isoprenaline (MARKSTEIN and WAGNER, 1975).

E. The Shape of Ergotamine and Dihydroergotamine in Relation to Their Interaction With α-Adrenoceptors

H.P. WEBER and T.J. PETCHER

From crystal structure determinations of a number of ergopeptins and *iso*ergopeptins (WEBER and PETCHER, 1976), certain conclusions may be drawn as to the preferred conformation of biologically active ergopeptins in solution and, by extension, at the biological receptor. The observed conformations of the potent molecules ergotamine and dihydroergotamine are presented in Figure 35, from which it is clear that, with the single exception of the D-ring conformation, the shapes of the two molecules are practically identical. This minor conformational difference between the molecules, although of negligible effect on the gross topography,

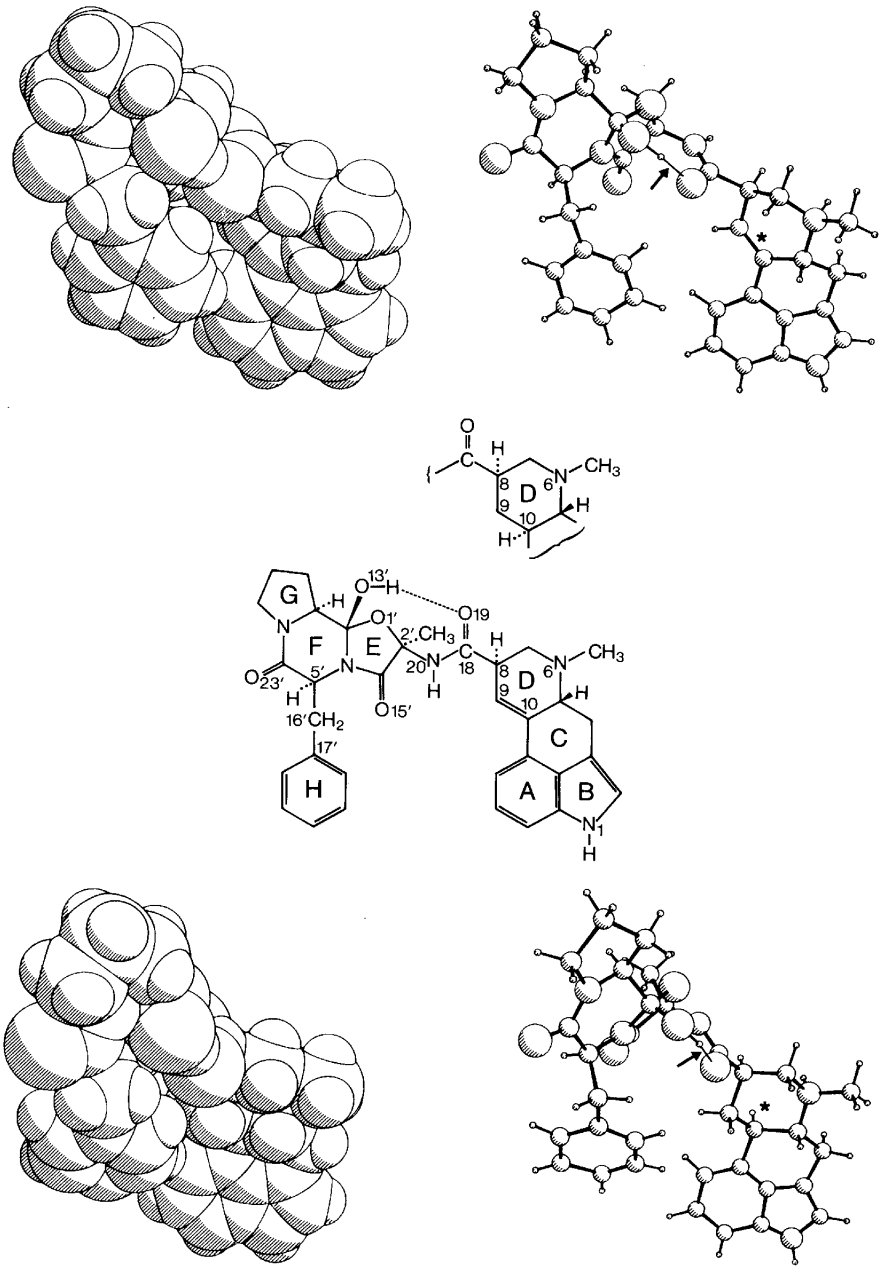


Fig. 35. Molecules of ergotamine and dihydroergotamine in the conformation observed in crystal structure determinations of their *para*bromobenzoate and hydrobromide salts respectively. Each molecule is shown in two representations, a space-filling, and a "ball and stick" model, respectively. The upper pair of diagrams are of ergotamine, the lower of dihydroergotamine. The *intra*molecular hydrogen bond discussed in the text is arrowed in both molecules, and the structural formula carries atom and ring labeling where mention is made of specific *intra*molecular rotations about single bonds. The double bond of ergotamine and the C(10) hydrogen atom of dihydroergotamine, discussed in the section on receptor binding, are labeled with asterisks for easy reference

must be responsible for the existing differences in biological activity between ergotamine and dihydroergotamine, namely: In α-adrenergic systems, dihydroergotamine has slightly greater affinity than ergotamine, but this latter is a more efficacious partial agonist. In the following paragraphs, an attempt is made to correlate these differences in the phenomenologic parameters "affinity" and "efficacy" with the observed structural differences and to explain the mode of interaction of biologically potent ergopeptins with the α-adrenergic receptor in physico-chemical terms.

Molecular flexibility of ergopeptins. It is clear from the molecular formulae of ergopeptins that the A/B/C- and the E/F-ring system (Fig. 35) each form a rigid molecular fragment. Apart from these fixed fragments, the molecules have in principle a fairly large number of degrees of conformational freedom, mainly rotations about formal single bonds, such as C(8)–C(18), N(20)–C(2′), C(5′)–C(16′), and C(16)–C(17′), together with pseudorotations in the two saturated rings D and G. From crystallographic studies of ergopeptins one may infer that much of this apparent flexibility is limited by various *intra*molecular forces. Prominent among these internal interactions is a strong *hydrogen bond* (Fig. 35) between the cyclol hydroxyl O(13′) and carboxyl oxygen O(19). Together with the invariably observed *trans* peptide bond C(18)–N(20), this hydrogen bond fixes the torsion angles around the single bond N(20)–C(2′) within a narrow range.

The proline ring G shows minor conformational variations in the different structures. The flexible benzyl group H, however, appears to be restricted to a certain orientation in four of the investigated structures, while another orientation is adopted in two other structures. It may be assumed that steric hindrance between neighboring atoms is responsible for this reduced flexibility. The major structural determinant is, however, the D-ring conformation, which is shown in Figure 36,

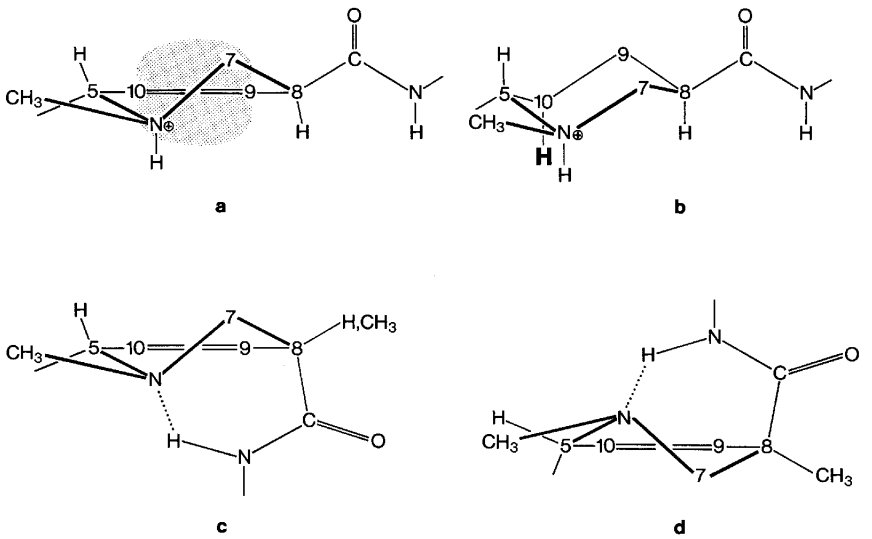


Fig. 36. The D-ring partial conformations of (a) ergotamine, (b) dihydroergotamine, (c) *iso*ergotamine and 8-methyl-*iso*-ergotamine, and (d) 8-methyl-ergotamine. The π-electron density cloud of the double bond is indicated in (a) and the C(10) hydrogen atom appears bold in (b). Note the entirely different conformations of (c) and (d) in comparison to (a) and (b)

