14. ERGOT ALKALOIDS AND THEIR DERIVATIVES AS LIGANDS FOR SEROTONINERGIC, DOPAMINERGIC, AND ADRENERGIC RECEPTORS

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14.1. INTRODUCTION

Among compounds from natural sources ergolines are of paramount importance as ligands for serotonin (5-hydroxytryptamine, 5-HT) receptors, dopamine receptors, and adrenoceptors. The tetracyclic structure of the ergolines contains the essential features of the monoamine neurotransmitters 5-HT, dopamine, and noradrenaline, and it is not surprising that many naturally occurring and (semi)synthetic ergolines have been shown to act as agonists, partial agonists or antagonists at receptors for these neurotransmitters. It is difficult to explain the complexity of the pharmacological profile of the ergolines without encountering the issue of receptor heterogeneity. The extent of the multiplicity of 5-HT receptors, dopamine receptors and adrenoceptors became fully apparent in the early 1990s, since at least 14 distinct subtypes of 5-HT receptors (Hoyer *et al.*, 1994; Martin and Humphrey, 1994; Boess and Martin, 1994), 5 subtypes of dopamine receptors (Sibley and Monsma, 1992; Strange, 1993; Seeman and Van Tol, 1994), and at least 10 subtypes of adrenoceptors (Bylund *et al.*, 1994; Hieble *et al.*, 1995a, b) could be identified on the basis of structural, transductional and operational information obtained from molecular biological, second messenger and radioligand binding as well as functional studies.

Although a number of structurally diverse classes of ligands demonstrate high affinity for serotoninergic, dopaminergic and adrenergic receptors, among the ergolines only few show specificity with regard to the different monoamine receptor systems and selectivity among subtypes of each of these major groups. Nevertheless, a number of ergolines has emerged as real targets for the treatment of vascular and neurological diseases and other disorders (Table 1). Moreover, it is entirely possible that any subtype-selective drugs that will be developed on the basis of the molecular biological advances of the past decade may not be as effective clinically as those that are currently available but less selective.

Table 1 Current therapeutical applications for selected natural and semisynthetic ergolines in clinical relevant doses

Compounds	*Therapeutical application*	*Receptors mostly involved*	*Quality of action*
Ergotamine, Dihydro-ergotamine	Migraine (acute)	5-$HT_{1B/1D}$	Partial agonism
Methysergide	Migraine (prophylactic)	5-HT_{2B}	Antagonism
Ergometrine, Me-Ergometrine	Postpartum haemorrhage	5-HT_{2A}	Partial agonism
Bromokryptine	Parkinsonism	D_2-like	(Partial) agonism
	Suppression of the secretion of prolactin	D_2-like	(Partial) agonism
Lisuride	Parkinsonism	D_2-like	(Partial) agonism
	Suppression of the secretion of prolactin	D_2-like	(Partial) agonism
Pergolide	Parkinsonism	D_1-like and D_2-like	(Partial) agonism
Cabergoline	Suppression of the on secretion of prolactin	D_2-like	(Partial) agonism

14.2. ERGOLINES AS LIGANDS FOR 5-HT RECEPTORS

There is a continued interest in the biological actions of ergot alkaloids and their semisynthetic derivatives at 5-HT receptors which can be divided into 4 main classes, termed 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4. The amino acid sequence of 3 additional types of receptors, denoted as 5-ht_5, 5-ht_6, and 5-ht_7 has been identified but their functional role is not yet clear; therefore they are abbreviated using lower case letters. With the exception of the 5-HT_3 receptor, which is a ligand-gated ion-channel, all receptors mentioned belong to the superfamily of G-protein-coupled receptors (proteins characterized by 7 transmembrane domains). The class of 5-HT_1 receptors comprises 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1Da}, and 5-$HT_{1Dß}$ receptors and two less well characterized subtypes (5-HT_{1E} and 5-HT_{1F}). The nomenclature of 5-$HT_{1B/1D}$ receptors has recently been simplified: rat 5-HT_{1B} and human 5-$HT_{1Dß}$ receptors are now termed r5-HT_{1B} and h5-HT_{1B}, respectively, whereas human 5-HT_{1Da} receptors are now termed h5-HT_{1D} (Hartig *et al.,* 1996) *(vide infra)*. The class of 5-HT_2 receptors includes 5-HT_{2A} (formerly "5-HT_2"), 5-HT_{2B}, and 5-HT_{2c} (formerly 5-HT_{1c}) receptors. Whereas 5-HT_1 receptors are negatively coupled to adenylyl cyclase and 5-HT_4, 5-ht_6, and 5-ht_7 receptors are positively coupled to adenylyl cyclase, 5-HT_2 receptors stimulate phospholipase C.

