CHAPTER I

Introduction to the Pharmacology of Ergot Alkaloids and Related Compounds as a Basis of Their Therapeutic Application

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"Truth is rarely pure and never simple"
OSCAR WILDE

This chapter, rather unorthodox for a volume of the Handbook of Experimental Pharmacology, is not intended as a summary of the wealth of information accumulated in this book. It is an attempt at a compact synopsis to help those teaching pharmacology or writing a textbook of pharmacology not to overlook the essential chemical and biological basis of the therapeutically most important compounds and those of their activities which are believed to be relevant for their therapeutic effects.

The present volume, entitled *Ergot Alkaloids and Related Compounds,* deals with *chemical entities containing the tetracyclic ergolene- or ergoline-ring system.* They can be obtained by extraction of different strains of the fungus claviceps—grown on rye or cultivated in fermentation tanks—or alternatively by partial or total synthesis. These compounds can be divided into four main structural groups: clavine alkaloids, lysergic acids, simple lysergic acid-amides, and peptide alkaloids. One example of each type of molecule is given in Figure 1.

The degree of oxidation is a criterion for further differentiation in the group of clavine alkaloids, all of which are compounds of minor biological importance.

The naturally occurring lysergic acids are divided into compounds with a double bond in the 8–9 position (8-ergolenes) and in the 9–10 position (9-ergolenes). All congeners are methylated in position 6. The two asymmetric carbon atoms in position 5 and 10 (in the case of 8-ergolenes) or 5 and 8 (in the case of

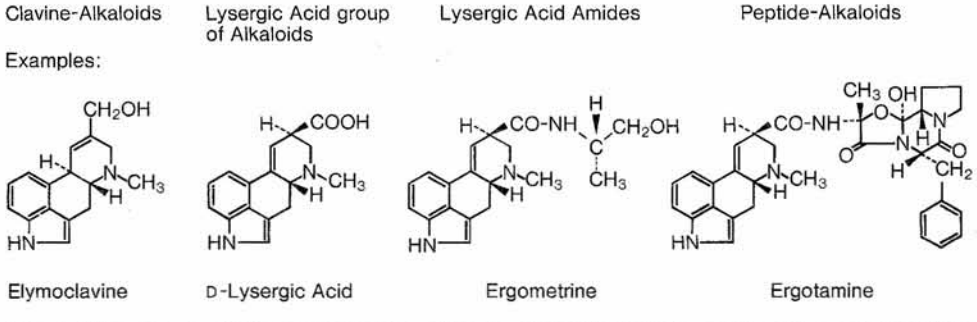


Fig. 1. One characteristic representative of each of the four main groups of ergot alkaloids

9-ergolenes) allow a further classification according to the steric position of the substituents in positions 8 or 10. (The 5-H atom always has the β-configuration.) Lysergic acid is inactive; only its derivatives are pharmacologically active.

In the group of the lysergic acid-amides the lysergic acid is in amide linkage to relatively small nonpeptide moieties.

For the group of peptide alkaloids, a relatively simple nomenclature has been adopted in this volume. The expression ergopeptine stands for the basic skeleton of a natural D-lysergic acid linked to a tricyclic peptide moiety by a peptide bond (see Fig. 2).

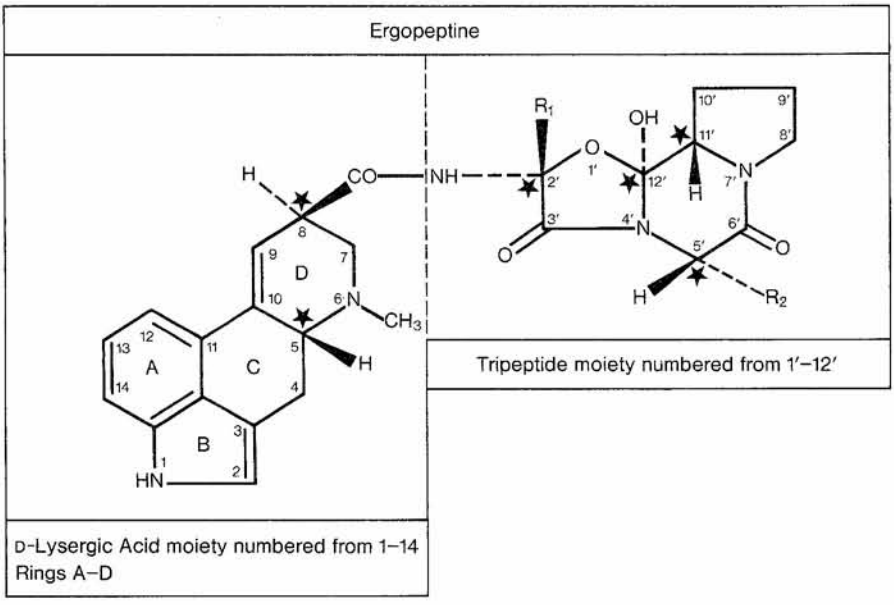
Only isomers that are derivatives of the natural D-lysergic acid have pharmacologic importance; derivatives of D-isolysergic acid are much less active. For convenience, the isomers of D-lysergic acid have been given endings in "-ine," while D-isolysergic acid isomers end in "-inine." Isomerization occurs during storage of the sclerotia and extraction of alkaloids and at a high rate in an alkaline milieu.

It is known that the biological activity of the ergopeptines depends largely on their configuration. This results from studies with the optical antipodes of ergotamine and dihydroergotamine and the corresponding diastereomers (natural D-lysergic acid combined with the antipode peptide moiety and antipode L-lysergic acid combined with the natural peptide moiety) which have been shown to be devoid of biological activity (STADLER and STÜRMER, 1970, 1972).

The chemical diversity of ergot alkaloids corresponds to the *diversity of the biological activities of these compounds.* It is probably correct to state that there are few chemical groups which comprise substances with such diversified actions. It has been accurately said that "ergot has been of the nature of a treasure chest to pharmacologists," (MOIR, 1932) and that it has become a "treasure-house for drugs" (STOLL, 1965). Many ergot compounds show a considerable spectrum of pharmacologic actions, and if the doses necessary to obtain a certain effect are taken into account, exhibit a high degree of specificity (selectivity). In Table 1 an attempt is made to demonstrate this, correlating ten biological activities and seven compounds. These figures are extracted from the pool of experimental data accumulated in our laboratories during the last decades. The figures should be regarded as working averages, as they were not always obtained synchronously, and they apply of course to particular species and methodologies. On the other hand, the methodologies employed in each case are uniform, and the data of Table 1 therefore provide a good idea of the range of variation encountered.

With regard to α-adrenoreceptor blocking activity on the isolated guinea pig seminal vesicle, dihydroergotoxine mesylate (Hydergine) is the most active compound, the ED_{50} being 0.7 ng/ml. The activity of dihydroergotamine and bromocriptine is lower but in the same range; that of ergotamine is 20 times weaker. At the other end of the scale are methylergometrine and methysergide, which are inactive or at least 2500 times less active than dihydroergotoxine mesylate.

The most potent antagonist of serotonin (5-HT) on the estrous rat uterus in vitro is methysergide—the ED_{50} being 0.6 ng/ml—followed by methylergometrine and LSD. Considerably less active than methysergide are dihydroergotamine (25 times), ergotamine and dihydroergotoxine mesylate (100 times), and bromocriptine ($\sim$300 times).



Substitutions possible in positions: 1, 2, 6, 9, 10 (Dihydro-compounds), 10, 12, 13, 14.
✱asymmetric centers: 6; in case of 9, 10 dihydrogenation: 7
(carbon atom 10 additionally).

2′ β R_1 / 5′ α R_2	CH_3	CH_2-CH_3	$CH(CH_3)_2$
$CH(CH_3)_2$	Ergovaline	Ergonine	Ergocornine
$CH_2CH(CH_3)_2$	Ergosine	Ergoptine	Ergokryptine
$CH(CH_3)CH_2CH_3$	β-Ergosine	β-Ergoptine	β-Ergokryptine
CH_2-Ph	Ergotamine	Ergostine	Ergocristine

Trivial names if coined are used in this volume.
Otherwise the ergopeptine nomenclature is used. In this terms
Ergotamine is 2′β-Methyl-5′α-benzyl-ergopeptine
Ergocornine is 2′β-5′α-Diisopropyl-ergopeptine

Fig. 2. The ergopeptines consist of a D-lysergic-acid moiety linked to a tricyclic peptide moiety by a peptide bond. Ergopeptines occurring in nature have a double bond in position 9,10. Dihydro-compounds are hydrogenated in positions 9 and 10. They do not occur in nature. Six asymmetry centers marked with * are present in natural—so called genuine—ergopeptines. Dihydrogenation in position 9,10 generates an additional asymmetry center in position 10

Table 1. Activity profiles of some ergot compounds. The relative activities of seven compounds on 10 biological parameters are listed. The potency of the most active compound in each test being arbitrarily set as 1000. These figures are extracted from the pool of experimental data accumulated in our laboratories during the last decades. A ratio between the highest and the lowest activity in each test is also given. For numerical data concerning effective doses – or concentrations – see text