for various ergopeptins. It may be seen that in the biologically active compounds ergotamine and dihydroergotamine, the amide group is *equatorial* to the D-ring, while in the biologically inactive forms this group is *axial* (and stabilized in this position by an internal hydrogen bond N(20)–H..N(6)). The torsion angles around C(8)–C(18) in the structures of ergotamine and dihydroergotamine fall in a rather narrow range, such that the plane of the amide group is roughly normal to the mean plane of the D-ring. This restricted rotation may be attributed to Van der Waals contacts between the atoms adjacent to the C(8)–C(18) bond.

Preferred conformation and receptor binding. The various factors discussed above, and the fact that one always observes the same conformational features in various *X*-ray crystal structure determinations in which the environments of the molecules studied are quite different, leads one to suggest that biologically active ergopeptins possess a preferred conformation which is faithfully represented in Figure 35. This conformation is likely to dominate the ensemble of solution conformers; in other words, this is the most likely shape of the molecule at the moment of approach to its receptor. The further passage of events at the receptor, such as mutual conformational change and production of the biological response, must, in the absence of direct evidence, remain matters for conjecture. A knowledge of the drug conformation, however, does enable one to speculate as to the nature of the interaction.

The structural differences between ergotamine and dihydroergotamine causing the known differences in biological activity must be sought in electronic and steric differences in the D-ring. The differences are small but obviously significant: Dihydroergotamine has a hydrogen atom projecting below the plane of the ring at C(10) in the same direction as the proton on N(6) where ergotamine has none; ergotamine has π-electron density at C(9)–C(10) where dihydroergotamine has none (Fig. 36).

It seems clear that the pharmacophore, or effector group of ergopeptins, is contained in the lysergic acid moiety, this molecular fragment exhibiting as it does "buried" catecholamine-like and 5HT-like segments (Fig. 37), which may explain why ergotamine and dihydroergotamine can react with both α-adrenoreceptors and 5-HT receptors. One may thus postulate the following binding areas for the pharmacophore, common to both ergotamine and dihydroergotamine:

(1) the indole nucleus
   - hydrogen bonding N(1)–H... receptor
   - π–π or hydrophobic interaction

(2) N(6), which is protonated at physiological pH
   - hydrogen bonding $N(6)^+$–H... receptor

One of these hydrogen bonds, N(6)–H..., is then directed below the plane of the lysergic acid fragment as drawn, while one, N(1)–H... is parallel to this plane.

Additionally, the peptide moiety seems intimately involved in α-antagonist activity: ergolines, for example, are not good α-blockers. Both ergotamine and dihydroergotamine exhibit high receptor affinity and both are long-acting. This has been thought to indicate "auxiliary binding"—which might loosely be attributed to the peptide part of ergot alkaloids. One obvious candidate to take part in a stereospecific binding of the peptide fragment to the receptor is the N(20)–H group, which maintains a constant orientation with respect to the lysergyl moiety,

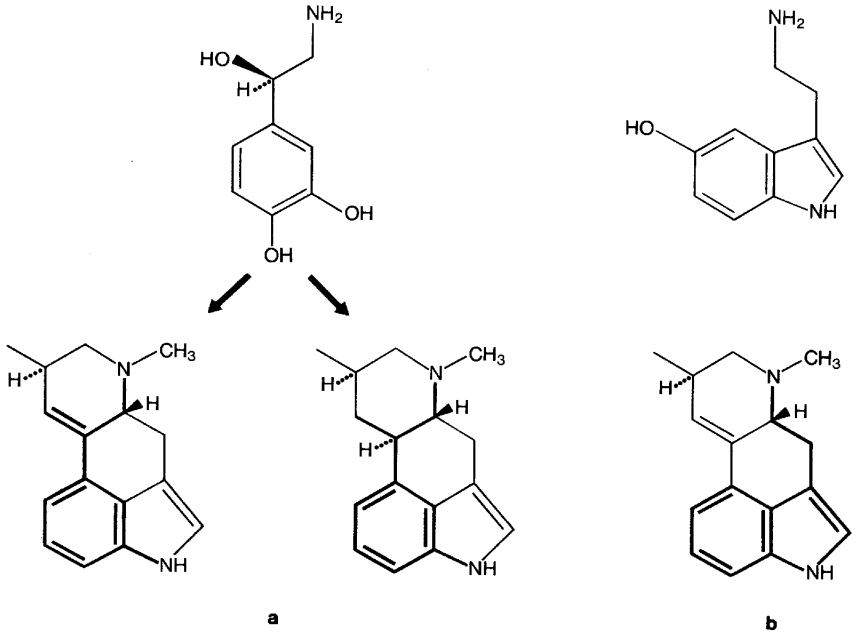


Fig. 37. The "buried" structural fragments of (a) noradrenaline and (b) serotonin in the lysergic acid skeleton. It may be seen that the important *meta*-hydroxyl group of the catecholamines comes into coincidence with N(1), an isosteric group, and that the absolute stereochemistry at the side chain α-carbon of noradrenaline is identical to that at C(10) of dihydroergotamine

and, like N(6)–H, is directed below the plane of this group. Whether one can, in fact, separate part of the total binding of a drug to its receptor and conveniently label this "auxiliary binding" is a moot point. Since, however, the peptide moiety is common to both ergotamine and dihydroergotamine and is in a similar spatial relationship to the lysergyl residue in both molecules, "auxiliary binding" sites are unlikely to contribute to *differences* in biological potency.

The differences between ergotamine and dihydroergotamine binding must therefore occur at the C(9)–C(10) position. In this area, the two molecules differ in both electronic structure and in conformation. If one superposes (–)-noradrenaline on the lysergic acid skeleton, one finds that the side chain hydroxyl group is approximately coincident with the double bond in ergotamine, and that the α-hydrogen atom of (–)-noradrenaline corresponds in position and absolute configuration to that of the C(10) hydrogen atom of dihydroergotamine. One may thus postulate that the greater efficacy of ergotamine is due to the presence of π-electron density of the C(9)–C(10) double bond, which mimics the lone pair electron density of the side chain hydroxyl group of (–)-noradrenaline. The greater affinity of dihydroergotamine might then be attributed to the presence of the C(10) hydrogen atom, which fits optimally into a receptor niche available for the corresponding hydrogen atom of (–)-noradrenaline.

F. Actions of Ergot Alkaloids at Acetylcholine Receptors

As far as is known, ergot alkaloids neither stimulate nor block receptors for acetylcholine. Observations suggesting that methysergide may cause release of acetylcholine by stimulating M-receptors in longitudinal muscle strips from human intestine are discussed in Section B, part 1, b, γ. Most reports describe enhancement of responses to cholinomimetic agents by ergot compounds. These experimental data are discussed in Section J.