Among naturally occurring ergolines, ergopeptines such as ergotamine and simple lysergic acid amides such as ergometrine show high affinity for different 5-HT receptor subtypes (e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}), whereas clavines show moderate affinity for rat 5-HT_{2A} receptors and high affinity (e.g., lysergol) for human 5-HT_{1D} receptors and 5-HT_{1F} receptors (for review, see Eich and Pertz, 1994; Pertz, 1996). The main disadvantage of naturally occurring ergot alkaloids is their lack of selectivity for each of the individual 5-HT receptor subtypes. During the last two decades various structural modifications of the ergoline skeleton have been reported and led to the discovery of highly potent and even more selective serotoninergic ligands. This chapter will focus on naturally occurring and semisynthetic ergolines which in concert with nonergoline derivatives represent the wide range of valuable tools to characterize 5-HT receptors (Table 2). Since the most important

Table 2 Pharmacological characterization of serotonin (5-HT) receptors by means of ergolines in functional and radioligand binding studies

Receptor name	5-HT_{1A}	5-$HT_{1B/1D}$	5-HT_{1E}	5-HT_{1F}
Compounds	Ergotamine	Ergometrine		
	DHE	DHE		
	Ergometrine	Ergometrine		
	Me-ergometrine	Me-ergometrine		Me-ergometrine
	Metergoline	Metergoline[a]		
	Methysergide	Methysergide		Methysergide
	LSD	LSD		
	Lisuride	Lysergol		Lysergol
	Bromokryptine			
Quality of action	(partial) agonism	partial agonism	–	agonism
Radioligand	–	–	–	2-|^{125}I|LSD
Receptor name	**5-HT_{2A}**	**5-HT_{2B}**	**5-HT_{2C}**	**5-HT_3**
Compounds	LY53857	LY53857	LY53857	–
	Mesulergine	Mesulergine	Mesulergine	
	LSD[b]		LSD[b]	
	Methysergide	Methysergide	Methysergide	
	Me-ergometrine[c]	Me-ergometrine		
	Ergometrine[c]			
	Metergoline		Metergoline	
	Ergotamine[d]	Ergotamine[c]	Ergotamine[c]	
	DHE[d]	DHE[d]	DHE[d]	
	Sergolexole	Lisuride		
	Amesergide			
	LY215840			
Quality of action	antagonism	antagonism	antagonism	–
Radioligand	–	–	|^{3}H|Mesulergine	–

Table 2 (*Continued*)

Receptor name	5-HT_4	5-$ht_{5A/5B}$	5-ht_6	5-ht_7
Compounds	–	Ergotamine	Lisuride	Lisuride
			Metergoline	Metergoline
		LSD	2-Br-LSD	LSD
			Pergolide	Pergolide
			Lergotrile	Bromocriptine
			DHE	Mesulergine
		Methysergide		Methysergide
				LY215840
Quality of action	–	?	?	antagonism
Radioligand	–	2-[^{125}I]LSD	2-[^{125}I]LSD	2-[^{125}I]LSD

