Pharmacology *16* (Suppl. 1): 12–26 (1978)

General Pharmacology of Ergot Alkaloids

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Key Words. Ergot alkaloids · Mechanism of action · Pharmacology · Review

Abstract. Ergot alkaloids possess a wide and divergent spectrum of central and peripheral pharmacodynamic actions. They interfere with different receptor sites to stimulate and/or inhibit effector structures. The concept of partial agonism on α-adrenoreceptors has replaced the ancient hypothesis of direct stimulation of vascular and uterine smooth muscle.

The mechanisms which are considered to be relevant for the therapeutic use of dihydroergotamine, a potent drug increasing venous tone, and of bromocriptine, a specific inhibitor of prolactin secretion, are discussed in more detail.

All ergot alkaloids contain a basic chemical element – lysergic acid – which is *per se* pharmacologically inactive. Only its various derivatives display pharmacological actions either in form of a very wide spectrum of various actions (e.g., ergotamine; fig. 1) or in form of highly specific effects (e.g., bromocriptine, methysergide).

The derivatives of lysergic acid can be classified chemically as follows: (1) lysergic acid amides such as ergometrine, methylergometrine, methysergide, etc.; (2) a combination of lysergic acid with tricyclic peptide moiety leads to the second group of so-called ergopeptide alkaloids such as ergotamine, ergocornine, ergocryptine and ergocristine and their dihydro (DH) derivatives. Various substituents

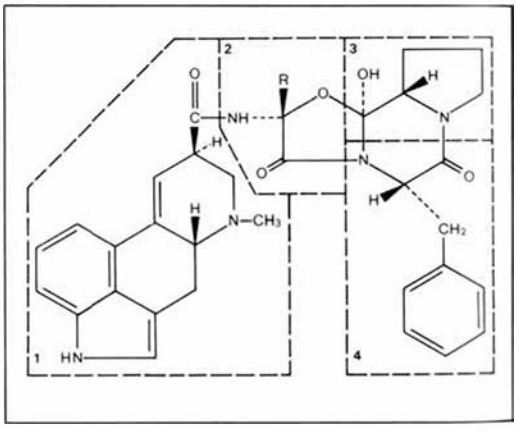

Fig. 1. Chemical structure of ergotamine (if R is $-CH_3$). 1 = Lysergic acid residue; 2 = α-hydroxyalanine residue (R = $-CH_3$); 3 = *L*-proline residue; 4 = *L*-phenylalanine residue. Note the five asymmetric centers.

can be introduced either at the lysergic acid moiety or in the peptide system, leading to a large number of either natural or synthetic ergot alkaloids.

The prerogatives for the tremendous progress in synthetic ergot peptide alkaloids chemistry were the elucidation of the absolute configuration of ergotamine (fig. 2) and the determination of the positions at the optical active centers, which have a fundamental influence on the pharmacodynamic activity of these compounds. There is no other class of chemically related substances which possesses such a wide and divergent spectrum of pharmacodynamic actions. The idea of ergot being a 'treasure chest' was already very true 40 years ago and it is even more meaningful today when the chemical barriers have been overcome by the synthesis leading to unlimited possibilities of variations.

In addition, new pharmacodynamic properties have been discovered in the recent decades, thus widening even further the spectrum of activity.

The biological properties of the ergot alkaloids (fig. 3) can, for practical reasons, be divided into central and peripheral effects. Central actions include stimulating activities probably based on dopaminergic mechanisms, as demonstrated in the EEG pattern, and, on the other side, inhibitory effects on vasomotor tone, heart rate and on circulatory reflexes. More recently, the central effect of bromocriptine as a prolactin inhibitor has been discovered. Again a dopaminergic mechanism is likely to be involved. Among the peripheral actions we find the two main classical properties of ergot-alkaloids, namely vasoconstriction and uterotonic effect. There is accumulating evidence that both actions are not elicited by a direct smooth muscle stimulation, as it has been postulated in former times, but are mediated by stimulation of α-adrenoreceptors. The classical adrenolytic action is generally found only with higher doses and is practically irrelevant for therapeutic purposes. On the other hand, the serotonin-inhibiting properties have a widespread pharmacodynamic implication and an eminent therapeutic relevance, especially in the migraine field.

Some ergot alkaloids (fig. 4) possess a very wide spectrum including various central and peripheral actions; a typical representative for this type is ergotamine. However, also dihydro-

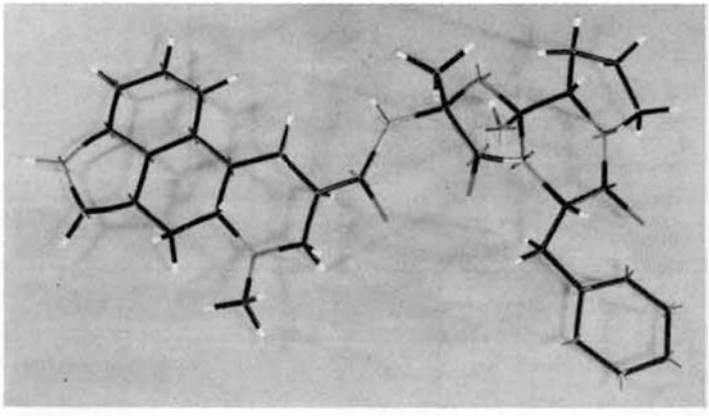

Fig. 2. Absolute configuration of 9,10-dihydroergotamine (DHE).