Parameter \ Substance	Ergot-amine	Bromo-criptine	Dihydro-ergotamine	Dihydro-ergotoxine mesylate[a]	Methyl-ergometrine	Methyser-gide	LSD	Max./Min.
α-Adrenoceptor blockade isol. guinea pig seminal vessel	50	230	350	1000	<0.4	<0.4	1	>2500
5HT-receptor blockade isol. rat uterus	10	3	40	10	250	1000	250	330
Pressor activity spinal cat, i.v.	1000	<10	120	30	<10	30	10	>100
Uterotonic activity rabbit in situ, i.v.	500	Inhibition of Me-ergo-metrine	Inhibition of Me-ergo-metrine	Inhibition of Me-ergo-metrine	1000	40	670	>1000
Inhibition of fertility in rats, s.c.	50	1000	<40	70	<80	<40	<40	>25
Influence on body temperature, rabbit, i.v.	+ 3	+ 2.5	–	–	+ 14	+ 0.2	+ 1000	>5000
Emetic activity in the dog, i.v.	1000	410	85	540	210	<1	<3	>1000
Dopaminergic stereotyped behaviour in rats, i.p.	<1	630	<1	<1	310	<1	1000	>1000
Contralateral turning behaviour in rats, 6-OHDA leasioned, s.c.	<1	1000	<1	10	400	<1	730	>1000
Inhibition of NA-stimulated cAMP-synthesis in rat cerebral cortex slices in vitro	400	190	240	1000	2.5	5	60	400

[a]Hydergine.

Considering the blood pressure increasing activity on the spinal cat, ergotamine is the most active compound, eliciting clear-cut rises of blood pressure from doses of 1 μg/kg i.v. Taking its activity as 1000, that of dihydroergotamine is 120, and that of the other substances ranges between 30 and 10 or less.

If the uterotonic activity in situ—anesthetized nonpregnant rabbit in spontaneous estrous—of methylergometrine (effective submaximal doses in the range of 0.1–0.2 mg/kg i.v.) is taken as 1000, that of LSD is 670, that of ergotamine 500, and that of methysergide around 40 (and not easily reproducible), whereas bromocriptine, dihydroergotamine, and dihydroergotoxine mesylate are devoid of this activity and inhibit spontaneous uterine motility and the uterotonic effect of methylergometrine.

Bromocriptine is the only compound in this table which, due to a long-lasting inhibition of prolactin secretion, has an outstanding antifertility effect in the rat when given on day 5 after insemination ($ED_{50}=0.75$ mg/kg s.c.). Other compounds listed are either more than 10 times less effective or are ineffective in this test.

If the influence on the body temperature of the nonanesthetized rabbit is considered, the seven compounds—given i.v.—show not only quantitative but also qualitative differences: LSD is the most potent inducer of hyperthermia (3 μg/kg eliciting on the average a rise of 1° C), methylergometrine, ergotamine, bromocriptine, and methysergide being 70–5000 times less potent. Dihydroergotamine and dihydroergotoxine mesylate—in rather high doses such as 2–3 mg/kg—lower body temperature.

Emetic activity in the nonanesthetized dog is most pronounced with ergotamine ($ED_{50}=3.1$ μg/kg i.v.), dihydroergotoxine mesylate and bromocriptine being somewhat less active. Methylergometrine is 5 times and dihydroergotamine 12 times less active than ergotamine; LSD and methysergide are devoid of this activity even if administered in doses 300 to 1000 times higher than ergotamine.

In eliciting stereotyped behavior in the rat—probably due to central dopaminergic stimulation—LSD is the most active compound (2 mg/kg i.p. being an effective dose). If its activity is taken as 1000, that of bromocriptine is 630 and that of methylergometrine 310, whereas ergotamine, dihydroergotamine, dihydroergotoxine mesylate, and methysergide are for all practical purposes ineffective.

Another test for central dopaminergic action is the (apomorphine type) contralateral turning behavior of rats with 6-OH-dopamine-induced degeneration of the nigro-neostriatal dopaminergic pathway. The most potent compound in this test is bromocriptine (effective dose 1 mg/kg s.c.). If this activity is taken as 1000, those of LSD and methylergometrine are 730 and 400, respectively. Dihydroergotoxine mesylate is about 100 times less effective. Ergotamine, dihydroergotamine, and methysergide are ineffective.

Noradrenaline-stimulated cyclic AMP synthesis in the rat cerebral cortex in vitro is inhibited by some ergot compounds, the most active being dihydroergotoxine mesylate (ED_{50} 5.8 ng/ml), pA_2 value ~ 8.0). If this activity is taken as 1000, that of ergotamine is 400, of dihydroergotamine 240, of bromocriptine 190, of LSD 60, and those of methysergide and methylergometrine 5 and 2.5, respectively.

In the last column of Table 1, a ratio is given between the highest and lowest activity for each listed pharmacologic activity. These ratios range between >25 and >5000. Considering the whole pharmacologic profile of the substances, qualita-

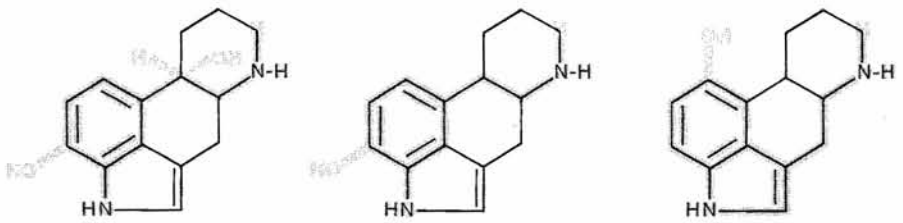


Fig. 3. Structural relationship between ergoline and three biogenic amines: noradrenaline, dopamine, and serotonin

tive rather than quantitative differences would appear to be more appropriate in distinguishing between at least some of the compounds.

There is indeed no evidence available which would suggest that these highly diversified activities could be explained by one "basic mechanism" on cellular or molecular level. The opposite seems to be more likely, and in a recent review (BRADLEY and BRIGGS, 1974) it was pointed out that "it is unlikely that a unified explanation of all the actions of these drugs can be formulated." Nevertheless, *this diversity of actions may be at least partially explained* by assuming that:

1. Ergot alkaloids interfere at more than one type of specific receptor site.
2. The population of receptor sites to which ergot alkaloids have access varies from organ to organ.
3. Affinity and efficacy (=intrinsic activity) vary from alkaloid to alkaloid as a function of their chemical configuration.

A specific relationship between ergoline—a vital part of all ergot alkaloids—and the biogenic amines noradrenaline, adrenaline, dopamine, and serotonin is evident from Figure 3. All the biogenic amines mentioned can be regarded as structural elements of ergoline. This structural relationship may contribute to the ability of different ergot alkaloids to interfere with various specific receptors. On the other hand, the structural differences between the ergot alkaloids and the biogenic amines can explain why some of the former act as partial agonists and/or antagonists on receptor sites of the biogenic amines mentioned.

An example for an ergot alkaloid eliciting partial agonism is given in Figure 4. This figure shows dose-response curves for noradrenaline, the so-called full agonist (its maximal effect is therefore set at 100%) and for ergotamine, a partial agonist, which reaches about 30% of the maximal possible stimulation in spiral strips of isolated canine femoral veins. Moreover it takes about three times longer with ergotamine than with noradrenaline for the rise in tone to develop fully and that it lasts much longer. Additionally, it is clear from Figure 4 that ergotamine is active in concentrations about 350 times lower than noradrenaline. In terms of receptor pharmacology, ergotamine is a partial agonist (30% efficacy compared with the full agonist noradrenaline) but possesses a higher affinity to the stimulating receptor sites of this vascular smooth muscle (ED_{50} for noradrenaline 7.6×10^{-7} M, while the ED_{50} for ergotamine was 2.2×10^{-9} M.)