Data shown are derived from a variety of published reports cited in the text. [a]Metergoline shows partial agonist activity (Miller *et al.*, 1992) or antagonist activity (Hamel and Bouchard, 1991; Bax *et al.*, 1992) at 5-HT_{1D} receptors. [b]LSD acts as a partial agonist at 5-HT_{2A} and 5-HT_{2C} receptors (Kaumann, 1989; Glennon, 1990; Pierce and Peroutka, 1990; SandersBush *et al.*, 1988). [c]Ergometrine and methylergometrine are partial agonists at 5-HT_{2A} receptors (Hollingsworth *et al.*, 1988; Milhahn *et al.*, 1993). [d]Ergotamine and dihydroergotamine (DHE) possess high affinity for 5-HT_{2A} receptors in mammalian brain membranes (Hoyer, 1989). [e]Ergotamine and dihydroergotamine show partial agonist activity at 5-HT_{2B} receptors (Glusa and Roos, 1996) and full agonist activity at 5-HT_{2C} receptors (Brown *et al.*, 1991)

effects of ergolines with regard to 5-HT are due to their action on the central nervous system (CNS) and the cardiovascular (CV) system, we will emphasize newer developments in the pharmacology of ergolines acting at 5-HT receptors in the CNS and the CV system.

14.2.1. Ergolines are Nonselective Ligands with High Affinity for 5-HT_{1A} Receptors

Most drugs with partial agonist properties at 5-HT_{1A} receptors are used for CNS applications. 5-HT_{1A} receptors in the CNS are localized on the cell bodies and dendrites of 5-HT neurones in the raphe nuclei and function as somatodendritic autoreceptors which mediate the inhibition of cell firing. Clinical interest in 5-HT_{1A} receptor partial agonists and silent antagonists with sufficient brain penetration is related to the putative involvement of 5-HT_{1A} receptors in anxiety and depression (Traber and Glaser, 1987; Fletcher *et al.*, 1993). Furthermore, the administration of 5-HT_{1A} receptor agonists results in a decrease of arterial blood pressure due to the inhibition of central sympathetic neurones (McCall and Clement, 1994). In peripheral tissues presynaptic 5-HT_{1A} heteroreceptors are possibly involved in the modulation of the gastointestinal motility. It has been shown that the activation of presynaptic 5-HT_{1A} receptors by e.g., lysergic acid diethylamide (LSD) can inhibit the electrically stimulated [^{3}H]acetylcholine release from cholinergic neurones of guinea-pig ileum (Pfeuffer-Friederich and

Kilbinger, 1985; Fozard and Kilbinger, 1985). On the whole, ergolines (e.g., lisuride, dihydroergotamine, LSD, methylergometrine, ergotamine, ergometrine, metergoline, methysergide, and bromokryptine) show high affinity for 5-HT_{1A} receptors but have not been used as principle agents for the determination of 5-HT_{1A} receptor-mediated activity due to their poor pharmacological selectivity (Hoyer, 1989).

14.2.2. Ergolines are Partial Agonists of High Potency at 5-$HT_{1B/1D}$ Receptors

According to molecular biological studies, 5-HT_{1B} and 5-HT_{1D} receptors form a subfamily of related receptors (Hartig *et al.,* 1992, 1996). Two human 5-HT_{1D} receptors (called 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$) within this subfamily have been cloned, which, due to their operational characteristics, resemble the 5-HT_1-like receptor of the functionally-based receptor classification of Bradley and colleagues (Bradley *et al.,* 1986). The human 5-$HT_{1D\beta}$ receptor (h5-HT_{1B}) is a species homologue of the rat 5-HT_{1B} receptor (r5-HT_{1B}). Both are presynaptic autoreceptors which are localized on the axon terminals of 5-HT neurones mediating inhibition of 5-HT release (Göthert *et al.,* 1996). In addition, 5-$HT_{1B/1D\beta}$ receptors occur as presynaptic 5-HT heteroreceptors on sympathetic nerve terminals in blood vessels (Göthert *et al.,* 1996). Whereas the rat 5-HT_{1B} receptor and the human 5-$HT_{1D\beta}$ receptor display striking differences in their pharmacological binding properties, the pharmacological profiles of human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors are quite similar (Weinshank *et al.,* 1992). 5-$HT_{1D\alpha}$ receptors have been identified as presynaptic inhibitory 5-HT heteroreceptors on sympathetic axon terminals in human atrial appendages (Molderings *et al.,* 1996). On the other hand, 5-HT_1-like receptors which mediate constrictor effects of 5-HT in blood vessels of various species including man, may correspond to the 5-$HT_{1D\beta}$ subtype (Martin, 1994).