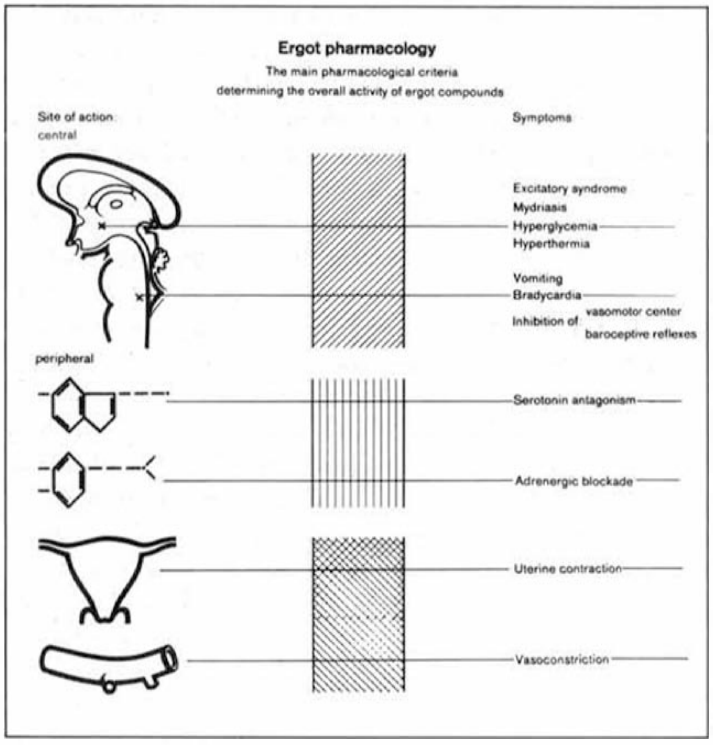

Fig. 3. Pharmacological profile of ergot alkaloids (*Cerletti*, 1959).

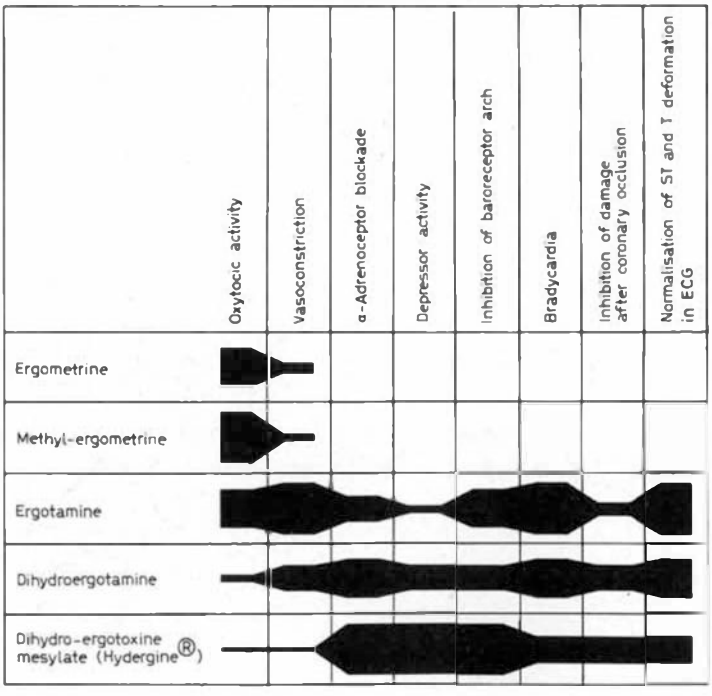

Fig. 4. Pharmacological profile of some ergot alkaloids.

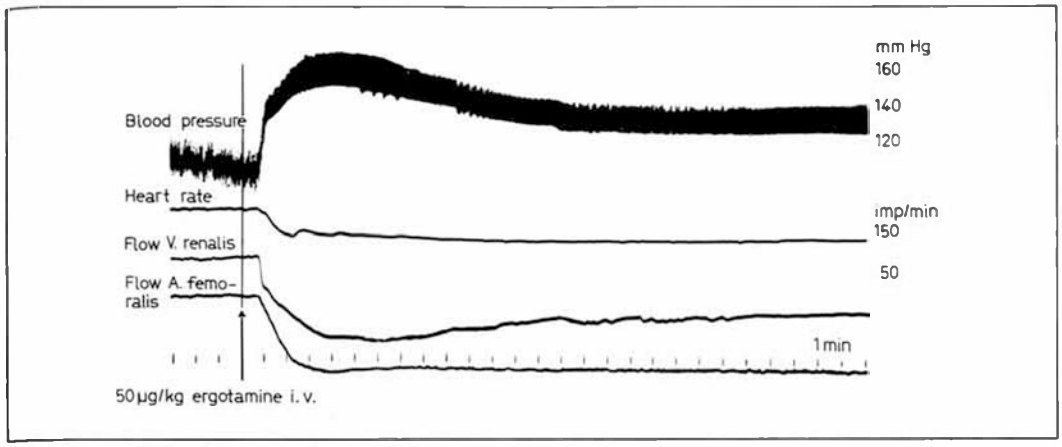

Fig. 5. Effect of ergotamine on blood pressure, heart rate and blood flow in the anesthetized dog.

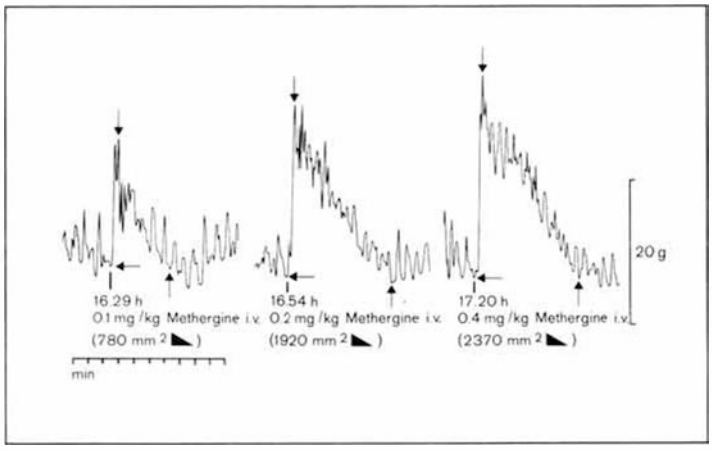

Fig. 6. Isometric recording of the uterotonic effect of methylergometrine (Methergine®) on the estrous rabbit uterus *in situ*. Increased uterine activity is calculated in terms of the area of the time-response curve (between arrows) (*Berde and Saameli*, 1966).

ergotamine (DHE) and Hydergine® exhibit a relatively large spectrum. On the other side of the scale we find ergometrine and methylergometrine as uterotonics, methysergide as serotonin antagonist and bromocriptine as prolactin inhibitor.

Now let us look at some of these individual actions: figure 5 shows the typical circulatory effects of ergotamine in an anesthetized dog after intravenous injection. The sustained increase in blood pressure, the bradycardia and the decrease in blood flow in different vascular beds can be recognized. The long duration of action of ergotamine is noteworthy.