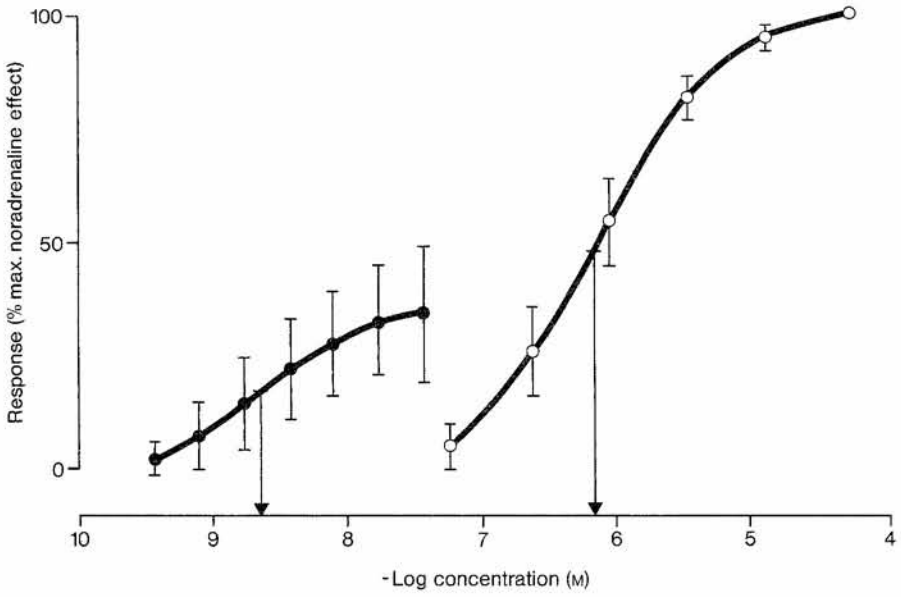


Fig. 4. Cumulative dose response curves for ergotamine (●) and noradrenaline (○). ED_{50} is represented by an arrow in each case. Organ: femoral vein of the dog. Recording: isometric. Vertical bars indicate s.d. (n=36) (MÜLLER-SCHWEINITZER and STÜRMER, 1974)

The combination of increasing concentrations of ergotamine with noradrenaline produced a series of log dose-response curves which are depicted in Figure 5. They start from progressively higher baselines but with similar maxima and show approximate parallelism in the upper reaches. In terms of receptor pharmacology, these curves correspond to curves calculated for the interaction of a full agonist and a partial agonist (so-called competitive dualist). They support the idea, that the stimulating action of ergotamine is due, at least in part, to stimulation followed by block of α-adrenoceptors. If two agonists (noradrenaline and ergotamine) act on the same receptor, they can be expected to be replaced in a similar fashion by a competitive antagonist. Indeed, it has been shown that this is the case, and that ergotamine fulfills the criteria of a partial agonist to α-adrenoceptors on this vascular smooth muscle.

It appears, therefore, that there is no reason to maintain the old concept of a "direct site of action"—as opposed to receptor sites for biogenic amines—as the mechanism of action of the agonistic (=stimulating) effect of ergot alkaloids on vascular and uterine smooth muscle.

An example of an ergot alkaloid antagonistic to serotonin (5-HT) (without partial agonistic stimulant activity) is given in Figure 6. On spiral strips from bovine basilar arteries the maxima of the log dose-response curves for 5-HT progressively decrease with increasing concentrations of methysergide: characteristic for noncompetitive antagonism.

An example in which the effect of an ergot alkaloid is probably due to stimulation (agonism) of central dopaminergic receptors is the induction of turning behav-

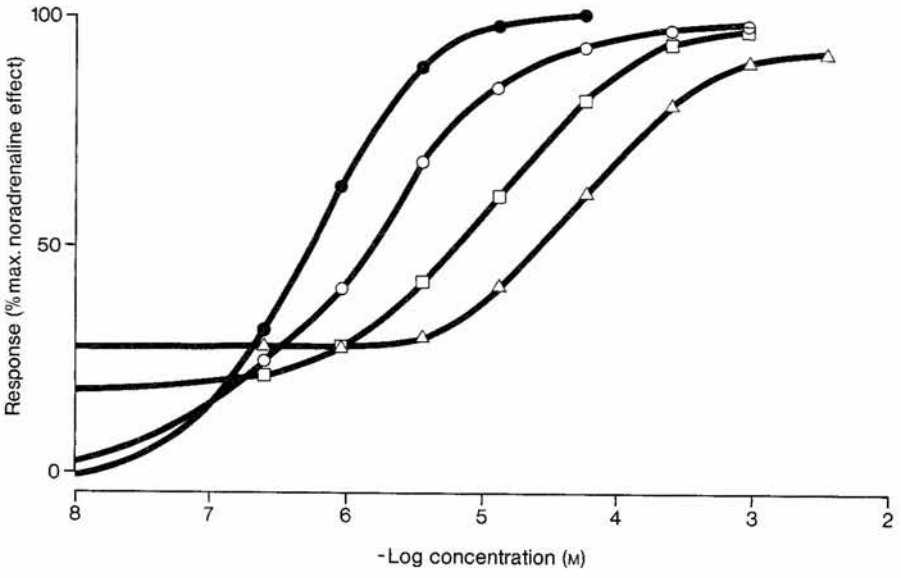


Fig. 5. Cumulative dose response curves for noradrenaline. Organ: femoral vein of the dog. Recording: isometric. (●) control curve (n=18); 15 min after ergotamine in the final concentrations of $10^{-8.76}$ (○), $10^{-7.76}$ (□) and $10^{-6.76}$M (△). n=6 for each curve (MÜLLER-SCHWEINITZER and STÜRMER, 1974)

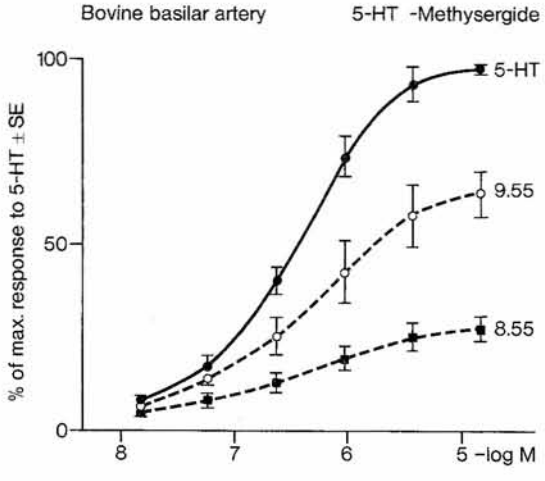


Fig. 6. Cumulative dose response curves for 5-HT without (●, n=5) and 60 min after methysergide in the final concentrations of $10^{-9.55}$M ($=2.8\times10^{-10}$M) (○, n=4) and $10^{-8.55}$M ($=2.8\times10^{-9}$M) (■, n=5) on spiral strips from bovine basilar arteries. Changes in tension were recorded isometrically (MÜLLER-SCHWEINITZER, unpublished)

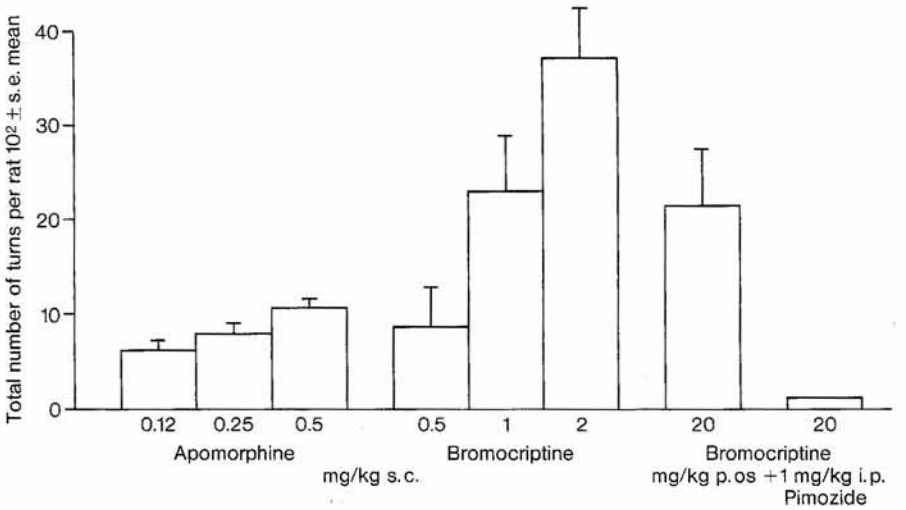


Fig. 7. The induction of turning behavior in rats lesioned unilaterally in the substantia nigra by a local injection of 6-hydroxydopamine after subcutaneous administration of bromocriptine and apomorphine. This effect of bromocriptine is blocked by pretreatment with pimozide (LOEW et al., 1976)

ior by bromocriptine in the rat with unilateral lesions in the substantia nigra produced by previous injection of 6-hydroxy-dopamine (CORRODI et al., 1973). Figure 7 shows that bromocriptine, like apomorphine, increases the number of turns in a dose-dependent way. This effect is blocked by the dopaminergic antagonist pimozide.

In many in vitro testing systems—particularly those involving vascular smooth muscle—the effective concentrations of many ergot compounds are extremely low: 10^{-8}–10^{-9} M. This corresponds to the relatively low therapeutic doses and blood levels (BERDE, 1975; MEIER and SCHREIER, 1976), e.g., steady-state plasma levels for dihydroergotamine are between 2.5 and 6.5 ng/ml after oral doses of 1 mg t.i.d. and 2.5 mg t.i.d. per os, respectively, and for methysergide 20 ng and 40 ng/ml after 1 mg t.i.d. and 2 mg t.i.d., respectively. It is widely accepted that the prophylactic effect of methysergide in migraine headache is connected with its modification of the effects of serotonin and/or metabolic handling of serotonin. On the isolated rat uterus, the serotonin antagonistic concentration of methysergide is in the range of 1 ng/ml (CERLETTI et al., 1960). The stimulating effect (irregular) of the same alkaloid on serotonin uptake in the perfused cat spleen was observed at concentrations around 100 ng/ml, and the inhibition of serotonin uptake (regular) was observed in the same system with those around 1000 ng/ml (OWEN et al., 1971). When considering the mechanism of action of methysergide, the exclusion of this last-mentioned phenomenon would not be necessary for the following reasons:

The aim of a rational therapy is the maintenance of a sufficient drug concentration at the receptor sites in order to achieve the desired pharmacologic effect during a certain time interval. Unfortunately, it is almost impossible to measure

and control the drug concentrations at the receptor site or even in the tissues. The next best alternative is to measure the concentrations of the active substance in the blood, plasma, or urine of the patients. These pharmacokinetic data can be used in connection with pharmacodynamic observations for the evaluation and the planning of dosage schemes of the drug. An important condition for such a procedure is the existence of a certain correlation between drug concentration in the plasma and the time course of pharmacologic action. This correlation is not required to be simple and direct. Even a very low drug concentration in the plasma may coincide with a sufficient drug action, if for instance, the active substance has a higher binding affinity to the receptor than to the plasma proteins. Plasma is thus considered in pharmacokinetics to be the central transport compartment and not a direct correlate of the biologic activity.