G. Actions of Ergot Alkaloids at Histamine Receptors

There is no evidence that ergot alkaloids interact with histamine receptors at concentrations which elicit therapeutic effects. In the isolated guinea-pig ileum ergot compounds, such as ergotamine, dihydroergotamine, dihydroergocristine, dihydroergokryptine and dihydroergocornine, inhibit responses to histamine only when used at extremely high concentration (4–500 μM) (BIRCHER and SCHALCH, 1948; GADDUM and HAMEED, 1954; GADDUM and PICARELLI, 1957). Similarly high concentrations of dihydroergotoxine mesylate or ergotamine are required to antagonize the vasoconstrictor effect of histamine in bovine arteries (PICHLER et al., 1953) and in rabbit cerebral arteries (POLITOFF and MACRI, 1966), respectively. Compared to their α-adrenoceptor and 5-HT receptor blocking activities, these ergot alkaloids are more than 10,000 times less potent in antagonizing responses to histamine, and it can be assumed that this effect is nonspecific. Ergotamine (up to 650 ng/ml) does not prevent the histamine-induced rise in perfusion pressure in isolated rat lungs (BAKHLE and SMITH, 1972) or the histamine-induced bronchospasm in guinea-pigs (LOEW et al., 1946). Neither D-LSD nor methysergide inhibit histamine-induced bronchospasm (CERLETTI, 1955; HOLGATE and WARNER, 1960; KONZETT, 1956; SICUTERI et al., 1960). Absence of histamine antagonism has been further reported for D-LSD on isolated guinea-pig atria (TRENDELENBURG, 1960), for both D-LSD (KRIVOY, 1957) and methylergometrine (BIRCHER and SCHALCH, 1948) on the isolated guinea-pig ileum, for BOL-148 on isolated strips from rat stomach (VANE, 1957) and cat spleen (INNES, 1962b) and for methysergide on the guinea-pig vas deferens (KATSURAGI and SUZUKI, 1974). In man, methysergide does not antagonize the hypertensive action of histamine on the cerebrospinal fluid, though it effectively reduces the action of the histamine liberator 48/80 (SICUTERI et al., 1959).

H. Interaction of Ergot Alkaloids With Prostaglandins

1. Interference of Ergot Alkaloids With Endogenous Prostaglandin Synthesis

In certain canine veins peptide alkaloids, such as ergotamine and dihydroergotamine, have been shown to enhance endogenous prostaglandin synthesis. Evidence for this was provided by the observation that a canine vein strip, contracted by ergotamine or dihydroergotamine, required for its complete relaxation the com-

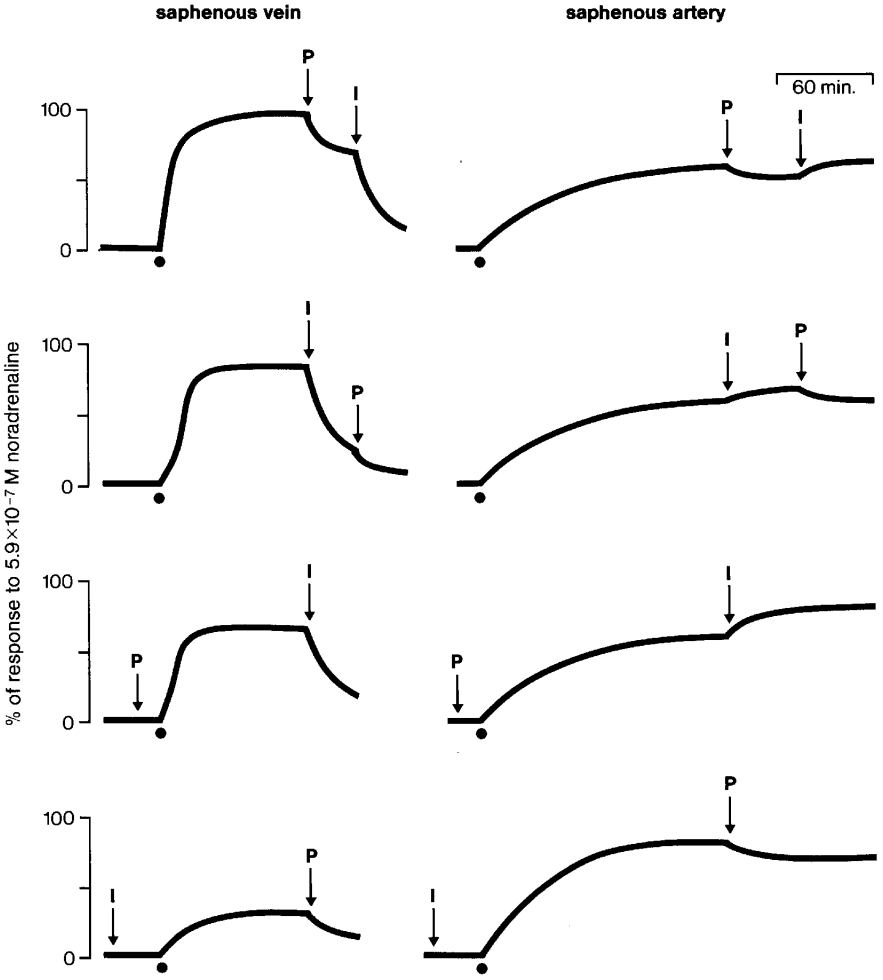


Fig. 38. Influence of phentolamine (*P*) and indomethacin (*I*) on dihydroergotamine-induced contractions in spiral strips from canine blood vessels. [From Figure 1, MÜLLER-SCHWEINITZER, E., BRUNDELL, J.: Europ. J. Pharmacol. **34**, 199 (1975)]

bined action of an α-adrenoceptor antagonist, phentolamine, and a drug which blocks endogenous prostaglandin synthesis, such as indomethacin (Fig. 38). Moreover, arachidonic acid, a prostaglandin precursor, was more effective in contracting vein strips in the presence of ergotamine or dihydroergotamine than in the presence of noradrenaline or potassium chloride or in control strips (MÜLLER-SCHWEINITZER, 1973, 1974a, b, c; MÜLLER-SCHWEINITZER and BRUNDELL, 1975a, b). Although a significant increase in the level of prostaglandin E-like activity in the bathing fluid occurred with both noradrenaline- and ergotamine-induced contractions, only the latter were decreased by indomethacin (MÜLLER-SCHWEINITZER and BRUNDELL, 1975a, b), indicating that in dogs the venoconstrictor responses to ergotamine and to dihydroergotamine are mediated at least partly by enhanced formation

of a vasoactive prostaglandin-like substance, possibly an intermediate of prostaglandin synthesis.

Enhancement of endogenous prostaglandin synthesis in venous smooth muscle cells by ergot alkaloids seems to be species-dependent, since it was not possible to repeat these observations either on human or on feline vein strips (MÜLLER-SCHWEINITZER, unpublished).

Contractions of canine saphenous arteries were also accompanied by formation of a prostaglandin-like material which, however, had opposite physiological effects. In arteries, indomethacin *enhanced* dihydroergotamine-induced contractions (Fig. 38) and arachidonic acid had *relaxant* activity. In contrast to the findings in veins, in canine arterial vascular smooth muscles endogenous prostaglandin synthesis was *not* significantly enhanced by dihydroergotamine (MÜLLER-SCHWEINITZER, 1974b; MÜLLER-SCHWEINITZER and BRUNDELL, 1975b). Ergotamine, dihydroergotamine, 1-methyl ergotamine and methysergide (1 μg/min) also failed to affect the prostaglandin output from the isolated perfused cat spleen induced by sympathetic nerve stimulation, and only a relatively high concentration (10 μg/min) of methysergide increased the prostaglandin output during sympathetic nerve stimulation (SALZMANN and PACHA, 1976). In isolated perfused rat lungs, where 5-HT has been shown to release prostaglandin-like material, methysergide (5–200 ng/ml) and ergotamine (650 ng/ml) alone failed to modify prostaglandin release (ALABASTER and BAKHLE, 1976; BAKHLE and SMITH, 1972, 1974a). In vitro, D-LSD slightly inhibited the conversion of 8,11,14-eicosatrienoic acid into prostaglandin E_1 by bovine seminal vesicles only when used at extremely high concentrations (372 μM) (BURNSTEIN et al., 1973).

In vivo, D-LSD (0.2 mg/kg i.p.) failed to induce changes in the level of prostaglandins in rat cerebral cortex (ZATZ and ROTH, 1975). These observations have been largely confirmed in cats using methysergide. In unanesthetized cats, injection of 5-HT into the rostral hypothalamus produced a biphasic response of body temperature of which the delayed and long-lasting hyperthermic phase could be abolished by pretreatment with indomethacin, indicating the involvement of endogenous prostaglandin synthesis. Methysergide attenuated the initial temperature increase but failed to reduce the secondary, by a sustained release of prostaglandin mediated, hyperthermia (KOMISKEY and RUDY, 1975).