Another classical property of ergot alkaloids is the uterotonic effect as illustrated in the rabbit uterus *in situ* (fig. 6).

The adrenolytic actions of ergot alkaloids also belong to the classical properties. There are a few examples from former experiments. More recent pharmacological investigations have resulted in a different receptor concept and terminology (α-adrenergic blocking action). One should give up using the older expression 'adrenolytic effect'.

Figure 7 illustrates the inhibition of adrenaline on the isolated guinea pig seminal vesicle. The next example (fig. 8) shows an *in vivo*

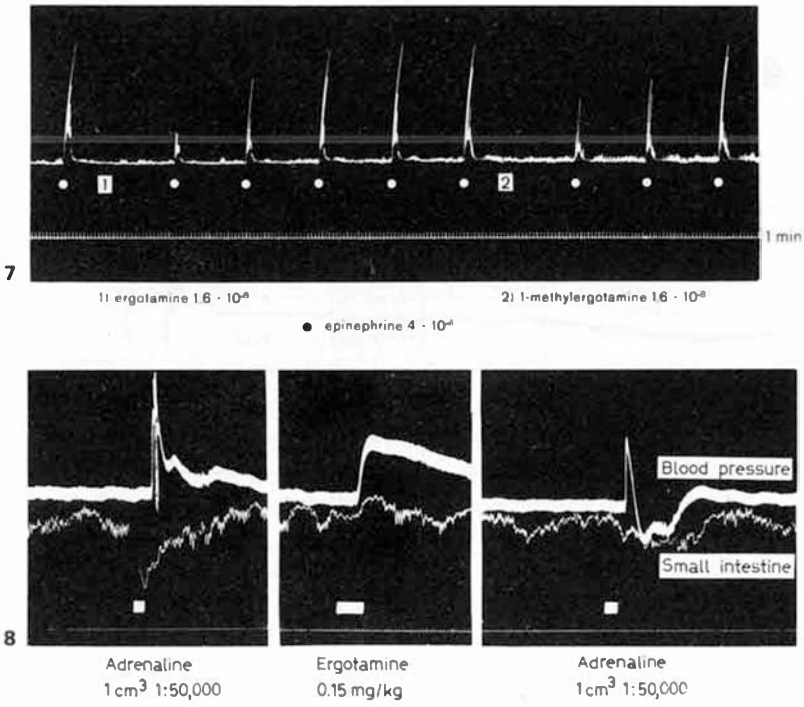

Fig. 7. Inhibition of adrenaline-stimulated ($4 \cdot 10^{-6}$) contractions of guinea pig seminal vesicles *in vitro* by ergotamine (at '1': $1.6 \cdot 10^{-8}$) and l-methyl-ergotamine (at '2': $1.6 \cdot 10^{-8}$).

Fig. 8. Registration of blood pressure and small intestine motility in an anesthetized dog. After i.v. administration of ergotamine, the pressor effect of adrenaline is diminished, the depressor effect due to β-adrenoreceptor stimulation is unmasked and the relaxation of the small intestine is completely abolished.

experiment where the hypertensive effect and the relaxation of the small intestine induced by adrenaline are inhibited by rather large doses of ergotamine. Another experiment (fig. 9) shows the adrenaline reversal induced by ergotamine on blood pressure and the nictitating membrane in a spinalized cat.

Even at the time of these experiments the pharmacologists often observed that small doses of ergotamine potentiate the action of adrenaline on stimulation of sympathetic nerves. Such observations however did not fit in the classical concept of so-called 'adrenolytic action'. Various explanations were given for these findings, e.g., inhibition of baroreceptor reflexes leading to potentiation of adrenaline, etc.

Figure 10 illustrates that a small dose of ergotamine does not inhibit but potentiates the action of adrenaline on blood pressure and contraction of the nictitating membrane. This is due to an agonistic interference of ergotamine with the adrenergic receptor system. A few examples will be given later on in this presentation.

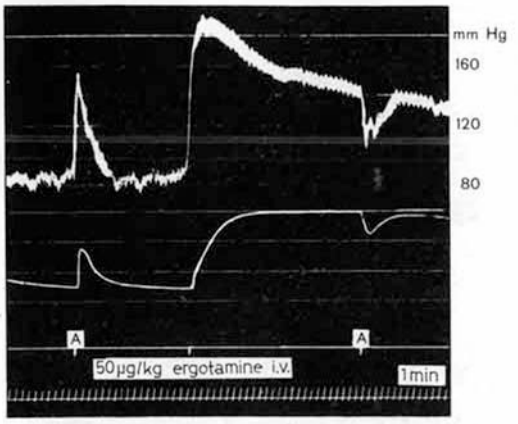

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Fig. 9. Registration of blood pressure and tone of the nictitating membrane in a spinal cat preparation. After administration of 50 µg/kg of ergotamine the effects of adrenaline are reversed. A = 1 µg/kg adrenaline i.v.

Fig. 10. Registration of blood pressure and tone of the nictitating membrane in a spinal cat preparation. After administration of 5 µg/kg ergotamine, the pressor effects of adrenaline and noradrenaline are enhanced. Before ergotamine, only adrenaline elicits an increase in the tone of the nictitating membrane whereas noradrenaline is ineffective. After ergotamine, the adrenaline effect on the nictitating membrane is enhanced and noradrenaline elicits a stimulation, too. A = 2 µg/kg adrenaline i.v.; N = 2 µg/kg noradrenaline i.v.