The *wide field of therapeutic application* of ergot alkaloids and related compounds corresponds to their chemical and pharmacologic diversity. Migraine and other vascular headaches, uterine atonia, orthostatic circulatory disturbances, senile cerebral insufficiency, and infertility due to hyperprolactinemia are probably the most important of a great number of indications. Considering the implications of some of the diseases mentioned in terms of human suffering, medical effort, and socio-economic consequences, the therapeutic importance of the ergot alkaloids and related compounds is indeed formidable. Due to the multiple pharmacologic actions of ergot alkaloids, the relationship between their pharmacologic activity and therapeutic effectiveness is not always obvious. In some cases their clinical use stems clearly from a pharmacologic action, e.g., the use of ergometrine in obstetrics; in others the connection is less evident. Thus, although much is known about the various receptor interactions of ergotamine, it is not clear which of these is responsible for the undoubted effectiveness of this drug in migraine therapy. For this reason, we thought it appropriate in this short introductory chapter to depart from the usual sequence in which all the pharmacologic actions of certain types of compounds are described. We intend instead to describe a few prototype compounds with established therapeutic value and to concentrate on those pharmacologic qualities which are currently considered to be relevant for the therapeutic action.

The use of ergot *in obstetrics*—namely increasing uterine motor activity—is the oldest therapeutic use of this drug. Although several ergot alkaloids have a more or less pronounced effect on the uterus, the prototype compounds used today to treat uterine bleeding of various origin are *ergometrine* (=ergonovine) (DUDLEY and MOIR, 1935; BROWN and DALE, 1935; KHARASCH et al., 1936) and *methylergometrine* (STOLL and HOFMANN, 1943; KIRCHHOF et al., 1944). They influence all three parameters of uterine contractility positively, namely frequency, amplitude, and basal tone. Whereas small doses increase only frequency and/or amplitude of contractions, higher doses also elevate the basic tone, thus decreasing blood loss from the postpartum uterus. This stimulant effect holds true for many species, including man in vivo as well as in vitro, indicating a peripheral site of action.

Two types of adrenergic receptors have been postulated to be present in the uterus: one for uterine stimulation (α) and one for inhibition (β) (AHLQUIST, 1948). The nonpregnant rabbit uterus in situ—in spontaneous or induced estrus—

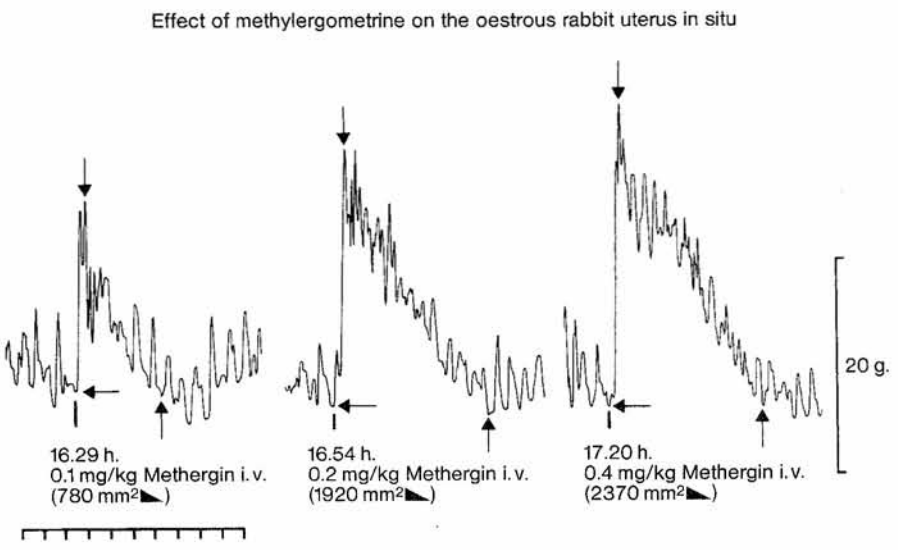


Fig. 8. Isometric recording of the uterotonic effect of methylergometrine on the estrous rabbit uterus in situ. Increased uterine activity is expressed in terms of the area of the time-response curve (BERDE and SAAMELI, 1966)

has been regarded as a particularly suitable experimental setup for the study of the uterotonic effect of many ergot alkaloids and related compounds (ROTHLIN, 1938) (Fig. 8). In this preparation, the uterine stimulating effect of methylergometrine, ergometrine, ergotamine, and some other ergot compounds—in doses between 0.1 and 0.4 mg/kg i.v.—seems to be mediated by α-adrenergic receptors; it can be blocked by α-adrenergic blocking agents such as phenoxybenzamine, phentolamine, dihydroergotamine, and dihydroergotoxine and its components (KONZETT, 1960; HOOL-ZULAUF and STÜRMER, 1976, 1977; ROTHLIN, 1947; ROTHLIN and BIRCHER, 1952) (Fig. 9). It seems that a cyclic change of the sensitivity of the uterus to uterotonic stimuli is due to changes in the number of and proportion of α- and β-adrenergic receptors brought about by the sexual hormone cycles (MILLER and MARSHALL, 1965; MILLER, 1967; BRODY and DIAMOND, 1967). It was regarded as a "rule" that on the estrous rabbit uterus, ergot compounds with a double bond in position 9,10 are oxytocics, whereas compounds dihydrogenated in this position are not oxytocic but, on the contrary, inhibit both spontaneous and induced uterine activity (ROTHLIN, 1947; ROTHLIN and BIRCHER, 1952). This is true for many compounds tested in our laboratories but not without exception, e.g., bromocriptine has no uterotonic activity (STÜRMER and FLÜCKIGER, 1974), and the dihydrogenated compound dibromo-dihydrolysergic-acid-glycinamide is a strong oxytocic (BERDE and SAAMELI, 1966) and so are some 6-Nor-6-isopropyl-9,10-dihydroergopeptines (HOOL-ZULAUF and STÜRMER, 1976, 1977). It appears, therefore, that the presence of the double bond in position 9,10 of the lysergic acid moiety is not the structural element exclusively responsible for determining α-adrenergic stimulation or inhibition.

Furthermore, there is no complete parallel between the estrous rabbit uterus

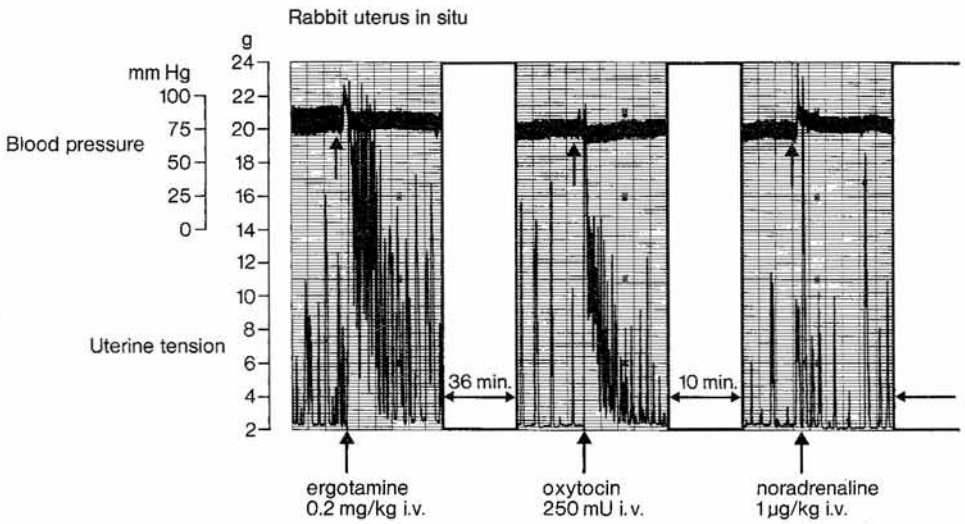
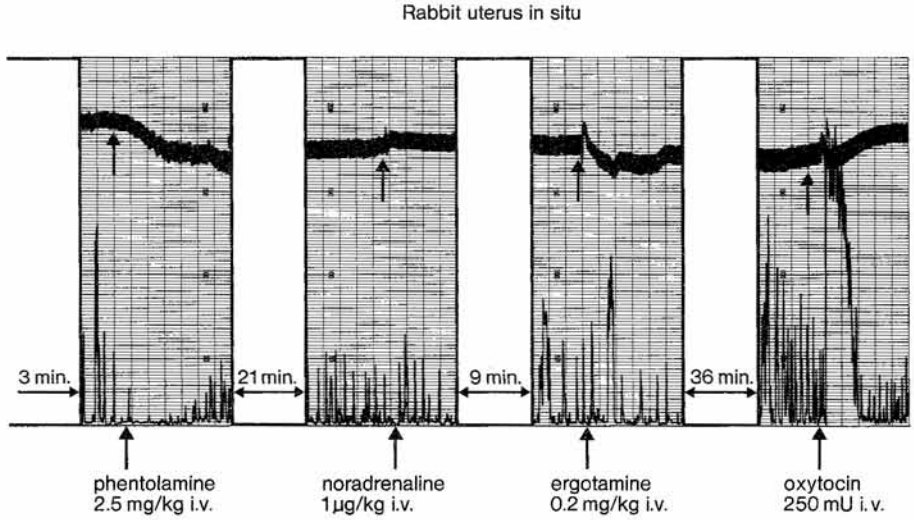