2. Interference of Ergot Alkaloids With Prostaglandin Effects

On isolated canine saphenous veins, the potency of exogenous prostaglandin E_2 was significantly increased in the presence of dihydroergotamine, whereas on isolated canine saphenous arteries dihydroergotamine did not change the responses to prostaglandin E_2 (MÜLLER-SCHWEINITZER and BRUNDELL, 1975b). Methysergide failed to change the vasoconstrictor activity of prostaglandin $F_{2\alpha}$ on canine basilar arteries in vitro (ALLEN et al., 1974) and in vivo in dogs (NAKANO, 1968) and monkeys (WHITE et al., 1971a, b) and failed to prevent death induced by prostaglandin $F_{2\alpha}$ in mice (HARPER and SKARNES, 1972). D-LSD also failed to affect responses to both prostaglandin A_2 in the isolated guinea-pig ileum (STRACZOWSKI et al., 1974) and prostaglandin E_1 on isolated canine mesenteric arteries (STRONG and BOHR, 1967a, b).

In addition to various mediators, e.g., biogenic amines such as histamine and 5-HT, prostaglandins are involved in changes of vascular permeability during inflammation. In rats, inflammatory effects of locally injected prostaglandins E_1 and E_2 were partially reduced by pretreatment of the animals with methysergide (RICO et al., 1973; GYIRES and KNOLL, 1975; CRUNCKHORN and WILLIS, 1971). Since methysergide is a potent 5-HT antagonist, it is likely that its effect in these experiments was due to inhibition of responses to 5-HT released by prostaglandins (CHAHL and LADD, 1976).

There is evidence that in some tissues prostaglandin E_1 interacts with structures of the cell membrane functionally related to the 5-HT D-receptors. Thus, when canine tracheal rings were made to contract by 5-HT, 8 ng/ml prostaglandin E_1 caused complete relaxation, whereas 64-times-higher prostaglandin E_1 concentrations induced only partial relaxation of tracheal rings contracted by acetylcholine. Methysergide (1–10 μg/ml) antagonized this relaxant activity of prostaglandin E_1 dose-dependently in the presence of acetylcholine, whereas dihydroergotamine showed no inhibitory effect. It was concluded that in dog tracheal smooth muscle, prostaglandin E_1 acts at the membrane surface at or close to the specific 5-HT receptor (TÜRKER and KHAIRALLAH, 1969). A further demonstration of an interaction between prostaglandin E_1 and 5-HT receptor sites was provided on the isolated duodenum from reserpinized rats. In this preparation, prostaglandin E_1-induced contractions, which are presumably mediated by some mechanisms other than release of 5-HT, could be antagonized by BOL-148 (20–40 ng/ml) but were unchanged after atropine or dihydroergotamine (KHAIRALLAH et al., 1967).

Binding studies with D-[^{3}H]LSD have suggested that the affinity of D-LSD to synaptosomes of rat cerebral cortical gray matter is increased by prostaglandin E_1 (FARROW and VUNAKIS, 1973).

In conclusion: (1) Interaction of ergot alkaloids with prostaglandin synthesis has been shown only in the smooth muscle cells of canine veins where both ergotamine and dihydroergotamine induced enhanced formation of a prostaglandin-like substance with venoconstrictor activity; (2) Interaction of ergot alkaloids with prostaglandin effects has been demonstrated in certain smooth muscles, like canine trachea and rat duodenum, where prostaglandin E_1 seems to act at or close to the 5-HT D-receptor and can be antagonized by methysergide or BOL-148, respectively.

J. Stimulation of Smooth Muscle by Ergot Alkaloids Mediated by Miscellaneous Mechanisms

In addition to interaction of ergot alkaloids with defined receptor sites of endogenous agents, as described in the preceding sections of this chapter, there exists the phenomenon of potentation of responses to other agonists by ergot alkaloids. This phenomenon, which concerns the effects of various endogenous amines, acetylcholine and other agents, such as angiotensin and vasopressin, appears to be mediated by different mechanisms.

1. Enhancement of Responses to Biogenic Amines by Ergot Alkaloids in Vascular Smooth Muscles

There exist arteries, predominantly branches from the external carotid vascular bed, where low concentrations of ergot derivatives cause enhancement of responses to biogenic amines, such as catecholamines, histamine and 5-HT. Potentiation of responses to biogenic amines has also been observed when these were tested after perfusion of an isolated rabbit ear artery with a high concentration of 5-HT or tryptamine (GINZEL and KOTTEGODA, 1953) or when catecholamines were tested during perfusion of an isolated rabbit ear or human temporal artery with 5-HT (CARROLL and GLOVER, 1973; CARROLL et al., 1974; DE LA LANDE and RAND, 1965; DE LA LANDE et al., 1966; SAVINI, 1956).

The most frequently used in vitro preparation showing enhanced responses to biogenic amines in the presence of ergot compounds is the isolated rabbit ear artery. In this preparation sensitization to the vasoconstrictor activity of catecholamines and also to that of histamine could be induced with 5-HT as well as with low concentrations of D-LSD (GADDUM, 1954; GADDUM and HAMEED, 1954; SAVINI, 1956), ergometrine (CARROLL and GLOVER, 1973), methysergide (APPERLEY et al., 1976; CARROLL and GLOVER, 1973; CARROLL et al., 1972, 1974; DE LA LANDE et al., 1966; FOZARD, 1973a, b, 1976a, b), and with low concentrations of peptide alkaloids, such as ergotoxin (JANG, 1941), ergotamine, 1-methyl-ergotamine and dihydroergotamine (CARROLL and GLOVER, 1973; CARROLL et al., 1972, 1974; OSSWALD and GUIMARÃES, 1962).

Contrary to these observations, BOL-148 (10–100 ng/ml) did not consistently sensitize the isolated rabbit ear artery to the vasoconstrictor activity of noradrenaline. BOL-148 enhanced the vasoconstrictor response to 5-HT at the 20 ng/ml concentration level and above (FOZARD, 1973b), but it markedly reduced the degree of sensitization produced by 5–10 ng/ml 5-HT (DE LA LANDE et al., 1966).

The responsiveness of the isolated perfused human temporal artery resembles that of the rabbit ear artery. Methysergide, injected at concentrations of 1–10 ng and 5-HT in the same concentration range enhanced responses to noradrenaline and histamine. The same phenomenon could be observed with dihydroergotamine or ergotamine (0.1–5 ng) and with 1-methyl-ergotamine (1–10 ng). Compared to the potentiation caused by 5-HT or methysergide, however, that induced by the ergot peptides did not occur immediately, but it was more prolonged (CARROLL and GLOVER, 1973; CARROLL et al., 1972, 1974). These in vitro findings were confirmed by clinical studies. In human subjects ergotamine (0.5 mg i.v.) caused constriction of the temporal artery, and this effect was enhanced in response to "cold pressure" and noradrenaline (PICHLER et al., 1956).

On spiral strips from dog external carotid arteries ergotamine shifted the dose-response curve for noradrenaline to the left. The maximum sensitization to the vasoconstrictor effects of noradrenaline (ca. 4-fold) was induced with about 2 nM ergotamine added 60 min previously to the bathing fluid, a concentration which in saphenous arteries from the same dogs had considerable α-adrenergic blocking activity (MÜLLER-SCHWEINITZER and STÜRMER, 1975). In canine nasal mucosa vessels ergotamine at low doses potentiated also 5-HT-induced vasoconstriction as

assessed by volume (pressure) changes in the closed nasal cavity (SCHÖNBAUM et al., 1974).