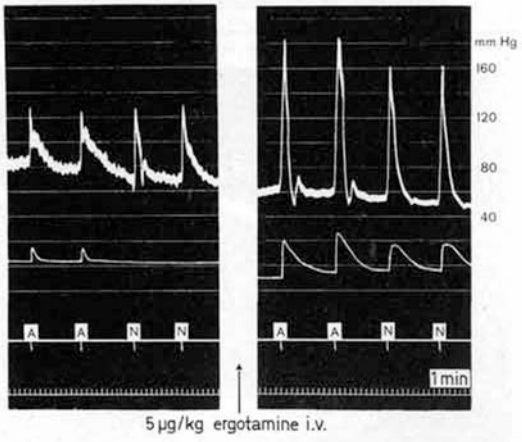

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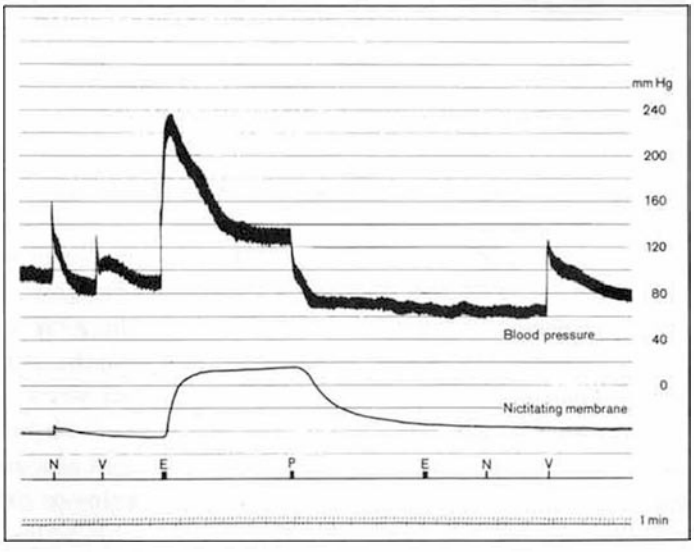
Fig. 11. Registration of blood pressure and tone of the nictitating membrane in a spinal cat preparation. Effects of noradrenaline, vasopressin and ergotamine before and after the α-adrenoreceptor blocker phenoxybenzamine. Note that α-blockade inhibits the long-lasting pressor effect of ergotamine on blood pressure and the stimulating effect on the nictitating membrane. Moreover, α-blockade completely blocks the effects of ergotamine and noradrenaline whereas the effect of vasopressin is enhanced. N = 2 µg/kg norepinephrine i.v.; V = 0.1 IU/kg vasopressin i.v.; E = 30 µg/kg ergotamine i.v.; P = 20 mg/kg phenoxybenzamine i.v.



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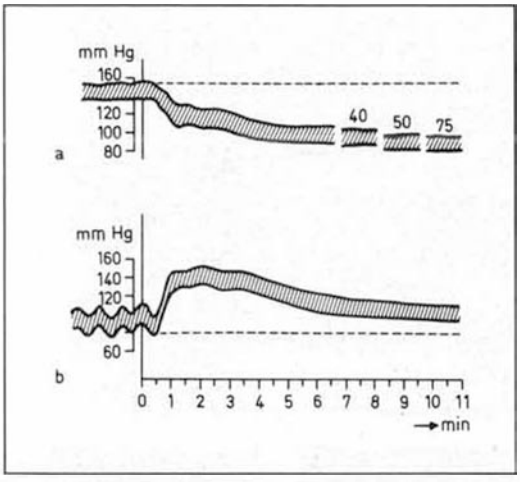

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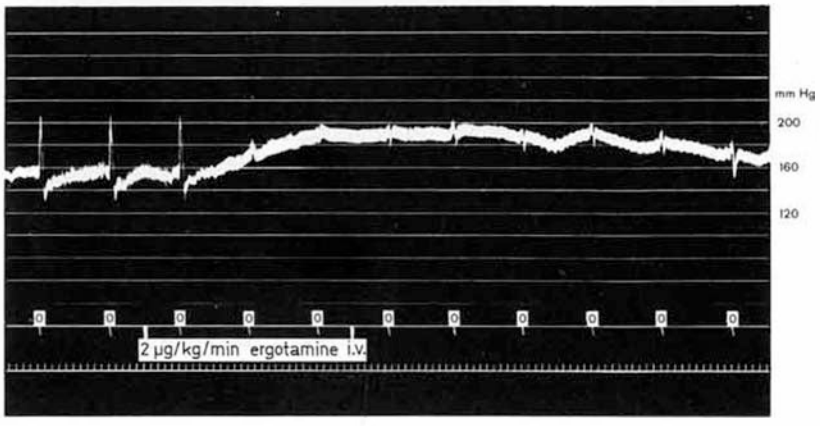
Fig. 12. Registration of blood pressure in an anesthetized cat (a) and in a decerebrated cat (b) before and after intravenous injection of 0.1 mg/kg (a) or 0.2 mg/kg (b) dihydro-ergocristine.

Fig. 13. Registration of blood pressure in an anesthetized cat. Pressor reactions due to carotid sinus occlusion (○) before and after an intravenous infusion of ergotamine (2 μg/kg/min) over 30 min. Time in minutes.



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These studies also led to a change of interpretation of the typical vasoconstrictor effect. It is no more considered to be a direct smooth muscle stimulating effect but rather due to an interference with the α-adrenergic system.

As the following experiment (fig. 11) illustrates, the pressure effect of ergotamine can be antagonized until complete blockade by an adrenergic blocking drug such as phenoxybenzamine. This experiment again demonstrates the interference of ergotamine with the α-adrenergic system and disproves any direct smooth muscle stimulation.

Some ergot alkaloids have virtually no vasoconstrictor effect, i.e., Hydergine®. With this drug the central effect on the vasomotor centers predominates, which leads to hypotension.

Figure 12 illustrates these properties of the dihydrogenated alkaloids. In the intact cat, DH-ergocristine induced hypotension (fig. 12a). The weak inherent vasoconstrictor effect can only be demonstrated in the decerebrated animal where the vasomotor center is destroyed.

A further example of central activities of ergot alkaloids is the inhibitory effect of ergotamine on cardiovascular reflexes (hypertension after occlusion of the carotid artery) (fig. 13).

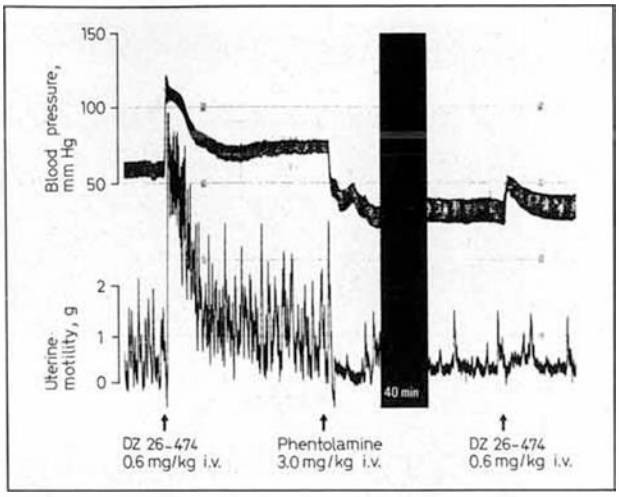


Fig. 14. Registration of blood pressure (above) and uterine motility (below) in an anesthetized rabbit in estrus. DZ 26-474, an ergot alkaloid, is injected intravenously before and after the α-adrenoreceptor-blocking drug phentolamine. Note the complete inhibition of the uterotonic effect of DZ 26-474 and the decrease of the pressor reaction (*Hool-Zulauf and Stürmer*, 1976).