Fig. 9. Original trace of an experiment in the rabbit demonstrating the effects of ergotamine, oxytocin, and noradrenaline on blood pressure (upper tracing) and uterine tension (lower tracing) before and after phentolamine injection. It can be seen from the tracings that blockade

and the human myometrium near term with regard to their response to ergot alkaloids. It was found, for example, that some compounds hydrogenated in position 9,10, such as dihydroergotamine and dihydroergotoxine mesylate, have some uterotonic activity on the human uterus near term both in vivo and in vitro (ALTMAN et al., 1952; EMBREY and GARRETT, 1955; ROTHLIN and BERDE, 1954) and on the cat uterus in situ (BERDE and ROTHLIN, 1953). The reason for these interspecies differences is not known.

Note that the receptor involved in the uterotonic effect of some ergot compounds is different from that involved in the uterotonic effect of oxytocin. The uterine effect of the latter is not antagonized by α-adrenergic blocking agents (Fig. 9).

The prototype compound for the treatment of the *migraine attack*, as well as for cluster headache and some other vascular headaches, is *ergotamine tartrate*. The possible relevance of its various pharmacologic qualities for its therapeutic effect has recently been reviewed and discussed (FOZARD, 1975a, b). It was emphasized that only those effects elicited by very low doses can be considered as relevant. These effects are vasoconstriction (ROTHLIN, 1923; ROTHLIN and CERLETTI, 1949), sensitization of vascular smooth muscle to nervous and chemical stimuli (e.g. ROTHLIN and CERLETTI, 1949; WEIDMANN and TAESCHLER, 1966), and inhibition of circulatory baroreceptor reflexes (e.g. v. EULER and SCHMITERLÖW, 1944). Based on the extensive clinical pharmacologic studies of the behavior of the extracerebral vessels before and during the migraine attack and under the influence of ergotamine (WOLFF, 1963), however, it is now generally accepted that the therapeutic effect of ergotamine is closely related to its long lasting peripheral vasoconstrictor activity in the dilated branches of the external carotid artery



of α-adrenoceptors by phentolamine decreased mean arterial blood pressure and completely abolished the uterotonic effect of noradrenaline and ergotamine but not that of oxytocin. Time: 2.4 min between the vertical lines (HOOL-ZULAUF and STÜRMER, unpublished)

(Fig. 10). Studies employing various experimental arrangements have indeed demonstrated that (1) the preexisting vascular tone is determinant for the vasoconstrictor effect of ergotamine (AELLIG and BERDE, 1969), (2) different vascular beds in the cat show different sensitivities to ergotamine (ROTHLIN and CERLETTI, 1949), and (3) the carotid artery bed in the dog is more sensitive to this substance than some other vascular beds (CARPI and VIRNO, 1957; SAXENA and DE VLAAM-SCHLUTER, 1974).

The most effective way of administering ergotamine to abort a migraine attack is by parenteral injection. For practical reasons, however, oral administration of ergotamine is preferred, usually in combination with caffeine, in order to accelerate and enhance absorption (BERDE et al., 1970; SCHMIDT and FANCHAMPS, 1974).

Studies of isolated arteries of dogs and man (PICHLER et al., 1953; TODA and FUJITA, 1973; MÜLLER-SCHWEINITZER, 1976) have shown that they respond to serotonin (5-HT), which stimulates arterial vascular smooth muscle in concentrations about 10 times lower than noradrenaline. If the maximal effect (efficacy or intrinsic activity) of serotonin is expressed in terms of the maximal effect of noradrenaline, it varies considerably in different types of arterial smooth muscle: in the dog saphenous artery the efficacy of serotonin is 60% of noradrenaline efficacy; in the dog external carotid artery and basilar artery it is 160% and 540%, respectively. Isolated dog arteries also respond to ergotamine (MÜLLER-SCHWEINITZER, 1976), which stimulates the three above-mentioned preparations in concentrations about 100 times lower than that of noradrenaline. The efficacy of ergotamine in the three preparations, measured in terms of noradrenaline, was found to be less than that of serotonin but paralleled it, being 20%, 50%, and

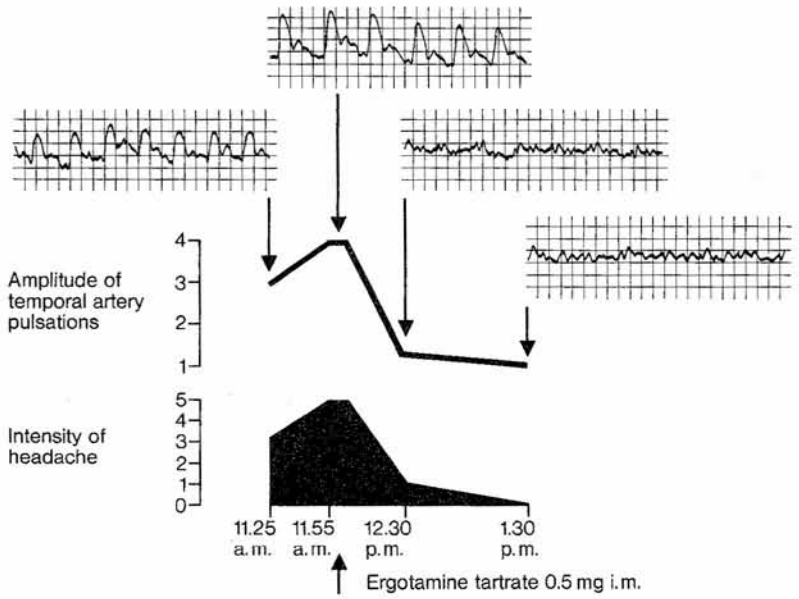


Fig. 10. Migraine attack in a woman of 22. The intensity of the pain runs parallel to the amplitude of pulsation of the temporal artery. Intramuscular injection of ergotamine tartrate exerts a tonic action on the vessels and terminates the headache. After a case of WOLFF (1955)—redrawn by permission of the author (FANCHAMPS, 1958)

210%, respectively, of noradrenaline efficacy (Fig. 11). These findings suggest that ergotamine stimulation of arterial smooth muscle may be partly mediated through serotonin receptor sites.

There is evidence that in man, a decrease in the serotonin blood level precedes the migraine attack and may be a factor in the fall of vascular tone responsible for the headache (LANCE, 1969). It is conceivable that the therapeutic effect of ergotamine is due to stimulation of serotonin receptors of cranial arteries.

Ergotamine also has a powerful effect on capacitance vessels, producing constriction (OWEN and STÜRMER, 1972; CHU et al., 1976). These effects of ergotamine on the venous site of the circulation are mediated by α-adrenoceptors, as previously mentioned. It is not known if this is of relevance to the antimigraine effect.

For the *prophylactic treatment of migraine*—and of some other vascular headaches—*methysergide* (1-Methyl-D-lysergic-acid-L-2-butanolamide-hydrogen-maleinate = Deseril = Sansert) is the prototype ergot compound.