The most consistent enhancement of responses to noradrenaline, tyramine, histamine, 5-HT, tryptamine and vasopressin in arteries from the external carotid vasculature was observed with methysergide. Besides potentiating effects of various biogenic amines in arterial preparations from the rabbit ear and human temporal artery in vitro (APPERLEY et al., 1976; CARROLL and GLOVER, 1973; CARROLL et al., 1972, 1974; DE LA LANDE et al., 1966; FOZARD, 1973a, b, 1976a, b), it enhanced vasoconstrictor responses to noradrenaline in the external carotid vascular bed from dogs (SAXENA, 1972a, b, 1975) and those to 5-HT in the vessels of canine nasal mucosa (SCHÖNBAUM and LAMAR, 1975; SCHÖNBAUM et al., 1975).

Besides the external carotid vasculature from different species, enhancement of the vasoconstrictor activity of catecholamines by an ergolene derivative has also been demonstrated in the isolated perfused rat kidney, where D-LSD even in large doses failed to inhibit the action of adrenaline or noradrenaline. On the contrary, D-LSD (0.1 μg) increased the vasoconstriction caused by adrenaline, while a comparable 5-HT vasoconstriction was diminished (CERLETTI, 1955).

In man, potentiation of the stimulating activity of adrenaline by D-LSD has been demonstrated in the venoconstriction test (DEL BIANCO et al., 1972). This finding was confirmed by the recent observation that in the same test responses to 5-HT were also potentiated by ng concentrations of D-LSD, methysergide and ergotamine (FANCIULLACCI et al., 1975; SICUTERI et al., 1975).

The mechanism by which ergot alkaloids sensitize vascular smooth muscle cells is still unclear. Based upon the observation that in rabbit ear and human temporal arteries neither cyproheptadine and pizotifen, which are very potent 5-HT antagonists, nor morphine prevented sensitization of smooth muscle cells by both 5-HT and ergot compounds, it has been assumed that potentiation is mediated by separate receptors which are not identical with the 5-HT receptor mediating vasoconstriction (CARROLL and GLOVER, 1973; CARROLL et al., 1974). Separate 5-HT vasoconstrictor and dilator receptors have been proposed to exist also in the dog carotid vasculature (SCHÖNBAUM et al., 1974; VARGAFTIG and LEFORT, 1974). Studies on common 5-HT antagonists suggested that in the carotid vascular bed of dogs receptors for 5-HT are of a "special" type that differ from the usual musculotropic D-receptors present in other vascular and nonvascular smooth muscles (SAXENA et al., 1971; SAXENA, 1972a, 1974a, b; SAXENA and DE VLAAM SCHLUTER, 1974).

An alternative explanation might be that ergot compounds cause potentiation by noradrenaline uptake inhibition. However, this would preclude potentiation of those agents which are not taken up by storage sites. Moreover, there is no evidence that ergot alkaloids at pharmacologically active concentrations block the amine-uptake by vascular tissue.

Findings that 5-HT enhanced vasoconstrictor responses not only to noradrenaline but also those to histamine and angiotensin, and that sensitization could also occur in the phenoxybenzamine-treated artery as well as in the chronically sympathectomized artery, indicated that the sensitization resulted from a nonspecific interaction (DE LA LANDE and RAND, 1965; DE LA LANDE et al., 1966). On

the other hand, no experimental data exist suggesting that 5-HT or ergot alkaloids interfere with a later step in the chain of events following the receptor stimulation by an agonist.

FOZARD (1973b, 1976a, b) suggested that sensitization of the rabbit ear artery results from a subthreshold vasoconstriction achieving threshold or greater levels in the presence of other vasoconstrictor agents. This would imply that only compounds with intrinsic activity will enhance the effects of other vasoconstrictor agents, and that the potentiating compound develops its stimulating activity via receptors or mechanisms which differ from those activated by the potentiated drug. This suggestion was supported by the observation that sensitization of the rabbit ear artery could be prevented if steps were undertaken to eliminate the vasoconstrictor properties of the potentiating drug and by the fact that other compounds, for example histamine, produced a similar degree of sensitization at concentrations producing comparable vasoconstriction (FOZARD, 1976a, b).

In spiral strips from canine external carotid arteries ergotamine caused constriction by stimulating 5-HT receptors (MÜLLER-SCHWEINITZER, 1976a). At the same time, ergotamine enhanced responses to noradrenaline while blocking those to 5-HT (MÜLLER-SCHWEINITZER and STÜRMER, 1975). In this preparation, responses to noradrenaline were also enhanced after treatment with cocaine (33 μM) as well as after inhibition of endogenous prostaglandin synthesis with indomethacin (0.3 μM). Both cocaine and indomethacin caused a slight increase in tension by themselves, indicating some (indirect) stimulating activity (MÜLLER-SCHWEINITZER, unpublished 1975b).

These results thus support the notion that the phenomenon of potentiation of responses to other vasoconstrictor agents is a nonspecific effect of compounds with intrinsic vasoconstrictor activity (FOZARD, 1976b).

2. Enhancement of Responses to Biogenic Agents by Ergot Alkaloids in Nonvascular Smooth Muscles

Investigations on the amine potentiating effect of ergot compounds on the nictitating membrane of the cat demonstrated that most ergolene derivatives of the amide type, such as methysergide (DALESSIO et al., 1962), D-LSD, ALD-52 (1-acetyl-lysergic acid diethylamide), LAE-32 (d-lysergic acid ethylamide) and LSM (d-lysergic acid morpholide) at threshold doses of about 2 μg/kg i.v. effectively enhanced responses to catecholamines. BOL-148 was about 100 times less potent than D-LSD (COSTA and ZETLER, 1959). As observed with blood vessels from the carotid bed, responses to adrenaline in the cat nictitating membrane could be also enhanced by 5-HT (LECOMTE, 1953).

By contrast the amine potentiation induced by ergot alkaloids of the peptide type, such as ergotamine, dihydroergotamine, 1-methylergotamine and ergostine could be observed only within a limited dose range because of an α-adrenoceptor blocking activity becoming manifest at doses of 50 μg/kg i.v. (COSTA and ZETLER, 1959; DA GRACA FERNANDES and OSSWALD, 1967; SALZMANN and PACHA, 1968; SALZMANN et al., 1967, 1968; SALZMANN and WEIDMANN, 1966; WEIDMANN and TAESCHLER, 1966).

Further studies demonstrated that in the cat nictitating membrane ergot compounds, besides potentiating responses to catecholamines, also augmented those

to 5-HT. When combined with 5-HT, however, the ergot alkaloids of the peptide type, e.g., ergotamine, dihydroergotamine and 1-methyl ergotamine, proved to be more potent than the ergolene derivative methysergide (SALZMANN and KALBERER, 1973; SALZMANN and WEIDMANN, 1966; WEIDMANN and TAESCHLER, 1966).

Besides potentiating the effect of various amines, ergot compounds, such as D-LSD, BOL-148, ergotamine and dihydroergotamine, produced gradually increasing contractions of the cat nictitating membrane in vitro, indicating intrinsic activity (THOMPSON, 1958). In vivo the ergotoxine-induced contraction of the cat nictitating membrane could be blocked by chlorpromazine, which has 5-HT receptor blocking activity (GYERMEK, 1966), as well as by the α-adrenoceptor blocking agents dibenamine and phentolamine (GYÖRGY et al., 1958a). Moreover, it has been demonstrated that the presence of sympathetic tonus or that of a physiological transmitter is not necessary, indicating that ergot compounds stimulate the cat nictitating membrane by acting directly at the periphery. WEIDMANN and TAESCHLER (1966) mentioned that the ergot compounds used in their studies caused amine potentiation in the cat nictitating membrane as well as vasoconstriction at the same dose ranges. The authors concluded that the same mechanisms might be involved in both potentiation and vasoconstriction. It seems likely, therefore, that in the cat nictitating membrane the amine potentiating activity of ergot alkaloids is mediated by the same mechanism as in the vessels of the carotid bed, i.e., by subthreshold stimulation.