Table I. Inhibition of serotonin-induced rat's paw edema by four different ergot alkaloids (s.c. ED_{50} values, μg/kg)[1]

Substance	Pretreatment time, h						
	0.5	2	4	6	8	16	24
Ergotamine	900	170	54		100	170	1,000
5'-Methylergoalanine	750	93		170			
1-Methylergotamine	800	150	80		84	150	1,050
Methysergide	13.5	32	175		1,000		

[1] Note the differences in the time course of the serotonin antagonism. For details see text.

The uterotonic action of ergot alkaloids belongs to the classical pattern. The first therapeutic application of ergot alkaloids was in obstetrics, namely to avoid excessive blood loss in the third stage of labor. The first pharmacological studies with ergot alkaloids concentrated on its uterotonic action, at that time mainly for the standardization of crude extracts. An example of the uterotonic action is shown in figure 14.

The ergotamine derivative DZ 26-474 induces, like ergotamine, hypertension and uterine contraction and stimulates rhythmic activity. The classical explanation of the uterotonic effect was a direct muscle-stimulating activity, as for the vasoconstriction. Again it can be shown that the uterotonic effect of ergot alkaloids is also mediated through an α-adrenergic mechanism because the stimulating effect can easily be blocked by α-adrenergic blocking drugs such as phentolamine.

Among the peripheral actions of the ergot alkaloids, its serotonin-inhibiting property is already out of the classical pattern and belongs to relatively newer studies. Ergot alkaloids inhibit, to a variable degree, the effect of serotonin *in vitro* and *in vivo*. Table I shows that ergotamine and methysergide display a differ-

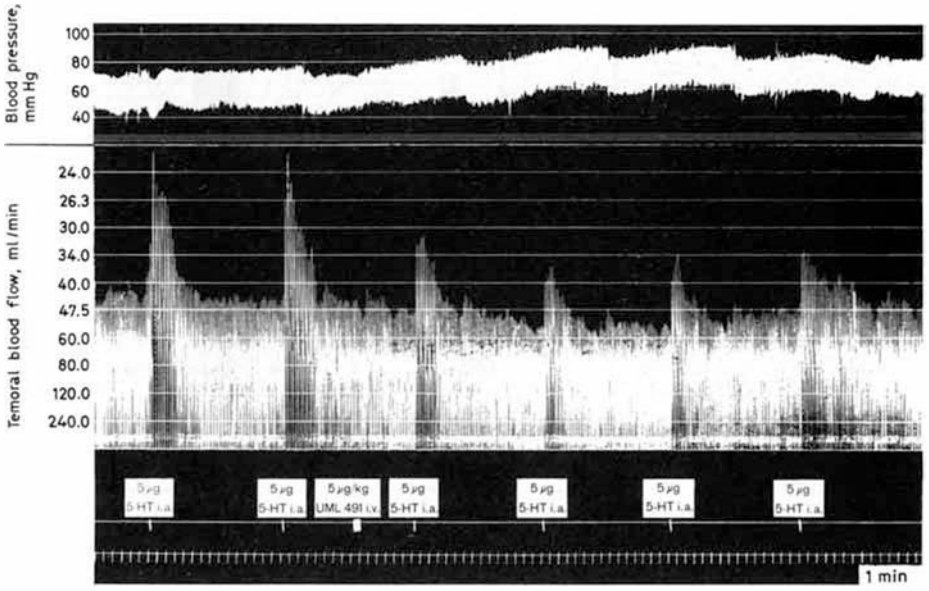


Fig. 15. Registration of blood pressure (above) and femoral blood flow (below) in an anesthetized dog. Intra-arterial injections of serotonin (5-HT) before and after intravenous injection of 1-methyl-α-lysergic acid butanolamide (UML 491). Time in minutes. Note the inhibition of the vasoconstrictor effect after UML 491 which lasts at least 60 min.

ent pattern of serotonin antagonism. Whereas methysergide is a powerful serotonin antagonist immediately after administration, but with relatively short duration, ergotamine, on the other side, needs a long latency period until it develops its full activity.

The next experiment (fig. 15) demonstrates the anti-serotonin activity of methysergide on the femoral blood flow. As already mentioned, some ergot alkaloids exhibit a wide spectrum of activity, i.e. ergotamine, whereas others are highly specific in one action, even if chemically closely related. Numerous examples can be given. Figure 16 just shows one of them. Methysergide, which is the 1-methyl-derivative of methylergometrine (Methergine®), exhibits practically no uterotonic effect. Another good example could be added, namely that methysergide does not induce substantial vasoconstriction and that it is devoid of 'adrenolytic' and important central effects.

In the first part of my presentation I tried to outline the classical pharmacology of ergots, demonstrating their wide spectrum of activity. In addition to that classical concept I gave a few outlooks on the modern concepts concerning the mechanism of action of ergot alkaloids. Let us now, in the second part, illustrate with a few examples the mechanisms which are considered to be relevant for the therapeutic use of some of the ergot representatives.

