

The History and Pharmacology of Dopamine Agonists

X. Lataste

ABSTRACT: The recognition of the dopaminergic properties of some ergot derivatives has initiated new therapeutical approaches in endocrinology as well as in neurology. The pharmacological characterization of the different ergot derivatives during the last decade has largely improved our understanding of central dopaminergic systems. Their development has yielded valuable information on the pharmacology of dopamine receptors involved in the regulatory mechanisms of prolactin secretion and in striatal functions.

The clinical application of such new neurobiological concepts has underlined the therapeutical interest of such compounds either in the control of prolactin-dependent endocrine disorders or in the treatment of parkinsonism. Owing to their pharmacological profiles, dopaminergic agonists represent a valuable clinical option especially in the management of Parkinson's disease in view of the problems arising from chronic L-Dopa treatment.

RÉSUMÉ: L'identification des propriétés dopaminergiques de certains dérivés de l'ergot a permis d'envisager de nouvelles approches thérapeutiques tant en endocrinologie qu'en neurologie. Au cours des dix dernières années, la caractérisation de leurs différents profils pharmacologiques, souvent complexes, a largement contribué au développement de nos connaissances sur les mécanismes dopaminergiques qui régissent la régulation de la sécrétion de prolactine ainsi que la régulation striatale des activités motrices. De plus, le développement de dérivés ergotés dopaminomimétiques a permis l'identification des différents sites récepteurs de la dopamine.

L'application clinique de ces nouveaux concepts neurobiologiques a révélé l'intérêt porté à ces substances notamment dans le contrôle des désordres endocriniens prolactino-dépendants ainsi que dans le traitement de la maladie de Parkinson. De par leur pharmacologie, les agonistes dopaminergiques constituent, notamment dans le cadre de la maladie de Parkinson, une alternative clinique non négligeable aux problèmes liés au traitement chronique par la L-Dopa.

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"Until we are better informed respecting the nature of this disease, the employment of internal medicines is scarcely warrantable".

J. PARKINSON, 1817.

Twenty years ago, pharmacologists were preoccupied with the characterization of the α -adrenergic and serotonergic properties of ergot derivatives as potentially beneficial in the treatment of migraine.

However, for many years, interactions with reproductive functions have been reported to result from the use of certain ergot alkaloids. Contamination of sow-feed with ergot of *Claviceps* sp. (Shone et al., 1959; Loveless, 1967; Mantle, 1968a) or *Sphacelia* sp. (Mantle, 1968b) was responsible for endemic agalactia in sows. Despite these observations, the inhibitory effect of prolactin secretion induced by ergot alkaloids and their derivatives was first suggested by Shelesnyak (1954). This original report underlined the inhibitory effects upon deciduoma formation and ovum implantation in the rat uterus induced by ergotoxine. This effect, reversed by injections of progesterone or prolactin (Shelesnyak, 1958), was indicative of a direct (pituitary) or indirect (hypothalamus) inhibition of prolactin secretion induced by ergotoxine.

This hypothesis was confirmed by Zeilmaker and Carlsen (1962). At that time, ergot chemists and pharmacologists in our

laboratories began their search for an ergot alkaloid or a derivative which would selectively inhibit prolactin secretion as its main action.

Among various compounds tested, 2-bromo- α -ergocryptine methanesulfonate (bromocriptine) was the most promising structure exhibiting such a specific action upon prolactin secretion. Bromocriptine (for synthesis and activity see e.g. Schneider et al., 1977), was chosen to be developed for testing in human in 1967. However the existence of human prolactin, as a separate pituitary hormone, was negated by most endocrinologists (Geschwind, 1972) except Pasteels (1973). Moreover, there was no receptor concept in support of a possible inhibition of prolactin secretion, adrenoceptors and serotonin receptors not being involved.

The clinical situation was dramatically changed by the recognition of human prolactin (h Prl) as a discrete hormonal entity (Frantz et al., 1970; Hwang et al., 1971; Lewis et al., 1971; Loewenstein, 1971; Turkington, 1971) and the concomitant development of a suitable radio-immunoassay for h Prl (Hwang, 1971).