D-LSD potentiated contractions elicited by noradrenaline in the isolated rabbit uterus (VALDECASA et al., 1956) and in isolated vasa deferentia from rats (AREFOLOV et al., 1975) and guinea-pigs, though it produced no observable effect by itself (HITNER and DI GREGORIO, 1974; HUGHES, 1973). Similarly, ergometrine, which alone had no stimulating activity, increased the maximum response to cumulative doses of noradrenaline in the isolated guinea-pig vas deferens. In the same preparation ergometrine decreased the maximum response to cumulative doses of dopamine, with some potentiation of the effects of low concentrations of the agonist (WOODRUFF et al., 1969, 1970).

The mechanism by which both D-LSD and ergometrine sensitize these preparations to the constrictor activity of noradrenaline appears to be different from that proposed for the amine potentiation in carotid vessels and cat nictitating membrane, since neither D-LSD nor ergometrine developed any stimulating activity. In addition, the possibility of motor transmission by 5-HT in the guinea-pig vas deferens has been excluded (AMBACHE and ZAR, 1971). Thus, it can be assumed that there exist no postjunctional 5-HT receptors which could function as binding sites for ergolene derivatives. However, D-LSD has been shown to interact with prejunctional α-adrenoceptors in the isolated guinea-pig vas deferens (HUGHES, 1973). Moreover, inhibition of noradrenaline uptake by various ergot alkaloids has been demonstrated in different extravascular tissues (cf. Section D, part 3 of this chapter). It seems possible, therefore, that both D-LSD and ergometrine potentiate noradrenaline effects in the guinea-pig vas deferens by uptake$_1$ inhibition via stimulation of prejunctional α-adrenoceptors.

There exist only a small number of reports concerning enhancement of 5-HT in extravascular smooth muscles. Using extremely low concentrations of D-LSD

(0.005–0.2 ng/ml), enhancement of 5-HT effects on the isolated rat uterus has been described (COSTA, 1956; DELAY and THUILLIER, 1956), an observation which, however, could not be confirmed by CERLETTI and DOEPFNER (1958b). Some enhancement of 5-HT effects has also been observed with relatively high concentrations of ergotamine (2.5–25 μg/ml) in the isolated rat duodenum (LEVY and MICHELBER, 1956) and with both ergotamine and BOL-148 in the gastric longitudinal muscles from the fish *Pleuronectes platessa* (GROVE et al., 1974). In the isolated heart from the snail *Helix pomatia,* 0.1 μg/ml D-LSD caused enhancement and prolongation of the effects of both 5-HT and intestinal nerve stimulation (RÓZSA and GRAUL, 1964).

Potentiation of smooth muscle stimulating effects of acetylcholine by methysergide has been observed in the isolated guinea-pig vas deferens (KATSURAGI and SUZUKI, 1974), human intestine (GLEGG and TURNER, 1971; METCALFE and TURNER, 1969, 1970; TURNER, 1973) and in the isolated dog trachea (TÜRKER and KHAIRALLAH, 1969). D-LSD appeared to enhance the bronchospasm induced by acetylcholine in anesthetized guinea-pigs while preventing that evoked by 5-HT (HOLGATE and WARNER, 1960). BOL-148 (0.2–1 μg/ml) enhanced responses to acetylcholine in the isolated rat stomach strip (VANE, 1957), while both methysergide (1 nM) and ergotamine (10 nM) failed to change responses to acetylcholine in this preparation (FRANKHUIJZEN, 1975; FRANKHUIJZEN and BONTA, 1974b). Within a small concentration range (0.1–1 μg/ml), however, ergotamine potentiated responses to acetylcholine in the isolated guinea-pig vas deferens (BOYD et al., 1960) and more consistently in the isolated rabbit uterus (BRÜGGER, 1938). Enhancement of the stimulatory activity of acetylcholine by dihydroergotoxine mesylate has been observed in the toad rectus abdominis muscle (BURN and NG, 1964).

Several authors attributed the mechanism by which ergot alkaloids enhance acetylcholine effects in smooth muscles to an anticholinesterase activity. In fact, inhibition of cholinesterase could be demonstrated with most ergot derivatives when used at sufficiently high concentrations (AMMON, 1935; BOYD et al., 1960; BRÜGGER, 1938; GAUTRELET and SCHEINER, 1939; GLEGG and TURNER, 1971; LOEWI and NAVRATIL, 1926; MATTHES, 1930; NAVRATIL, 1937; SIMON and WINTER, 1976; THOMPSON et al., 1954, 1955). However, several observations contradict the assumption that potentiation of acetylcholine effects by ergot alkaloids is caused by cholinesterase inhibition. BRÜGGER (1938) already mentioned that the mode of action of the ergot alkaloids ergotamine and ergometrine differed from that of physostigmine. While physostigmine potentiated acetylcholine effects in both rabbit uterus and guinea-pig vas deferens, the ergot alkaloids consistently enhanced acetylcholine effects only in the rabbit uterus. Both ergot alkaloids developed intrinsic activity, while physostigmine failed to stimulate the rabbit uterus. On the other hand, physostigmine proved to be about 100 times more potent than the ergot alkaloids when tested as cholinesterase inhibitor (BRÜGGER, 1938). In the guinea-pig vas deferens, methysergide potentiated not only responses to acetylcholine but also those to arecoline which were unchanged after cholinesterase inhibition by neostigmine (KATSURAGI and SUZUKI, 1974). Together these observations indicate that ergot alkaloids act quite differently from a cholinesterase inhibitor.

In conclusion, the most consistent enhancement of effects of biogenic agents induced by ergot alkaloids has been observed in vascular smooth muscles and seems to be a characteristic property of the external carotid bed.

K. Biochemical Identification of Specific Binding Sites for Ergot Alkaloids

D. HAUSER

It is generally accepted that the first event in drug action is the formation of a reversible complex between the drug (D) and a specific receptor (R) following second order reaction kinetics:

$$R + D \underset{k_d}{\overset{k_a}{\rightleftarrows}} RD$$

Under steady-state conditions the affinity constant K_A is given by

$$K_A = \frac{1}{K_D} = \frac{k_a}{k_d} = \frac{[RD]}{[R][D]}$$

where K_D is the dissociation constant, k_a and k_d are the rate constants of association and dissociation, and $[RD]$, $[R]$ and $[D]$ are the concentrations of drug-receptor complex, unoccupied receptor and free drug, respectively.

During the past few years considerable progress has been made in the identification and purification of a variety of specific membrane and intracellular binding sites, the binding characteristics of which are consistent with those expected of a receptor.

It is now generally agreed that the term "receptor" refers to a molecule or molecular complex, which is capable of recognizing and selectively interacting with an endogenous compound or a drug, and which, after binding it, is capable of generating some signal that leads ultimately to a biological response (EHRENPREIS et al., 1969; BIRNBAUMER et al., 1974; KAHN, 1976). Since receptors have not yet been identified as pure chemical entities, KAHN (1976) has defined a receptor as "a cellular component which has the ability to selectively recognize and bind an endogenous molecule or a drug and which has binding characteristics consistent with a potential for signal generation."

Cytoplasmic receptors are the prime target of steroid hormones (LIAO, 1975; O'MALLEY and HARDMAN, 1975), whereas receptors for other hormones, neurotransmitters, and antigens are associated with the cell surface (CUATRECASAS and GREAVES, 1976).

In the early 1960's radioactively labeled ligands were already being used to study directly the interaction of endogenous compounds or drugs with their specific receptors, but the problem of nonspecific adsorption tended to complicate these studies. Most radioactive compounds bind to biological membranes and to many other surfaces besides. Since the number of such nonspecific sites is virtually infinite by comparison with the small number of hormone or neurotransmitter receptors, it seemed impossible to identify specific sites in the presence of a vast majority of nonspecific sites.