Recent evidence has implicated 5-HT_{1D} (5-HT_1-like) receptors in neurological and cardiovascular diseases such as the acute migraine attack or cerebral and coronary vasospasm. 5-HT_{1D} (5-HT_1-like) receptor agonists such as the nonergoline derivative sumatriptan and the ergolines ergotamine and dihydroergotamine belong to the most effective drugs in aborting migraine attacks (Moskowitz, 1992; Ferrari and Saxena, 1993). The acute migraine attack is characterized by a pathological dilatation of extracerebral intracranial arteries which evokes an increase in vascular pulsations followed by a stimulation of perivascular sensory afferents of the Vth cranial nerve to cause the typical symptoms such as pain, nausea, vomiting and photophobia. In addition, a neurogenic inflammatory response, which mediates plasma protein extravasation in blood vessels of dura mater and is induced via the release of vasoactive neuropeptides from perivascular nerve terminals, may play an important role in the pathogenesis of migraine attacks. The effectiveness of antimigraine drugs such as sumatriptan, ergotamine and dihydroergotamine

is based both on the 5-HT_{1D} receptor-mediated contraction of pathologically dilated intracranial arteries and the inhibition of neuropeptide release via activation of prejunctional 5-HT_{1D} receptors, thereby blocking the development of neurogenic inflammation. The 5-$HT_{1D\beta}$ receptor is presumably responsible as the mediator of cranial vasoconstriction, since mRNA for this subtype has been found in human cerebral arteries (Hamel *et al.,* 1993). Furthermore, cardiac side effects such as coronary vasospasm, myocardial infarction, and possibly stroke which may complicate the treatment of migraine with the 5-HT_{1D} receptor agonists sumatriptan, ergotamine, and dihydroergotamine can be explained by the stimulatory effect of these drugs on 5-$HT_{1D\beta}$ receptors in the coronary vasculature (Kaumann *et al.,* 1993, 1994). On the other hand, it has been suggested that the 5-HT_{1D} receptor which modulates neuropeptide release in migraine, may be of the 5-$HT_{1D\alpha}$ subtype, since mRNA for this subtype has been found in human trigeminal ganglia (Rebeck *et al.,* 1994).

A large number of studies has shown conclusively that ergolines possess high affinity for 5-HT_{1B} and 5-HT_{1D} receptors (Figure 1). For example, it has been demonstrated that dihydroergotamine displays high affinity for the rat 5-HT_{1B} receptor (Hamblin *et al.,* 1987), and ergolines such as lysergol, ergotamine, dihydroergotamine, LSD, metergoline, and methysergide are ligands with high affinities for human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors (Weinshank *et al.,* 1992; Hamblin and Metcalf, 1991; Jin *et al.,* 1992; Hamblin *et al.,* 1992; Oksenberg *et al.,* 1992; Miller *et al.,* 1992; Peroutka, 1994; Levy *et al.,* 1992a; Demchyshyn *et al.,* 1992). Among the ergolines mentioned, it was the natural clavine alkaloid lysergol that exhibited the highest affinity among 20 nonergoline and ergoline-based 5-HT receptor ligands tested for both human 5-HT_{1D} receptor subtypes (Weinshank *et al.,* 1992). Within a series of pharmacological agents, which were analyzed for their ability to discriminate effectively between the two closely related subtypes, the nonergoline 5-HT_{2A} receptor antagonist ketanserin showed 120-fold selectivity and ergolines such as ergotamine, dihydroergotamine, metergoline, and methysergide showed 10 to 26-fold selectivity for the 5-$HT_{1D\alpha}$ receptor relative to the 5-$HT_{1D\beta}$ subtype (Peroutka, 1994).