As the prolactin concept was developed, bromocriptine was intensively investigated to improve our understanding of its action profile. Among the various investigations performed, the interaction of bromocriptine and ergocornine with hypothalamic catecholaminergic neurons (Fuxe et al., 1970; Hoekfelt

et al., 1972) provided an essential clue in ergot pharmacology by demonstrating their ability to reduce dopamine (DA) turnover in hypothalamic and neostriatal dopaminergic neurons. Such central dopaminomimetic properties were confirmed by Corrodi et al. (1973), Myamoto et al. (1974) and Johnson et al. (1976). Hence the ability to stimulate DA receptors was recognized for ergot compounds and the clinical relevance of this property was soon demonstrated in patients with Parkinson's disease (Calne et al., 1974a and b).

However, the nature of the regulation of prolactin secretion was still unknown. The link between DA receptor stimulation and inhibition of prolactin secretion induced by bromocriptine was clearly demonstrated only somewhat later (Flueckiger et al., 1976; MacLeod, 1976).

This brief review of the most recent aspects of the development of the pharmacology of ergot derivatives underlines the broad spectrum of their potential activities resulting from their ability to interact with different receptor systems.

Dopaminomimetic Agents and Parkinson's Disease

The clinical use of dopaminergic compounds in the treatment of Parkinson's disease was suggested by Fuxe et al. (1970) and established by Calne et al. (1974a). However, ergot derivatives were proposed a century ago in the treatment of *paralysis agitans*, on the basis of their parasympatholytic properties. Charcot (1892) reported the lack of beneficial effects of ergot alkaloids as well as for *atropa belladonna* in parkinsonian patients. At that time, only low-molecular-weight ergot alkaloids were used in such clinical conditions. In the early 1940's, it was proposed mainly in Germany, to use a dry extract of bovine striatum for parkinsonism. The drug, called Striaphorin, was produced for some years without any significant success. We know now that if the active principle of such a preparation was dopamine, this could never cross the blood-brain barrier to reach its target.

The first real attempts to use dopaminergic agents in the treatment of Parkinson's disease were made when the dopamine theory of Parkinson's disease was verified (Ehringer and Hornykiewicz 1960, Barbeau, 1960). Apomorphine was a prime clinical candidate after the identification of its pharmacologic similarities with dopamine (Ernst, 1967; Ungerstedt et al., 1969).

Despite its beneficial effect in early clinical trial (Cotzias et al., 1970, Castaigne et al., 1977), the use of apomorphine appears to be limited clinically owing to its nephrotoxicity (Papavasiliou et al., 1978), strong emetic action, rapid metabolism and lack of oral activity (Castaigne et al., 1971; Schwab, 1951). Some derivatives of apomorphine (n-propyl-norapomorphine) were proposed (Cotzias et al., 1976; Papavasiliou et al., 1978).

The profile of apomorphine as a dopaminergic stimulant and its beneficial effects upon parkinsonian symptoms had encouraged the search for other dopaminomimetic agents. A dopaminergic profile was proved for different ergoline derivatives, including bromocriptine (Corrodi et al., 1973; Fuxe et al., 1978), lergotril (Fuller and Perry, 1978; Wong and Bymaster, 1978), pergolide (Fuller et al., 1979; Wong et al., 1979) and lisuride (Graf et al., 1976), indicating their possible use for the management of parkinsonism.

More recently a number of other ergot compounds have also been found to interact with DA receptors within the striatum, e.g. CH 29-717, CQ 32-084 and CU 32-085 (Flueckiger et al., 1979).

For many of these dopaminomimetic agents, the starting point for chemists was the ergoline skeleton of ergot leading to three ergot families: clavines, lysergic acid amides and 8 α -amino-