"Specific binding" usually refers to that portion of bound radioactivity, which is displaced in the presence of an excess of structurally and stereochemically specific ligands. A typical example of the relationship between specific and nonspecific binding is given in Figure 39. Nonspecific binding of [^{3}H]dihydroergotamine to brain membranes, measured in the presence of a large excess of nonradioactive dihydroergotamine, increases by contrast with total binding linearly with [^{3}H]dihydroergotamine concentration (CLOSSE and HAUSER, 1976). At 0.2 nM [^{3}H]dihydroergotamine nonspecific binding represents only about 20% of total binding. In

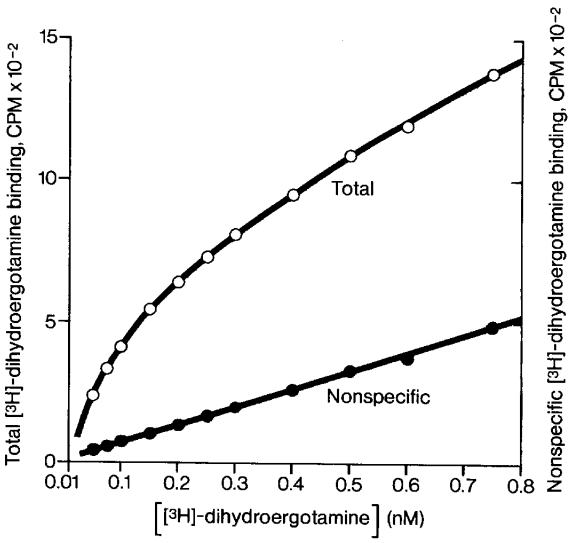


Fig. 39. Saturation of [^{3}H]dihydroergotamine binding. Increasing concentrations of [^{3}H]dihydroergotamine were incubated with rat brain membranes in the presence (nonspecific) or absence (total) of 10 μM unlabeled dihydroergotamine. Incubation was terminated by cooling to 0° C, and bound and free [^{3}H]dihydroergotamine were separated by centrifugation. (CLOSSE and HAUSER, unpublished)

order to perform binding studies at such low concentrations, a specific radioactivity of more than 15 Ci/mmole is desirable.

The problem of nonspecific binding was overcome by using ligands of high pharmacologic potency and labeled to high specific radioactivity. This method was first used successfully with the peptide hormones ACTH and angiotensin (ROTH, 1973). Since then numerous analogous studies have been undertaken in order to identify specific hormone and neurotransmitter binding sites (SNYDER and BENNETT, 1976).

Such binding measurements are supposed to reflect the interaction with a pharmacologic receptor, if a number of criteria is satisfied: (1) The labeled ligand used as a membrane probe must be fully active biologically, so as to mimic the activity of the parent endogenous compound. The binding must demonstrate (2) strict structural and steric specificity and (3) saturability, which indicates a finite and limited number of binding sites. (4) The presence of the binding should be restricted to tissues known to be physiologically sensitive to the parent agonist. (5) The binding should in most cases demonstrate reversibility, which is kinetically consistent with the physiological effects of the parent compound (CUATRECASAS et al., 1975; HOLLENBERG and CUATRECASAS, 1975).

1. Interaction of Ergot Compounds With Specific Sites in the Central Nervous System

D-LSD is a highly potent 5-HT antagonist in smooth muscle preparations (cf. Section B, part 1,c), and it has been assumed that the hallucinogenic effects of D-LSD are mediated by an interaction with 5-HT receptors. It is therefore not

surprising that most of the earlier studies dealing with the biochemical identification of 5-HT receptors employed D-LSD and other ergot compounds as inhibitors of 5-HT binding.

Using [^{14}C]5-HT of low specific radioactivity MARCHBANKS et al. (1964) and MARCHBANKS (1966) identified three binding sites in nerve ending particles obtained from rat brain. [^{14}C]5-HT binding at the "high" affinity site ($K_D = 5 \cdot 10^{-7}$ M) was inhibited by both D-LSD and the pharmacologically inactive antipode L-LSD (MARCHBANKS, 1967). This binding site therefore lacked the stereospecificity expected of a receptor binding site. In analogous studies with [^{14}C]5-HT, binding was partially inhibited not only by D-LSD (WISE and RUELIUS, 1968; DETTE and WESEMANN, 1975) but also by morphine and D-tubocurarine (UNGAR et al., 1976). Stereospecificity was not determined in any of these studies.

With the availability of D-[^{3}H]LSD of higher specific radioactivity (> 1 Ci/mmole), it became possible to identify low concentrations of high affinity binding sites (dissociation constant $K_D < 10^{-8}$M). FARROW and VAN VUNAKIS (1972, 1973), using equilibrium dialysis, characterized high ($K_D = 9$ nM) as well as medium ($K_D =$ 1,2 μM) affinity binding of D-[^{3}H]LSD to subcellular fractions of grey matter in rat cerebral cortex. Bound D-[^{3}H]LSD was displaced by 5-HT, certain other hallucinogenic drugs, and the D-LSD antagonist L-methyl-1,2,5,6-tetrahydropyridine-N,N-diethylcarboxamide (CHRISTIAN et al., 1975) but not by L-LSD, the unnatural antipode. In other words, the binding was found to be stereospecific by contrast with earlier findings. DIAB et al. (1971) demonstrated by autoradiography of freeze-dried sections, binding of D-[^{3}H]LSD in vivo to specific neurones in the caudate nucleus, midbrain, medulla, and cortex of rats.

Using either centrifugation or the more efficient and rapid filtration technique of PERT and SNYDER (1973), saturable, stereospecific D-[^{3}H]LSD binding of high affinity ($K_D = 4$–10 nM) has been confirmed in several rat brain regions (BENNETT and AGHAJANIAN, 1974; BENNET and SNYDER, 1975; LOVELL and FREEDMAN, 1976). The highest concentrations of D-[^{3}H]LSD binding sites are found in the corpus striatum, cerebral cortex, and hippocampus. The association and dissociation rates of binding are temperature dependent, equilibrium being reached most rapidly at 37°C (Fig. 40).

Lesion in the midbrain raphé nuclei, which results in degeneration of the serotoninergic input to the forebrain (KUHAR et al., 1972a), does not affect D-[^{3}H]LSD binding (BENNETT and AGHAJANIAN, 1974; BENNETT and SNYDER, 1975). Hence D-LSD binding is probably not associated with presynaptic sites.

D-LSD (but not L-LSD), BOL-148, D-isolysergic acid amide, and methysergide are potent inhibitors of specific [^{3}H]5-HT binding to rat brain membranes (BENNETT and SNYDER, 1976; FILLION et al., 1976). In fact, D-[^{3}H]LSD and [^{3}H]5-HT binding sites have a close resemblance (BENNETT and SNYDER, 1976). The regional and developmental patterns are similar for both sites. Furthermore, BENNETT and AGHAJANIAN (1976) have shown that the concentration required for half-saturation of specific D-LSD binding in vitro corresponds to the concentration in vivo, at which the activity of raphé neurones containing 5-HT are inhibited by D-LSD.

Dihydroergotamine, which has been found to antagonize 5-HT effects in basilar arteries (Table 1), binds saturably, reversibly, and with high affinity ($K_D = 0.2$ nM) to rat brain membranes (CLOSSE and HAUSER, 1976).

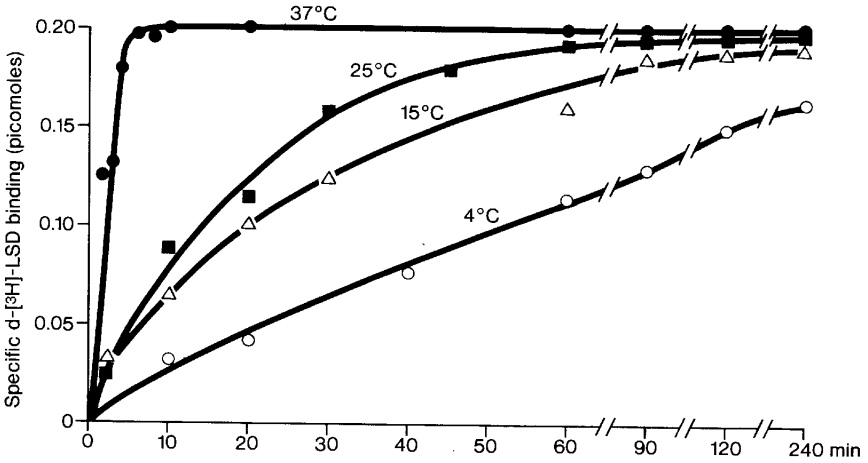


Fig. 40. Association rates of D-[^{3}H]LSD binding at different temperatures. Aliquots of cerebral cortex P3 membranes were incubated with 3 nM D-[^{3}H]LSD at various temperatures for varying lengths of time in 50 mM TRIS·HCl buffer with 0.1% ascorbic acid. The samples were then filtered and specific D-[^{3}H]LSD binding was counted after the addition of 15 ml scintillation liquid. [From Figure 2, BENNETT, J.P., SNYDER, S.H.: Brain Res. **94**, 523 (1975)]

Specific [^{3}H]dihydroergotamine binding, which is defined as the difference between binding in the absence (total binding) and presence (nonspecific binding) of a large excess of unlabeled dihydroergotamine, is saturable, half-maximal saturation occurring at approximately 0.2 nM (Fig. 41, *inset*). Scatchard analysis of the same data gives a curve with upward concavity (Fig. 41), which can be interpreted as negative cooperativity of a single class or the existence of multiple classes of binding sites.