It is beyond any doubts that ergolines are among the most potent partial agonists at vascular 5-HT_1-like receptors. Ergotamine and dihydroergotamine, for example, acted as powerful partial agonists at 5-HT_1-like receptors in human basilar artery, of which a contractile response via α-adrenoceptors could be excluded at least for ergotamine (Müller-Schweinitzer, 1983, 1992). Furthermore, ergotamine was about 100-fold more potent than the antimigraine drug sumatriptan as a constrictor of human coronary artery, which is characterized by the coexistence of 5-HT_1-like receptors, 5-HT_{2A} receptors, α-adrenoceptors and other (as yet unknown) receptors (Bax *et al.,* 1993). In this connection it is worth pointing out that the carotid vascular effects of ergotamine and dihydroergotamine in the pig were only partially blocked by the 5-HT_1-like receptor antagonist methiothepin, suggesting that the vasoconstrictor response to these ergolines is not exclusively mediated via

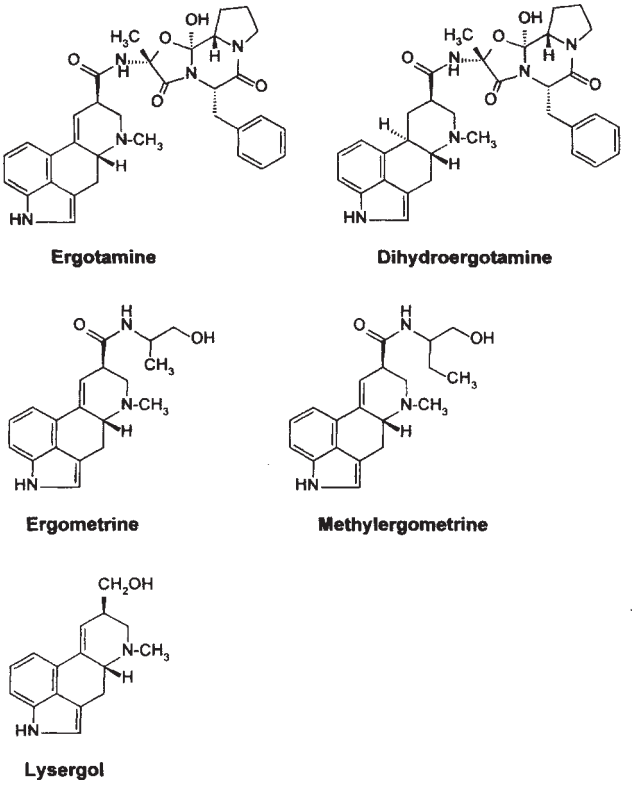


Figure 1 Structures of ergolines with partial agonist activity at 5-$HT_{1B/1D}$ receptors. Metergoline and methysergide are further partial agonists of which the structures are shown in Figure 2

5-HT_1-like receptors but additionally *via* an unknown receptor or mechanism (Den Boer *et al.,* 1991). Such a phenomenon has also been reported in rabbit saphenous vein (MacLennan and Martin, 1990) and guinea-pig iliac artery (Pertz, 1993), where contractions to ergometrine, methylergometrine, and methysergide resulted in biphasic concentration-response curves, of which only the first phase was mediated via 5-HT_1-like receptors and the second phase mediated via unknown receptors. It is also worth pointing out that ergometrine, although exhibiting only weak activity at α_1-adrenoceptors (Müller-Schweinitzer and Weidmann, 1978), provokes coronary artery spasm in patients with Prinzmetal's angina and is used in the diagnosis of this disease (Prinzmetal *et al.,* 1959; Maseri *et al.,* 1977; Heupler *et al.,* 1978). Affinity and efficacy of ergometrine and methylergometrine for 5-HT_1-like receptors were higher than those of methysergide (MacLennan and Martin, 1990; Pertz, 1993). In human and canine blood vessels powerful but extremely slow development of the contractile response to ergotamine and ergometrine has been observed

(Mikkelsen *et al.,* 1981; Bax *et al.,* 1993; Brazenor and Angus, 1981). Therefore, undesirable cardiac side effects in the treatment of migraine may limit the therapeutical benefit of the highly efficient vasoconstrictor ergotamine.