Ever since the possible involvement of serotonin in the pathophysiology of migraine was first discussed by H.G. Wolff's research team (OSTFELD et al., 1957), a steadily increasing body of evidence has supported the view that this autacoid indeed does play a rôle in these forms of headache (see e.g. LANCE, 1969). The first successful therapeutic experiment with methysergide (SICUTERI, 1959) was based on this assumption, methysergide being given for its serotonin-antagonistic effect. It was thereafter generally maintained that the key pharmacologic quality of methysergide in this application is its outstanding serotonin-antagonistic effect; the com-

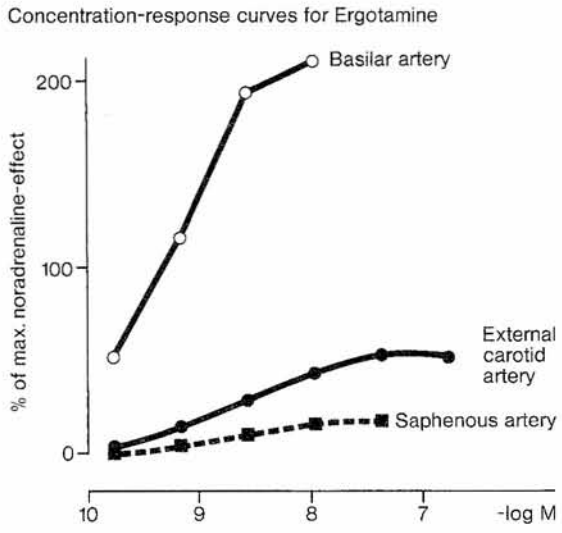


Fig. 11. Dose–response curves for ergotamine in spiral strips from canine saphenous arteries (■ ---- ■, for each point, n=6), external carotid arteries (● —— ●, for each point, n=6) and basilar arteries (○ —— ○, for each point, n=5) expressed as percentages of the maximum responses to noradrenaline (MÜLLER-SCHWEINITZER, 1976)

pound shows a high antiserotonin activity in many pharmacologic tests—not only on different types of smooth muscle, blood pressure, etc., but also on the inflammatory effect of subcutaneously injected serotonin—whereas it is practically devoid of uterotonic and vasoconstrictor activity in tests generally used for the characterization of ergot compounds (CERLETTI et al., 1960; FANCHAMPS et al., 1960; BERDE, 1972). It has recently been shown (SAXENA, 1972, 1974), however, that in the carotid artery bed of the dog, low doses of methysergide bring about a selective dose-dependent vasoconstrictor effect (Fig. 12). Although this effect of methysergide is much less pronounced than that of ergotamine, it is remarkable in itself; the threshold dose is about 20 μg/kg i.v. (that of ergotamine being about 1 μg/kg i.v.). Furthermore, it was shown that the antiserotonin effect of methysergide is present but not prominent in this particular vascular bed (SAXENA, 1972). These findings opened up new possibilities for the pharmacologic explanation of the therapeutic effect of methysergide, since it has been established (TODA and FUJITA, 1973; MÜLLER-SCHWEINITZER, 1976) that in the cerebral arteries of the dog serotonin is a potent vasoconstrictor, and the vasoconstrictor effect of ergotamine in these arteries is mediated by serotoninergic receptors. It has indeed been suggested recently that methysergide may exert its therapeutic effect as an agonist rather than an antagonist of serotonin in the carotid vascular bed (LANCE, 1974).

The pharmacologic effects of the peptide alkaloid *dihydroergotamine* (as methansulfonate=Dihydergot) differ quantitatively rather than qualitatively from those of its nonhydrogenated parent compound ergotamine. Thus, the peripheral vasoconstrictor effect of dihydroergotamine both in dogs and cats is considerably weaker than that of ergotamine (AELLIG and BERDE, 1969; OWEN and STÜRMER, 1972),

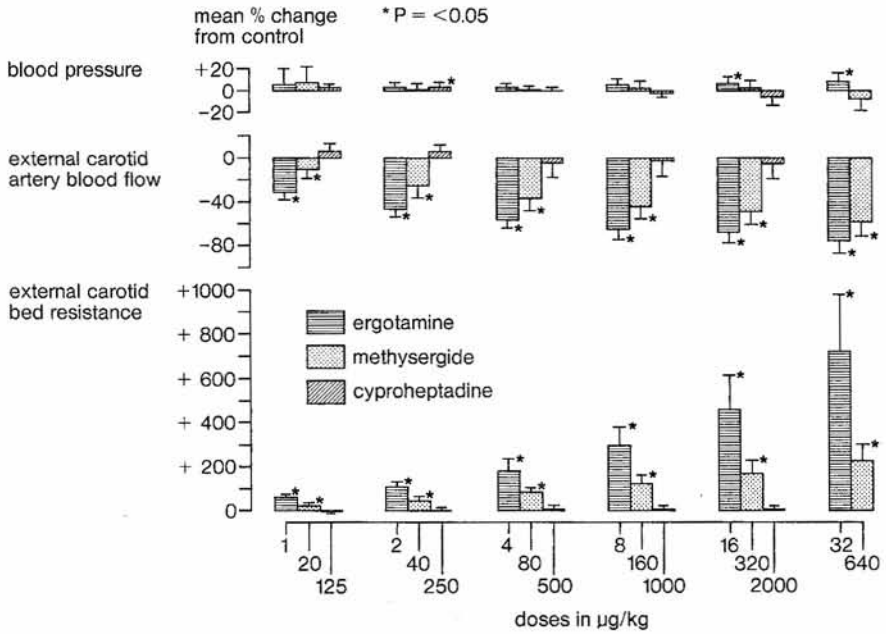


Fig. 12. Effect of the antimigraine drugs on the mean arterial blood pressure and the mean flow and resistance in the external carotid bed of the dog. Note the decrease in the carotid flow and the increase in the resistance by ergotamine and methysergide but not by cyproheptadine (SAXENA, 1972)

whereas the α-adrenergic blocking activity on smooth muscle is (several times) stronger than that of ergotamine (BRÜGGER, 1945; ROTHLIN, 1947). Dihydroergotamine is also a relatively strong antagonist of serotonin (GADDUM and HAMEED, 1954). It inhibits baroreceptor circulatory reflexes (v. EULER and HESSER, 1947) and sensitizes some smooth muscle preparations to the effect of sympathetic stimulation and noradrenaline (WEIDMANN and TAESCHLER, 1966) and, like ergotamine, inhibits the re-uptake of noradrenaline at sympathetic nerve endings (PACHA and SALZMANN, 1970) (Fig. 13).

Interestingly, dihydroergotamine is of therapeutic value both for the treatment of the *migraine attack* and for the *prophylaxis of migraine* and some other vascular headaches. For the discussion of the possible or probable relevance of different pharmacologic properties for these therapeutic applications see the above paragraphs concerning ergotamine and methysergide.

For the therapeutic use of dihydroergotamine in *orthostatic hypotension,* its constrictor effect, which is mainly confined to the capacitance vessels, is of relevance. Experiments on the autoperfused hind limb of the cat have shown that some ergot alkaloids increase the tone of capacitance vessels dose-dependently in the vascular beds of skin and skeletal muscle. Dihydroergotamine is more selective than ergotamine in that it influences resistance vessels less at the same dosage, the difference being more pronounced in skin (OWEN and STÜRMER, 1972; CHU et al., 1976) (Fig. 14). The effect of dihydroergotamine on venous tone is compar-

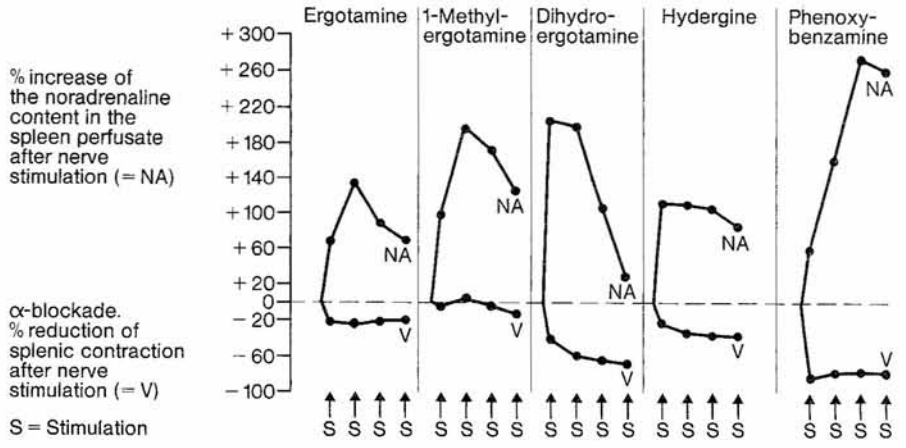


Fig. 13. The altered response of the isolated perfused spleen of the cat to postganglionic sympathetic stimulation (contraction, noradrenaline output) after administration of 1 μg/min i.a. of ergotamine, l-methylergotamine, dihydroergotamine, Hydergine, and phenoxybenzamine (PACHA and SALZMANN, 1970)

able with that of electric sympathetic stimulation, but dihydroergotamine is more selective than sympathetic stimulation in that it constricts capacitance vessels while having a negligible effect on resistance. The effect of dihydroergotamine on capacitance vessels is most probably mediated by long-lasting α-adrenoceptor stimulation, because it is abolished by α-adrenoceptor blocking drugs.

The venoconstrictor effect of dihydroergotamine was first described in man (MELLANDER and NORDENFELT, 1970) when it was shown that in resting normal subjects 10 μg/kg i.v. of dihydroergotamine mobilized about 350 ml of blood by contracting capacitance vessels in skin and skeletal muscle. In patients with orthostatic hypotension, the same doses increased cardiac output by somewhat less than half a liter in the supine position and somewhat more than half a liter in the erect position (NORDENFELT and MELLANDER, 1972).