The dissociation constant K_D of the high affinity site under steady-state conditions is 0.23 nM, which agrees well with the value obtained independently from kinetic analysis of [^{3}H]dihydroergotamine binding. Both the association and dissociation rates of [^{3}H]dihydroergotamine binding are comparatively slow. In the forward reaction at 37° C, equilibrium is reached in 30 min, whereas in the dissociation reaction the half-life is approximately 20 min (Fig. 42, *inset*).

The regional and subcellular distribution of specific [^{3}H]dihydroergotamine binding (CLOSSE and HAUSER, 1976) resembles the localization of [^{3}H]5-HT binding in rat brain (BENNETT and SNYDER, 1976). In both cases the concentration of specific binding sites is highest in the hippocampus and the corpus striatum and lowest in the cerebellum. At the subcellular level specific binding sites are most numerous in the "synaptosomal" fraction.

[^{3}H]Dihydroergotamine binding is stereospecific, the pharmacologically inactive antipode of dihydroergotamine (STADLER and STÜRMER, 1970) being more than 2000 times less potent than dihydroergotamine in inhibiting specific [^{3}H]dihydroergotamine binding. Assay of membranes from the whole rat brain reveals that 5-HT is the only neurotransmitter capable of inhibiting specific [^{3}H]dihydroergotamine binding (CLOSSE and HAUSER, 1976). l- and d-noradrenaline in particular,

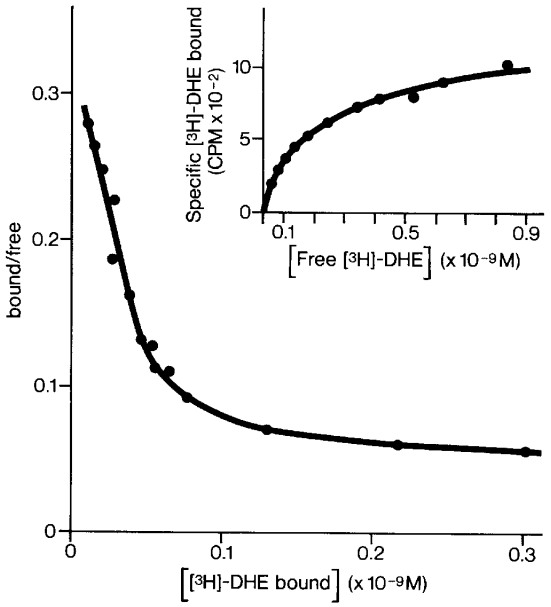


Fig. 41. Binding of [^{3}H]dihydroergotamine to rat brain membranes as a function of [^{3}H]dihydroergotamine concentration. Increasing concentrations of [^{3}H]dihydroergotamine were incubated with rat brain membranes in the presence (nonspecific) and absence (total) of 10 μM nonradioactive dihydroergotamine. Values of total [^{3}H]dihydroergotamine binding are plotted according to SCATCHARD. Inset: Saturation of specific [^{3}H]dihydroergotamine binding. [From Figure 4, CLOSSE, A., HAUSER, D.: Life Sci. **19**, 1857 (1976)]

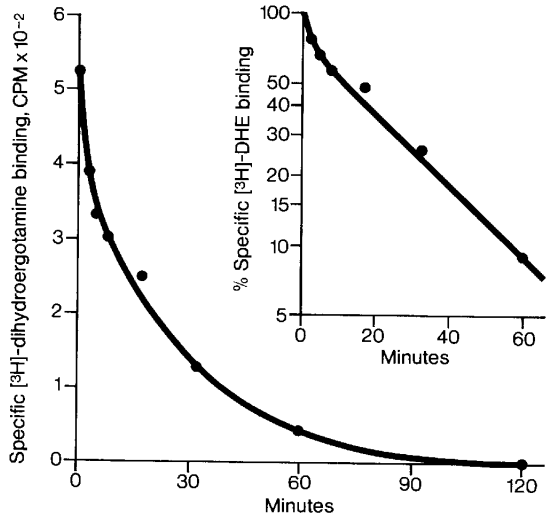


Fig. 42. Time course of dissociation of bound [^{3}H]dihydroergotamine. Rat brain membranes were incubated with [^{3}H]dihydroergotamine (nM) for 30 min at 37°C. Nonradioactive dihydroergotamine (20 μM final concentration) was added and [^{3}H]dihydroergotamine binding was assayed at various times. Inset: Semilogarithmic plot of the same data. [From Figure 3, CLOSSE, A., HAUSER, D.: Life Sci. **19**, 1856 (1976)]

and a variety of α-adrenergic agonists and antagonists, are very weak inhibitors of specific [^{3}H]dihydroergotamine binding (CLOSSE and HAUSER, 1976).

The characteristic of D-LSD binding suggest (BENNETT and AGHAJANIAN, 1974; BENNETT and SNYDER, 1976) that in most brain regions specific D-LSD binding sites are related to postsynaptic 5-HT receptors. The differential ligand specificity at D-[^{3}H]LSD and [^{3}H]5-HT binding sites is consistent with a two-state receptor model as proposed by SNYDER and BENNETT (1976). Thus [^{3}H]5-HT would bind with 5-HT receptors in the "agonist state," while D-LSD, a mixed agonist-antagonist, binds with equal affinity to both the "agonist" and "antagonist states."

With dihydroergotamine the available evidence is less conclusive.

In some regions of the brain D-[^{3}H]LSD binding appears to involve other than 5-HT receptor sites. In calf caudate nucleus D-[^{3}H]LSD binding has been linked, in part at least, with postsynaptic dopamine receptors (BURT et al., 1976a). Ergotamine, ergocornine, ergocristine, α-ergokryptine, ergometrine and bromocriptine have substantial affinity for specific dopamine binding sites as well (CRESSE et al., 1976; BURT et al., 1976b), which is compatible with many of the known pharmacologic effects of these drugs (cf. Section C).

Several ergot compounds, including dihydroergotamine, are very potent inhibitors at binding sites of both the α-adrenoceptor agonist [^{3}H]clonidine and the α-adrenoceptor antagonist [^{3}H]WB-4101 (GREENBERG et al., 1976; S.H. SNYDER, personal communication). Whether these central α-adrenoceptor binding sites are relevant to the action of ergot compounds remains to be seen.

2. Peripheral Binding Sites for Ergot Compounds

Recently, a specific binding site for [^{3}H]dihydroergokryptine has been identified on cell membranes of the rabbit uterus (WILLIAMS and LEFKOWITZ, 1976). The characteristics of this site differ from those of the binding site for the closely related [^{3}H]dihydroergotamine identified in the rat brain (CLOSSE and HAUSER, 1976). In the peripheral tissue preparation, steady-state binding is reached much more rapidly, and ligand specificity satisfies the criteria that must be fulfilled for the identification of α-adrenoceptors. Binding of [^{3}H]dihydroergokryptine is rapid and stereospecific; α-adrenoceptor agonists and antagonists have binding affinities that parallel their potencies in eliciting or blocking physiological α-adrenergic responses.

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