One field of therapeutic use of ergot alkaloids is the use of DHE in orthostatic hypotension. According to the classical concept, it would appear to be paradox to use an α-adrenergic blocking agent in this indication. I have repeatedly mentioned, however, that this adrenolytic effect of ergots can only be demonstrated under special experimental conditions. Let us therefore look at recent findings offering

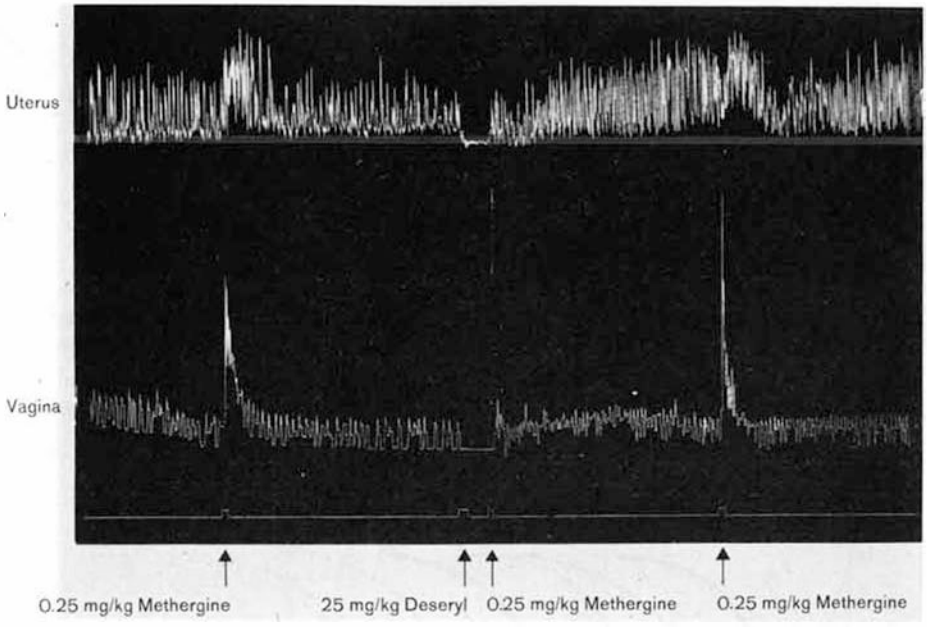


Fig. 16. Registration of motility of the uterus (above) and the vagina (below) *in situ* of a rabbit in estrus. Intravenous injection of 0.25 mg/kg methylergometrine (Methergine®) stimulates uterine and vaginal activity. 25 mg/kg 1-methylergometrine (Deseril®) (100 times the dose of methylergometrine) lacks completely the stimulating effect of methylergometrine but inhibits the stimulating effect of the latter given shortly afterwards. 30 min later the stimulating effect of methylergometrine is back to the starting level.

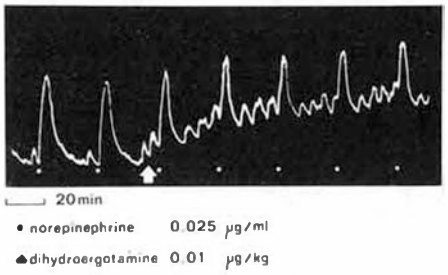


Fig. 17. Isotonic recording from an isolated human femoral vein (spiral strip, 62-year-old female). At the white dots noradrenaline was added to the bath (final concentration 0.025 µg/ml) and washed out after reaching the full contraction height. Addition of DHE, 0.01 µg/kg, elicits a long-lasting rise in tone. Changing the bathing fluid does not remove the ergot alkaloid from its binding sites (*Stürmer*, 1976).

a new concept for the action of DHE on the peripheral circulation.

Very small doses of DHE induce a long-lasting increase in basal tone of isolated human femoral veins (fig. 17); this is in contrast to the short-lasting effect of noradrenaline.

The venoconstrictor effect of DHE is dose-dependent as demonstrated by the three dose-response curves in figure 18. This figure also shows that veins from different origins exhibit a different sensitivity. It is interesting to note that the human varicose vein responds to DHE with the most pronounced constriction.

The venoconstriction induced by DHE or ergotamine can be antagonized by α-adrenergic blocking agents in the same fashion as with noradrenaline. The parallel shift of the dose-response curves of ergotamine and noradrena-line under the influence of increasing concen-

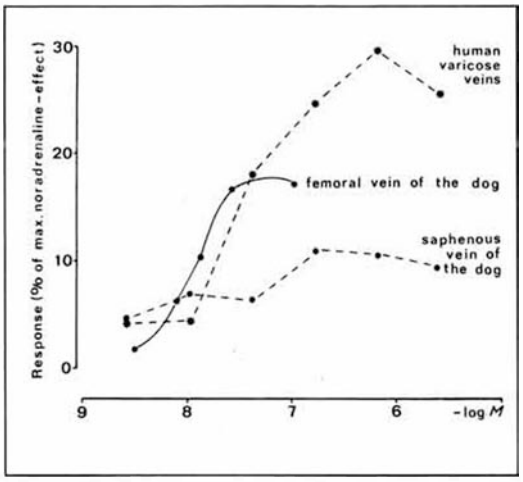


Fig. 18. Dose-response curves for DHE obtained from helical strips of human varicose veins (n = 6), and from femoral veins (n = 6) and saphenous veins (n = 4) of the dog. Isometric recording. Note that the stimulating effect in human varicose veins reaches 30% of the maximal noradrenaline effect (*Müller-Schweinitzer*, 1974). *M* = Molar.

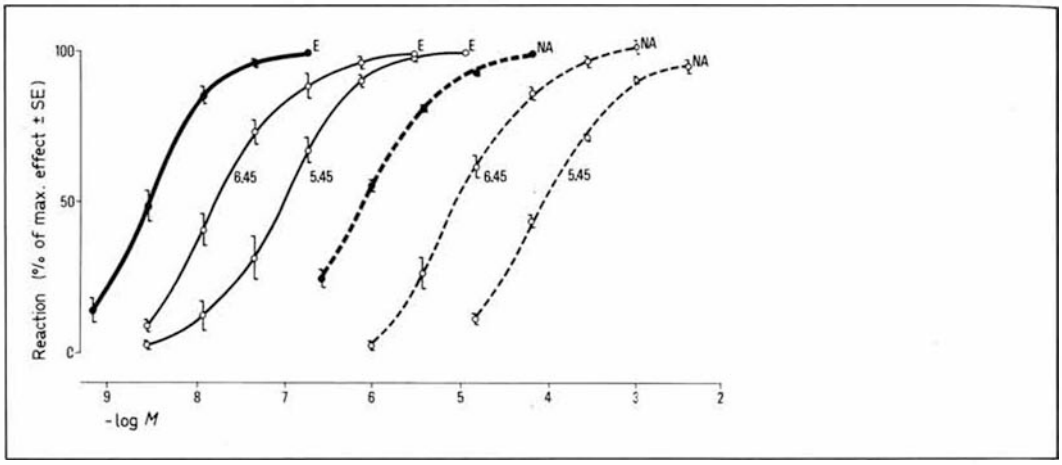


Fig. 19. Helical strips of dog femoral vein. Isometric recording. Cumulative dose-response curves for ergotamine (E) and noradrenaline (NA) before (heavy lines, n = 18) and 5 min after phentolamine (narrow lines, n = 6); mean ± SEM. Phentolamine displaces the dose-response curves of both noradrenaline and ergotamine to the right in a dose-dependent fashion. pA_2 values calculated from these shifts were 7.5 for phentolamine versus noradrenaline and 6.8 for phentolamine versus ergotamine (*Stürmer*, 1976). *M* = Molar.

trations of phentolamine demonstrates that the venoconstrictor effect of ergot alkaloids is mediated mainly through stimulation of α-adrenoreceptors (fig. 19).