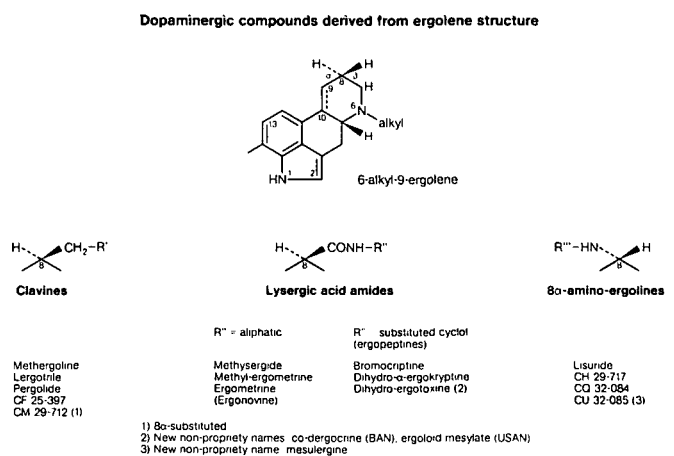


Figure 1 — Chemical structures of the different families of ergot compounds exhibiting dopaminomimetic properties. (from Vigouret et al., 1978; Flueckiger et al., 1979, 1983b).

Table 1: Comparison of central dopaminergic properties of various ergot compounds

	(1)	(2)	(3)	(4)	(5)	(6)		
	Prl δ Rat (2 hr) ID ₅₀ (μ g/kg s.c.)	Turning Behaviour Ungerstedt Rat MED (μ g/kg)	Ach Release Rat Striatum IC ₅₀ (nM)	DA Release Rat Striatum Ag. (nM)	DA - AC Rat Striatum Er pD ₂ /pKi	Calf Caudatum 3H-DA/3H-Spiro IC ₅₀ (nM)		
Ergopeptine = Bromocriptine	8	100 s.c.	5.0	Ag. (nM)	0	6.4	84	13
Clavines = Lergotril	16	100 s.c.			0	6.2		
Pergolide	0.44	10 s.c.	3.2		30	6.0	0	
CF 25-397	720	300 s.c.	40.0		34	6.6	0	
CM 29-712	16	50 i.p.	Antag.	0	34	5.4	0	
Amino-Ergoline = Lisuride	3.9	10 s.c.			0	7.0		
CH 29-717	0.89	50 i.p.	5.0		0	<5	210	120
CQ 32-084	5	10 s.c.	2.5	Ag. (μ M)	32	5.8	0	120
Mesulergine	10	300 s.c.	1580	Antag.	0	6.3	1400	140
Dopamine			?	Ag. (?)	100	6.3	0	
Apomorphine	1800	10	25.0	Ag. (nM)	69	6.3	0	

Results from (1) Flueckiger et al. (1979); (2) Vigouret et al. (1978); (3)-(5) Markstein (1981) and unpublished; (6) Closse et al. (1980).

Table 2: Comparison of neurochemical properties: bromocriptine and mesulergine (from Markstein, unpublished)

	(1) DA Receptors		(2) 5HT-Receptors (5 HT ₂)	(3) Adrenoreceptors $\alpha 1 + \alpha 2$
	DA - AC (+) (D1)	DA - AC (-) (D2)		
Bromocriptine	-	+++	--	--
Mesulergine (CU 32-085)	-	+++	++ (Antagonism)	-

Table 3: Comparison of clinical profiles of ergot derivatives in Parkinson's disease (from Rinne, 1983 with permission)

Compound	Therapeutic Response		Adverse Reactions				
	Antiparkinsonian efficacy	Mood elevation	Nausea - vomiting	Cardiovascular activity*	Sedation	Hallucinations + confusion	Dyskinesia
Bromocriptine	+	+	++	+	++	++	+
CM 29-712	+	-	+++	+	+++	±	-
CQ 32-084	++	+	++	++	++	++	-
CU 32-085	+	+++	+	±	++	+	-

*Decrease of blood pressure and the occurrence of postural hypotension.

Effect of mesulergine on DOPAC in rat striatum

(Enz et al., 1983)