It has been known for some time that certain ergot alkaloids may interfere with lactation and/or reproduction. It was observed, for example, that ergotoxine prevented the formation of deciduomas in the uteri of pseudo-pregnant rats, and it was suggested that this effect may be due to an influence—possibly via the hypothalamus—on the pituitary gland, resulting in inhibition of prolactin secretion (SHELESNYAK, 1954, 1958).

The prototype of an ergot compound which selectively inhibits prolactin secretion is *bromocriptine* (=CB 154=Parlodel). This is the compound which is now clinically used to suppress normal or pathologically increased prolactin secretion in man, i.e., for *suppression of lactation* and for *treatment of certain types of hypogonadism due to hyperprolactinemia* in both males and females. It has also helped to better our understanding of how prolactin secretion is controlled and what role this hormone plays in the physiology of different species.

This substance was developed from ergotoxine with the aim of retaining the

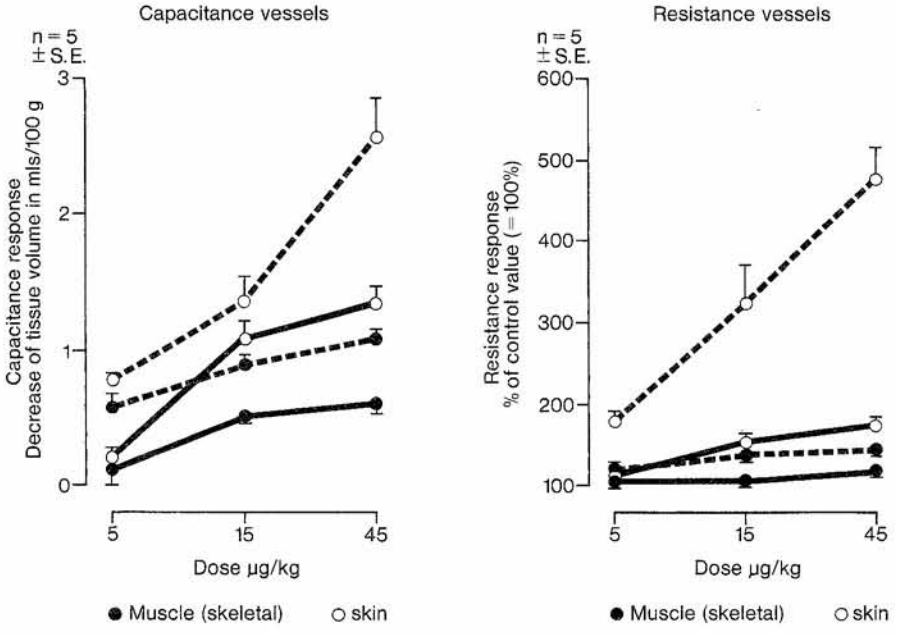


Fig. 14. Effects of ergotamine (broken lines) and dihydroergotamine (solid lines) on skeletal muscle (●) and skin (○) vasculature of the cat. The capacitance response was calculated from the rapid reduction in tissue volume on drug administration and is expressed as ml/100 g tissue. The resistance response is plotted as the post-treatment value expressed as a percentage of the pre-treatment value. The doses are expressed as µg/kg (calf muscle: µg/kg muscle i.a.; skin: µg/kg cat body weight) (CHU et al., 1976)

prolactin-inhibiting effect and eliminating the oxytocic and cardiovascular side-effects of the parent compound (FLÜCKIGER, 1972, 1975; FLÜCKIGER et al., 1976b).

As a result of many observations, the inhibition of prolactin secretion was suggested as the mode of action of bromocriptine: termination of pseudo-pregnancy in the rat (FLÜCKIGER, 1972) and prevention of implantation—an "all or nothing" type reaction—with an ED_{50} of 0.7 mg/kg s.c. in the rat (FLÜCKIGER and WAGNER, 1968), lack of effect on early pregnancy in the rabbit (FLÜCKIGER, 1972), increase in ovarian weight and number of persisting corpora lutea after daily administration of 3 mg/kg p.o. and more to adult rats (BILLETER and FLÜCKIGER, 1971), inhibition of milk secretion in several animal species at different dose levels (FLÜCKIGER and WAGNER, 1968; FLÜCKIGER, 1972; FLÜCKIGER et al., 1976a; MAYER and SCHÜTZE, 1973), suppression of the development of chemically induced mammary tumors with 6 mg/kg i.p. daily (STÄHELIN et al., 1971), etc.

With the development of highly sensitive and specific bioassays (FRANTZ et al., 1972) and radioimmunoassays (FRIESEN et al., 1972), the direct measurement of plasma prolactin levels became possible. Bromocriptine was demonstrated to decrease plasma prolactin concentration in several species, e.g., in mice (SINHA et al., 1974), in rats (MARKO and FLÜCKIGER, 1974; DÖHLER and WUTTKE, 1974), in sheep (NISWENDER, 1974), in goats (HART, 1973), in cows (KARG et al., 1972;

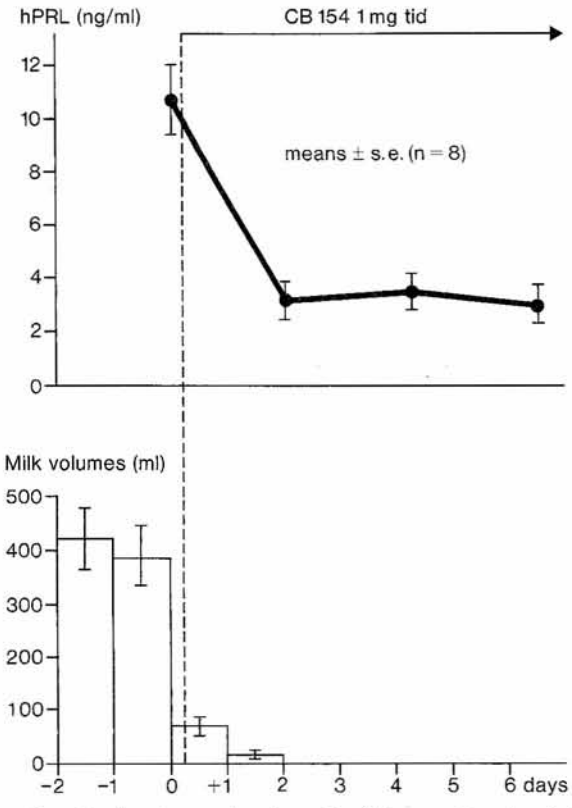


Fig. 15. Inhibition of prolactin plasma levels and milk secretion in eight lactating women exhibiting normal basal plasma prolactin concentrations (DEL POZO et al., 1975)

SCHAMS et al., 1972), and in man with a few milligrams per os (DEL POZO et al., 1972; DEL POZO et al., 1975) (Fig. 15).

The mechanism of action of bromocriptine is not fully understood. It is, however, clear that bromocriptine is not a prolactin antagonist in the sense that it would compete for peripheral prolactin-receptor sites. Its effect is the inhibition of the release of prolactin from the pituitary: it was found by in vitro studies on rat pituitary glands (PASTEELS et al., 1971; NAGASAWA et al., 1973) and pituitary cell cultures (TASHJIAN and HOYT, 1972) to inhibit prolactin secretion by a direct action on the prolactin secreting cell. In the mammal, prolactin release by the adenohypophysis is under tonic inhibition by the hypothalamus. The inhibitory effect is maintained hormonally, but the identity of the hypothalamic hormone responsible for inhibiting prolactin secretion is uncertain, some authors maintaining that it is a specific polypeptide acting on dopamine receptors, others suggesting that it may be dopamine itself. The action of bromocriptine bears some resemblance to the hypothetical hypothalamic factor which inhibits prolactin secretion. It is probable that the membrane-stabilizing effect of bromocriptine at the prolactin

secreting cell itself is also due to dopamine receptor stimulation (TAKAHARA et al., 1974; MACLEOD and LEHMEYER, 1974; HILL-SAMLI and MACLEOD, 1975).

Other findings suggest an additional hypothalamic effect brought about by dopaminergic stimulation of tuberoinfundibular neurones which control both prolactin and gonadotrophin secretion (HÖKFELT and FUXE, 1972). The two sites of action, the prolactin cell of the pituitary and the hypothalamic dopaminergic stimulation, do not necessarily suggest two different mechanisms of action.

Inhibition of prolactin secretion is of course only one consequence of *stimulation of dopaminergic receptor sites* by bromocriptine. It is well established that this alkaloid also stimulates dopaminergic neurone systems in the central nervous system which are involved in nonendocrine functions (CORRODI et al., 1973; JOHNSON et al., 1973; JOHNSON et al., 1976). This long-acting central dopamine receptor stimulating activity is probably the basis of the therapeutic effect of bromocriptine in *Parkinson's disease* (e.g. CALNE et al., 1976).