Further evidence of this concept is provided by comparative experiments in cats *in vivo* where DHE elicits the same effect as the electric stimulation of the sympathetic nerve (fig. 20). This affinity of DHE to α-adrenergic receptors is very specific for the venous system.

Figure 21 illustrates that DHE is much less active in increasing peripheral resistance than

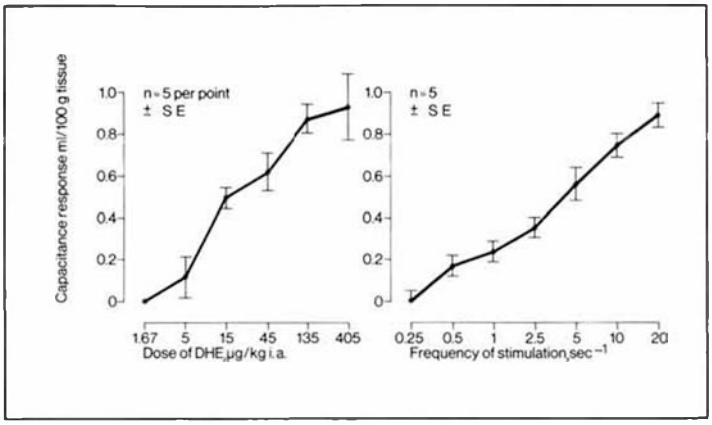


Fig. 20. Calf muscle of the cat. Comparison of the effects of DHE with those of electrical sympathetic nerve stimulation on the capacitance vessels (*Chu et al.*, 1976).

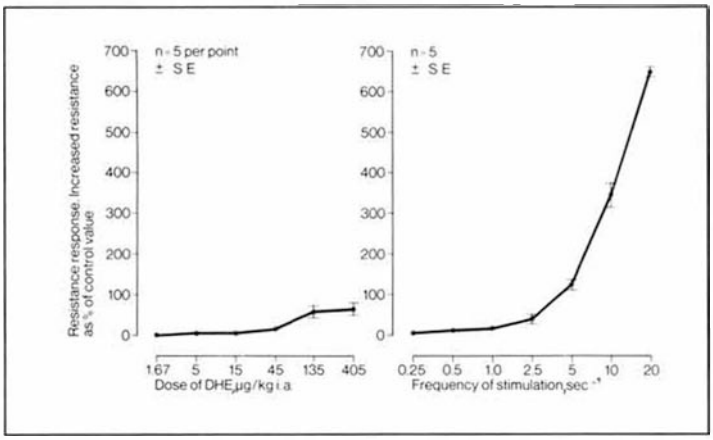


Fig. 21. Calf muscle of the cat. Comparison of the effects of DHE with those of electrical sympathetic nerve stimulation on the resistance vessels. • = Muscle (skeletal); ○ = skin.

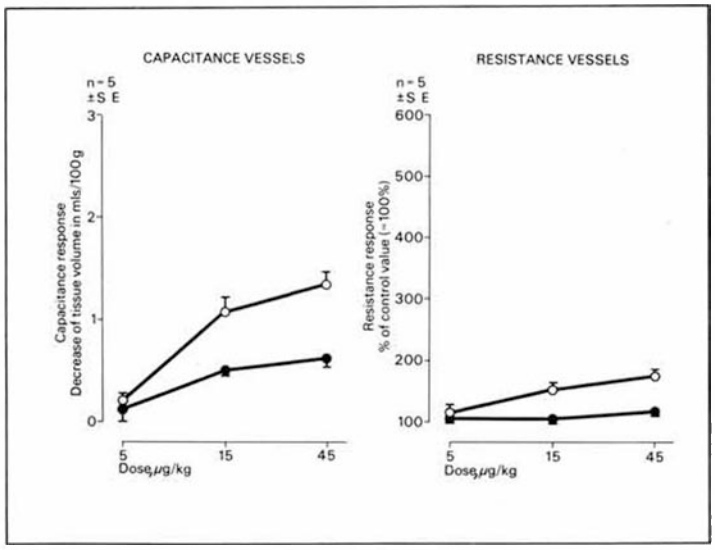


Fig. 22. Cat calf muscle and skin. Comparison of the effect of DHE on capacitance and resistance vessels in both vascular beds (*Stürmer*, 1972).

Table II. Present concept of the vascular pharmacology of DHE

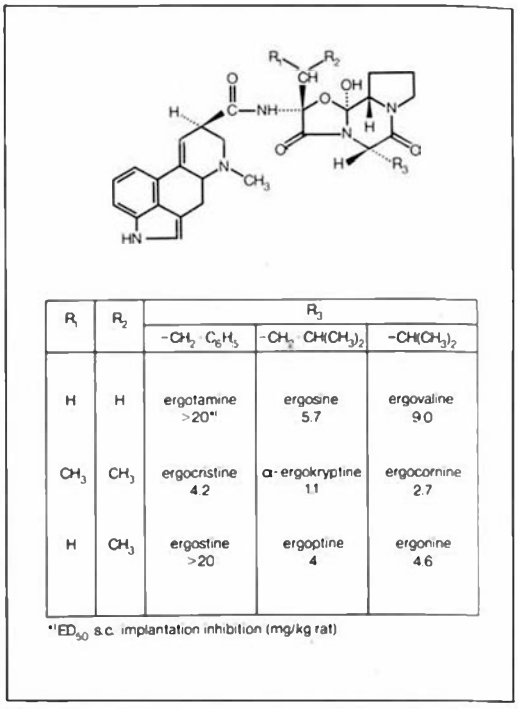
1 Ergot alkaloids increase the tone of capacitance vessels dose-dependently in the vascular beds of skin and skeletal muscle