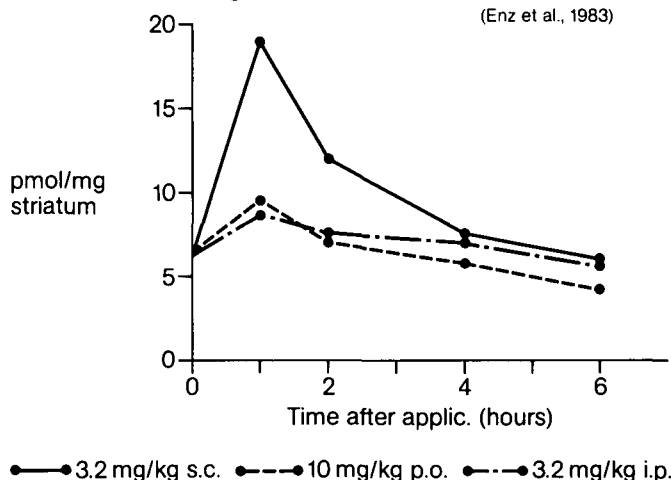


Figure 2 — Effect of Mesulergine on DOPAC level in rat striatum. (from Enz et al., 1983 with permission).

ergolines (Fig. 1). The pharmacological profile of these derivatives is quite different in terms of structure-activity relationships as agonists and/or antagonists upon α -adrenoreceptors, serotonin receptors and DA receptors. The pharmacology of ergot alkaloids and their derivatives has been extensively reviewed recently (Berde and Schild, 1978; Clark et al., 1978; Fuxe, 1979; Thorner et al., 1980; Flueckiger et al., 1981; Lataste, 1981; Flueckiger and Markstein, 1982; Flueckiger, 1983a; Flueckiger et al., 1983b; Tran et al., 1983; Calne, 1983; Fuxe et al., 1983). In Table 1 are summarized the available pharmacological data of a number of ergot compounds of proven activity in parkinsonism, compared with apomorphine and dopamine.

Specific Aspects of Ergot Pharmacology

Among the various pharmacological aspects of ergot derivatives, I would like to concentrate my review upon some pharmacodynamic properties which could be relevant for their therapeutic use. When central dopaminergic activities are compared, quite different overall potency profiles can be characterized.

Compared with bromocriptine, mesulergine (CU 32-085) as a 8- α -amino-ergoline derivative has a different potency in *in vivo* models (Table 1).

The distinctive pharmacological profiles obtained from ergot derivatives include not only their specific interactions with the different subtypes of DA receptors but also their possible interferences with other transmitter receptors including adrenoreceptors and serotonin receptors (Table 2).

Such a complex pharmacology suggests that these compounds may induce different clinical responses in the management of parkinsonian symptoms. However, the clinical results so far obtained with these compounds (Rinne, 1983) do not yet allow correlation of their efficacy and tolerability with their respective pharmacological profile (Table 3).

Moreover, for some of these compounds, their metabolic pattern appears to be essential to explain their activities. As an example, mesulergine seems to exhibit a biphasic action on the DA turnover: after an initial receptor blockade, an agonistic effect was observed only 4 hours later (Flueckiger et al, 1979; Enz, 1981, 1982; Ringwald et al., 1982). However, this effect was mainly observed after subcutaneous administration (Fig. 2). When the compound is given orally, the initial activation of DA turnover is much reduced (Enz et al., 1983). Such a difference can be explained by the metabolic pattern of this agent, which is actively and rapidly transformed into various metabolites. Among these metabolites, the major two (CH 29-717 and 204-079) exhibit potent dopaminergic properties. In addition to the metabolic pattern, it is important to compare the pharmacokinetics of these agents within the plasma and the striatum as the target organ.

The claimed advantage of dopaminergic drugs over L-Dopa was the longer half-life inducing a longer clinical benefit. However such a statement was referring only to the plasma kinetic properties, not taking into account the drug kinetics within the target organ, i.e. the striatum. With mesulergine, however, this last effect was investigated. After an oral dose of 10 mg/kg (Fig. 3), there is in the striatum a rapid appearance of the active metabolites with a concomitant decrease of the parent drug (Enz et al., 1983).

Another controversial aspect of ergot pharmacology concerns the concept of DA-receptors (see Seeman P. and Keibadian J.)