The therapeutic use of bromocriptine is not restricted to prevention or inhibition of lactation, but it is also successfully used to treat certain types of infertility. With regard to the mechanism of this effect, one has to consider that inhibition of prolactin secretion increases gonadotrophin secretion and vice versa. Both are under the control of the hypothalamus; therefore, bromocriptine can be used to increase gonadotrophin secretion in cases of hypogonadism due to an imbalance in hypothalamic control, i.e., to an unduly high prolactin secretion. This was demonstrated in mice (YANAI and NAGASAWA, 1970), in rats (FLÜCKIGER et al., 1972), and in man (LUTTERBECK et al., 1971; BESSER et al., 1972; DEL POZO and FLÜCKIGER, 1973).

From animal work in the goat (HART, 1974), the cow (SMITH et al., 1974), and in the mouse (SINHA et al., 1974), there is no evidence that bromocriptine significantly alters the secretion of TSH, ACTH, or growth hormone. An apparent paradox is that bromocriptine depresses growth hormone secretion in acromegalic patients but not in normal subjects (e.g., THORNER and BESSER, 1976).

The ergoline derivative *lergotrile* (=2-chloro-6-methyl-ergoline-8β-acetonitrile mesylate) shows effects similar to those of the peptide alkaloid bromocriptine. It inhibits dose-dependent prolactin secretion as well as milk secretion in vitro and in vivo in rats (CLEMENS et al., 1975) and in humans (CLEARY et al., 1975). There is evidence to show that this compound also acts as an agonist on some dopaminergic receptor sites (CLEMENS et al., 1975; LIEBERMAN et al., 1975).

Amongst ergot compounds which have been shown to be of therapeutic value in *senile cerebral insufficiency* (=psycho-organic disease or psycho-organic defect of aging=the syndrome of mental and behavioral deterioration in aging) *dihydroergotoxine mesylate* (Hydergine=equal parts of the mesylates of dihydroergocornine, dihydroergocristine and dihydroergokryptine [dihydro-α-ergokryptine and dihydro-β-ergokryptine in the proportion 2 to 1]) is the prototype. It is therapeutically the most widely used preparation and the one for which a modern clinical pharmacologic methodology has been developed.

The mechanism of its action in the human is not fully understood, and it is not possible to say which of the measurable pharmacologic effects of dihydroergotoxine mesylate in animal experiments are relevant for the clinical activity. There is, however, some reason to believe that receptor-mediated interactions involving

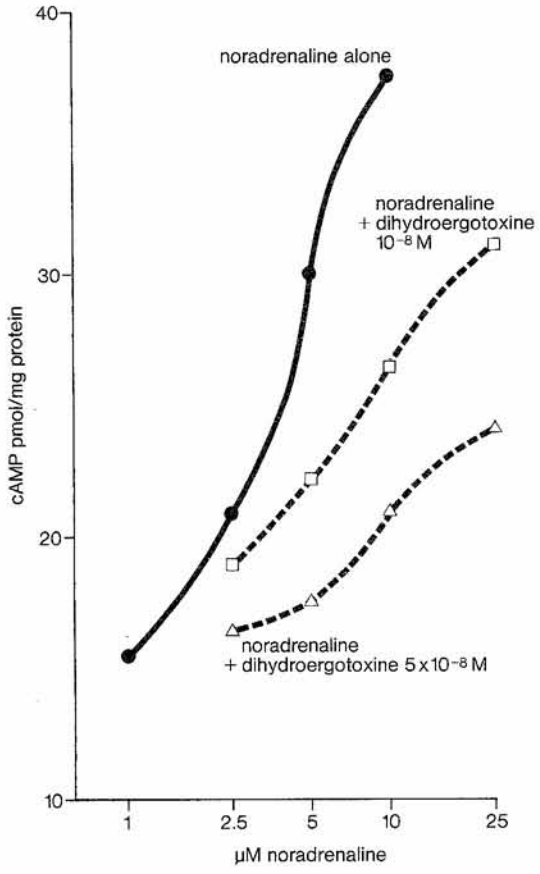


Fig. 16. Noradrenaline dose-dependently increases the cAMP content of rat cerebral cortex slices in vitro by stimulating adenyl cyclase activity. Pretreatment with dihydroergotoxine mesylate inhibits dose-dependently the effect of noradrenaline (MARKSTEIN and WAGNER, 1978)

cyclic AMP and other metabolic parameters, rather than effects on cerebral blood flow, are of primary importance (MEIER-RUGE et al., 1975). The following findings underline this aspect.

The influence of dihydroergotoxine mesylate on cyclic adenosine monophosphate (cAMP) of the brain was investigated in in vitro systems. In rat cortex slices it inhibited dose-dependently ($EC_{50} = 10^{-8}$ M) the noradrenaline-stimulated adenyl cyclase activity, resulting in a decrease of cAMP synthesis as depicted in Figure 16 (MARKSTEIN and WAGNER, 1978). In homogenates of cat cerebral cortex, dihydroergotoxine mesylate inhibits—albeit in higher concentrations (range 10^{-5} M)—the predominantly membrane-located so-called "low-K_m phosphodiesterase," resulting in a relative increase of the cAMP concentration (IWANGOFF et al., 1975).

In the more complex system of the perfused cat brain preparation some metabolic parameters were studied by means of semiquantitative histochemical methods

(EMMENEGGER and MEIER-RUGE, 1968). Changes in some enzyme activities following the reduction of the temperature of the perfusion fluid from 36° C to 29° C were shifted in the direction of the prae-hypothermic values by adding to the perfusion fluid a few μg/min dihydroergotoxine mesylate. In the same experimental setting, hypothermia-induced increase of cerebral lactic acidosis was counteracted by dihydroergotoxine mesylate (8 μg/min for 30 min) which increased the ratio of ΔAV-pyruvate to ΔAV-L-lactate (CERLETTI et al., 1973).

In the isolated perfused cat brain preparation, infusion of 8 μg/min dihydroergotoxine mesylate facilitates EEG-recovery after temporary ischemia (CERLETTI et al., 1973). In superficially anesthetized cats a marked reduction of cerebral blood flow leads to a decrease of EEG activity. This can be partially prevented by the infusion of 4 μg/kg/min dihydroergotoxine mesylate for 20 min, although the reduced cerebral blood flow is not significantly altered (GYGAX et al., 1976). In the curarized cat 0.1–0.8 mg/kg dihydroergotoxine mesylate i.v. reduced the number of reserpine-induced spike potentials in the pontogeniculo-occipital system ("PGO-spikes") in a dose-dependent way and reversed reserpine-induced electroencephalographic arousal to a high-amplitude, slow-wave pattern in cortical recordings (DEPOORTERE et al., 1975). In the rat 1 mg/kg dihydroergotoxine mesylate i.p. altered the electroencephalographically monitored sleep/wakefulness cycle by prolonging wakefulness and by shortening classical and paradoxical sleep (LOEW et al., 1976).

There is evidence that dihydroergotoxine mesylate can interfere with at least three types of receptors in the brain: In the case of inhibition of noradrenaline-stimulated adenyl-cyclase activity, adrenergic receptors in the cortex are involved (MARKSTEIN and WAGNER, 1975); in the case of inhibition of reserpine-induced potentials, a serotoninergic structure located in the pontine reticular formation is probably involved (DEPOORTERE et al., 1975). It could further be shown that i.v. administration of 2.5–10 mg/kg dihydroergotoxine mesylate reduced, in a dose-dependent manner, the antinociceptive effect of morphine in the rabbit, probably via a dopaminergic system close to the fourth ventricle (DEPOORTERE et al., 1975).

Obviously most of the above-mentioned experimental parameters cannot be investigated in man. However, EEG-studies have revealed characteristic effects of dihydroergotoxine mesylate. Electrical brain activity undergoes steady changes in frequencies and abundance during life. With age, there is a slowing of the dominant alpha frequency, an increase of the slow delta and theta activities, and a decrease in the percentage of alpha activity (ROUBICEK et al., 1972, 1973; MATEJCEK and DEVOS, 1976). In hospitalized, nonpsychotic geriatric patients, daily oral doses of 4.5 mg dihydroergotoxine mesylate brought about a shift in the dominant frequency to the fast part of the electrical spectrum and an increase in the amplitude and a better modulation of the alpha frequency (ROUBICEK et al., 1972).

Among other ergot alkaloids, *dihydroergonine* (DN 16-457) has in many respects effects similar to those of dihydroergotoxine mesylate, both in animal models (MEIER-RUGE et al., 1975) and in the human EEG (MATEJCEK and DEVOS, 1976).

Nicergoline (Sermion) was also reported to be of therapeutic value in senile cerebral insufficiency. Of its pharmacologic effects, the following may be relevant

in this respect: The recovery of a normal EEG-pattern after cerebral ischemia in the cat was accelerated by 150 μg/kg nicergoline i.v. or 15 μg/kg injected into the carotid artery (SUCHOWSKY and PEGRASSI, 1974). The same is true for the postischemic recovery of cortical-evoked potentials of the cerebral hemispheres in the cat; unilateral intracarotid injection of 20–400 μg nicergoline produced a more rapid recovery on the treated side (BOISMARE and LORENZO, 1975). On the isolated dog brain in situ in the recovery phase following hypoxia, intracarotid infusion of the compound increased glucose utilization and decreased pyruvic acid formation (BENZI et al., 1972).

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