2 DHE is more selective than ergotamine in that it influences resistance vessels less at the same dosage, the difference being more pronounced in skin

3 The effect of DHE on venous tone is comparable with that of electrical sympathetic stimulation

4 DHE is more selective than sympathetic stimulation; it constricts capacitance vessels while having a negligible effect on resistance

5 The effect of DHE on capacitance vessels is abolished by the α-adrenoreceptor-blocking drug phenoxybenzamine



R_1	R_2	R_3		
		$-CH_2 \cdot C_6H_5$	$-CH_2 \cdot CH(CH_3)_2$	$-CH(CH_3)_2$
H	H	ergotamine >20*	ergosine 5.7	ergovaline 9.0
CH_3	CH_3	ergocristine 4.2	α-ergokryptine 1.1	ergocornine 2.7
H	CH_3	ergostine >20	ergoptine 4	ergonine 4.6

*ED_{50} s.c. implantation inhibition (mg/kg rat)

Fig. 23. The ovum implantation inhibitory potencies of the natural (9,10-unsaturated) ergot peptide alkaloids as a measure of their prolactin secretion inhibitory activity. ED_{50} values, subcutaneous injection in inseminated rats on day 5 (*Flückiger et al.*, 1976).

sympathetic nerve stimulation. This property of DHE is underlined by the experiment described in figure 22. Again it can be seen that the constrictor effect of DHE is much more pronounced on the capacitance vessels (veins) than on the resistance vessels (arteries). As already mentioned, a different sensitivity of different vascular beds can be demonstrated. In this example the skin vasculature exhibits a higher reactivity than the muscular vasculature.

Table II summarizes the present concept of the vascular pharmacology of DHE.

Before concluding, I shall briefly touch one of the newest findings of ergot pharmacology, which has already clinical implication.

A large number of ergot alkaloids inhibit prolactin secretion in animals and in man. The first method to assess the prolactin inhibitory potency was the inhibition of ovum implantation in rats, a process which – in this species – is prolactin-dependent (fig. 23).

Whereas the ergot alkaloids usually present a large spectrum of activities, bromocriptine is a highly specific prolactin secretion inhibitor (fig. 24, table III).

The main therapeutic applications of prolactin secretion inhibition are the inhibition of puerperal and non-puerperal lactation and the restoration of fertility in patients with hyperprolactinemic hypogonadism. One example of the former property is illustrated in figure 25. Administration of 2.5 mg 3 times daily of bromocriptine (CB 154) given after delivery, immediately decreases serum prolactin levels and, in consequence, the secretion of milk. The

ERGOTOXINE TYPE			
R_3	name	ED_{50} mg/kg s.c. (rat)	
		ovulation ↓	implantation ↓
$-CH_2-C_6H_5$	Ergocristine	1.3	4.2
$-CH_2-CH(CH_3)_2$	α-Ergokryptine	1.7	1.1
	2-Br-α-Ergokryptine	~20	0.7
$-CH\begin{matrix}CH_3\\CH_2-CH_3\end{matrix}$	β-Ergokryptine	1.7	2.8
$-CH(CH_3)_2$	Ergocornine	1.7	2.7
	2-Br-Ergocornine	>20	>5

Fig. 24. Inhibition of ovulation and ovum implantation in the rat by ergot alkaloids of the ergotoxine group (2′β-isopropyl). R_3 is the residue in position 5′α of the peptide moiety. Note that the implantation inhibition of bromocriptine (2-Br-α-ergokryptine) is specific compared to the other compounds.

Table III. Prolactin secretion inhibitory potency of bromocriptine in rats

Condition	ED_{50}, mg/kg s.c. hours after treatment			
	2	4	8	24
Adult male rats: inhibition of nonstimulated secretion	0.009	0.006	0.08	1.0
Female inseminated rats: inhibition of ovum implantation		0.7		

normal situation is depicted in the upper part of the figure.

There is increasing evidence that a dopaminergic mechanism is responsible for the prolactin secretion inhibitory property of bromocriptine. As dopaminergic mechanisms seem to be involved in various pathological conditions such as Parkinson's disease, acromegaly, Cushing's disease, and perhaps depression, new therapeutic applications of bromocriptine – the newest

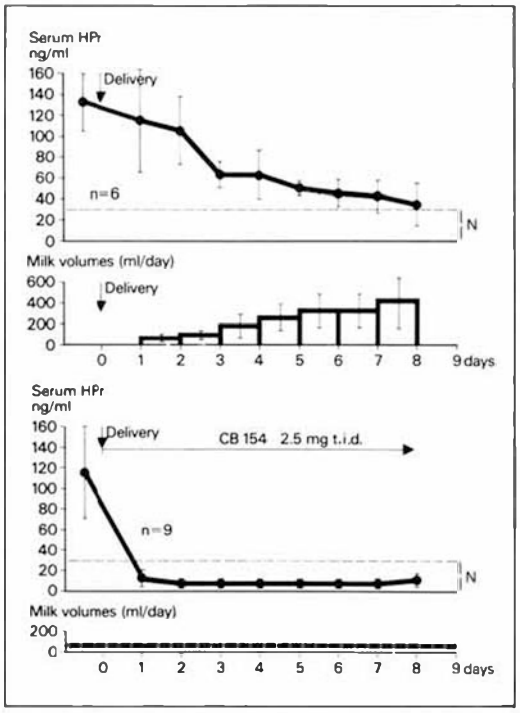


Fig. 25. Postpartum period. Human serum prolactin levels (HPr) and milk volume (mean ± SD) up to 9 days after delivery in an untreated control group (upper traces) and in women treated with bromocriptine (CB 154). Note the complete suppression of prolactin secretion with inhibits milk secretion completely.

drug out of the ergot series – are under investigation.

In this presentation I tried to give a panorama view of an interesting class of compounds which started as dangerous poisons in medieval times, then turned to important applications in obstetrics and after intensive chemical and pharmacological research, diversified in a variety of clinical indications and are still in progression in even newer areas.

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