Comparative pharmacokinetics of mesulergine and metabolites

(Enz et al., 1983)

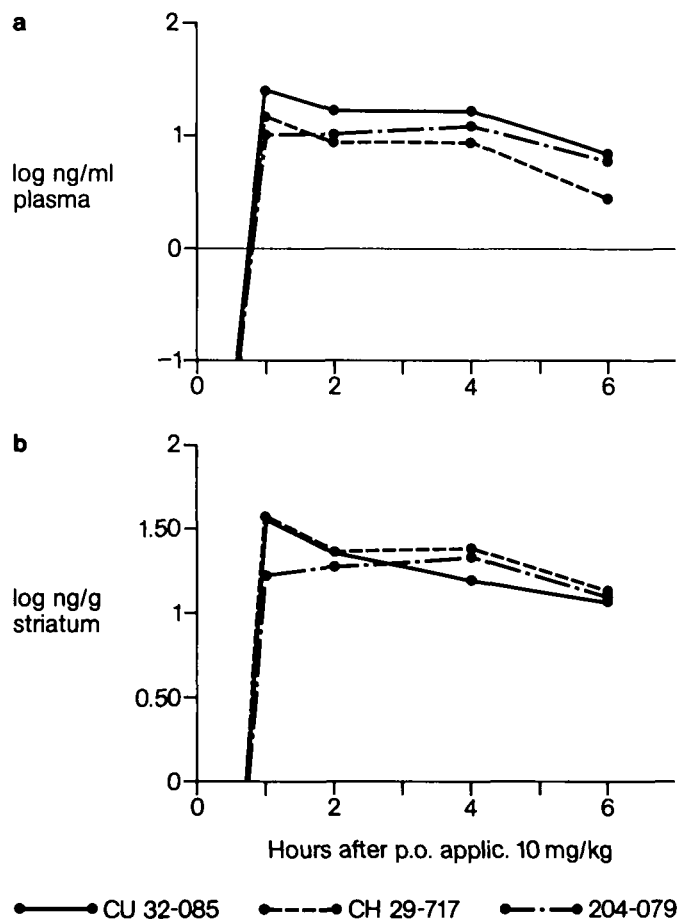


Figure 3 — Comparative pharmacokinetics of Mesulergine and metabolites in plasma and striatum. (from Enz et al., 1983 with permission).

In animal models, the central dopaminergic activities of bromocriptine were investigated mainly in acute conditions. Few data are available upon the effects observed during chronic administration. Recently such a chronic treatment was performed (Vigouret et al., 1983) in the stereotyped behaviour model in intact rats as well as in the Ungerstedt model.

As reviewed in Table 4, behavioural dopaminergic stereotypies were generally observed with acute doses over 30 mg/kg given orally. In chronic conditions, pronounced stereotypies appeared after 5 weeks at a daily dose of 12 mg/kg with a concomitant significant decrease of DOPAC level within the striatum. The DA turnover was not significantly influenced in acute stimulation. These observations indicate the appearance of a behavioural and biochemical hypersensitivity to bromocriptine during the chronic use of oral doses inactive when given acutely. Moreover the unilateral lesioning of nigrostriatal pathways by local injection of 6-OH-DA leads to a hypersensitivity of DA receptors within the striatum. Dopaminomimetic agents such as apomorphine or bromocriptine induce a contralateral turning behaviour by stimulation of the "denervated" DA receptors. Such behaviour was observed for acute doses of bromocriptine over 9 mg/kg, but reproducible effects were obtained with 20 mg/kg. A comparable turning pattern was recorded in chronic

condition after the third week at a daily dose of 6 mg/kg (Table 5). The latency of the turning behaviour was about 2 hours, followed by a longer period of dopaminergic stimulation (more than 7 hours).

The comparison of the effects obtained after either acute or chronic administration points out the complex pharmacology of dopaminergic agents. A repeated administration seems to induce a functional hypersensitivity probably related to post-synaptic DA receptors. However the participation of other DA receptors cannot be excluded, i.e. presynaptic DA receptors. The biochemical mechanisms underlying such dynamic aspects of receptor stimulation are still unknown. However the clinical implication of these results appears to be essential especially for the initiation of dopaminergic agents in parkinsonian patients. The titration period should be carefully built-up before the onset of an optimal effect. The therapeutic response seems to require a certain delay, depending for each patient upon the dynamic situation of his DA receptor systems. Moreover the antiparkinsonian effect can increase over time without additional increase in the daily regimen after the appearance of the first signs of clinical improvement.

These pharmacological elements emphasize the complexity of the DA receptor concept. From biochemical *in vitro* tests, it seems difficult to extrapolate to *in vivo* conditions related to Parkinson's disease. Our understanding of the dynamics of receptors is yet quite uncertain, as is that of the compensatory mechanisms which probably take place during the natural progression of the degenerative process.

Table 4: Effects of acute and chronic administration of bromocriptine in stereotyped behaviour (from Vigouret, unpublished)

	Dose mg/kg p.o.	Score (N = 6)	
Acute Dose	3	0.6 ± 0.7	
	10	0.6 ± 0.8	
	30	7.3 ± 1.2 (p<0.05)	
Control		0.5 ± 0.4	
	Dose mg/kg p.o./Day	Week	Score (N = 6)
Chronic Dose	1	1	0.3 ± 0.3
	3	2	0.3 ± 0.2
	6	3	0.4 ± 0.2
	9	4	0.8 ± 0.3
	12	5	13.4 ± 1.3 (p<0.01)

Table 5: Effects of acute and chronic administration of bromocriptine in Ungerstedt model (from Vigouret, unpublished)

	Dose mg/kg p.o.	Week	Total Number of Contralat. Rotations (7 h.)
Acute Dose (N = 6)	1	—	0
	3		0
	6		0
	9		152 ± 21
	20		1600 ± 185
Chronic Dose (N = 12)	1	1	24 ± 14
	3	2	15 ± 57
	6	3	1093 ± 200
	9	4	1080 ± 320

As an example, the balanced activation of 2 types of DA receptors (pre- and post-synaptic) seems to be essential for an adequate integration of striatal functions. The mechanisms underlying this balance are still unknown within normal physiological conditions as well as during the natural course of the degenerative process underlying Parkinson's disease (Flueckiger and Vigouret, 1981).

Conclusions

In recent years, the dopaminergic properties of ergot compounds have attracted much attention whereas other aspects of their receptor pharmacology still remain unclear. Moreover small differences within their chemical structure may produce qualitative changes in their profile of actions. Particularly interesting is the possible relationship between *in vivo* and *in vitro* activities to explain such a multiplicity of profiles. Ergot derivatives have had an important impact on our understanding of central dopaminergic functions and have served as useful tools for pharmacological research. However, the DA receptor concept is not yet satisfactory, especially when confronted to its clinical implications. The clinical contribution of dopaminomimetic ergots is essential but far from being completely understood. New approaches, perhaps more specific ones, are required to provide ample and clear information to optimize their pharmacodynamic properties. According to their mechanism of action, they allow continued treatment for parkinsonian patients who become resistant to L-Dopa or no longer tolerate it because of adverse reactions, such as dyskinesia or "on-off" phenomenon (Lieberman et al., 1976; Calne et al., 1978; Ringwald, 1982).

In newly diagnosed patients, dopaminergic agents such as bromocriptine or mesulergine may represent an alternative to chronic L-Dopa treatment. According to preliminary results (Lees et al., 1978; Rascol et al., 1982; Hirt et al., 1983) these compounds given as monotherapy had a low potential for producing dyskinesia or "on-off" phenomenon over at least 5 years. The extension of this experience over time is essential to provide clear evidence of the therapeutic potential of ergots in the chronic management of parkinsonism, avoiding the disabling problems associated with L-Dopa.

Despite the real improvement in the quality of life of parkinsonian patients with L-Dopa and/or dopaminergic agents, the natural course of disease remains unchanged. In this respect no real progress was made since the optimistic conclusion of Parkinson (1817) in his original essay:

"There appears to be sufficient reason for hoping that some remedial process may ere long be discovered by which at least the progress of the disease may be stopped".

Recently new prospects were offered to pharmacologists with the recognition of chemically induced parkinsonism in young addicts (Davis et al., 1979; Langston et al., 1983; Burns et al., 1983). The development of a more accurate model for parkinsonism in rhesus monkeys receiving NMPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) could probably improve our understanding of the basic pathological mechanism of parkinsonian degeneration. This model, if it truly reproduces the neurological syndrome, could be a useful tool in the selection of new antiparkinsonian drugs among ergot derivatives. This is the future challenge offered to neuropharmacology.

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