14.2.3. Ergolines Show Low Affinity for 5-HT_{1E} Receptors and High Affinity for 5-HT_{1F} Receptors

The most distinguishing feature between the 5-HT_{1D} receptor and the 5-HT_{1E} receptor (Levy *et al.,* 1992b; McAllister *et al.,* 1992; Zgombick *et al.,* 1992) is the low affinity for 5-carboxamidotryptamine (5-CT) and ergotamine (Beer *et al.,* 1993). The 5-HT_{1E} receptor has been detected only in the brain where it possibly plays a role of an autoreceptor. There are no functional correlates and no selective ligands for this subtype. Another less well characterized receptor within the 5-HT_1 receptor group is the 5-HT_{1F} receptor, which has the highest homology to the the 5-HT_{1E} receptor. 5-HT_{1F} receptors has been detected in the brain, uterus, and mesentery (Adham *et al.,* 1993a). The high affinity of the antimigraine drug sumatriptan for this subtype indicates a possible role of 5-HT_{1F} and/or 5-HT_{1D} receptors in migraine. This idea was supported by the agonist profile of the ergolines lysergol, methylergometrine, and methysergide, which showed similar affinity and efficacy for 5-HT_{1F} receptors than did sumatriptan (Adham *et al.,* 1993b).

14.2.4. Ergolines are Potent Antagonists/Partial Agonists at 5-HT_{2A} Receptors

It has been suggested that the classical hallucinogenic agent LSD may exert its psychotic effect by acting as partial agonist at 5-$HT_{2A/2C}$ receptors (Glennon, 1990; Pierce and Peroutka, 1990). The ability of many 5-HT_{2A} receptor antagonists to block both 5-HT_{2A} and 5-HT_{2C} receptors seems to be a key factor for the therapeutical benefit in the treatment of psychiatric disorders (Clarke, 1992). Therapeutic indications for S-$HT_{2A/2C}$ receptor antagonists include schizophrenia, depression, and anxiety (Peroutka, 1995). The antipsychotic therapy has been improved due to the recent development of so-called atypical antipsychotic drugs with combined D_2/5-HT_{2A} receptor blocking properties which avoid extrapyramidal side effects (Meltzer and Nash, 1991). Recently it has been shown that 5-HT_{2A} receptor antagonism alone may be sufficient for antipsychotic activity, since selective 5-HT_{2A} receptor blockade increases dopamine release in the prefrontal cortex, thereby providing an improvement of the negative symptoms of schizophrenia (Schmidt *et al.,* 1995). In the CV system, the ability of S-HT_{2A} receptor antagonists to inhibit 5-HT-induced platelet aggregation which is mediated via platelet 5-HT_{2A} receptor stimulation, and to block the direct contractile effects of platelet-released 5-HT on vascular smooth muscle (Vanhoutte, 1990), makes them candidates for the treatment of ischemic heart disease and other vascular occlusive disorders (for review, see Audia and

Cohen, 1990). An important application for certain simple lysergic acid amides is related to their powerful contractile effect on uterine smooth muscle. Ergometrine and methylergometrine are used frequently in the treatment of postpartum haemorrhage. Functional studies have suggested that the stimulatory effect of the partial agonist ergometrine in rat uterus is mediated via S-HT_{2A} receptors due to the blockade by methysergide and the nonergoline 5-HT_{2A} receptor antagonist ICI 169,369, respectively (Hollingsworth *et al.,* 1988).

A variety of ergolines (e.g., metergoline, methysergide, dihydroergotamine, LSD, lisuride, α-dihydrergokryptine, ergometrine, ergotamine, methylergometrine, and *ß*-dihydroergokryptine) displays high affinities for 5-HT_{2A} receptors in radioligand binding studies (Hoyer, 1989). The interaction of ergolines, however, with vascular 5-HT receptors which may be of the 5-HT_1-like type, the 5-HT_{2A} type or a mixture of both (Saxena and Villalón, 1990), is complex, since ergolines may act as partial agonists at 5-HT_1-like receptors *(vide supra)* and as antagonists or partial agonists at 5-HT_{2A} receptors (Figure 2). To characterize a given response as being of the 5-HT_{2A} type, the investigation of the antagonism by both the nonergoline 5-HT_{2A} antagonist ketanserin and the ergoline-based 5-HT_{2A} antagonist methysergide is of great value. Ketanserin shows high affinity for 5-HT_{2A} receptors, low affinity for 5-HT_1 receptors (Hoyer, 1989) but appreciable affinity for α_1-adrenoceptors (Van Nueten *et al.,* 1981). In contrast, the potent nonselective 5-HT_{2A} receptor antagonist methysergide has negligible affinity for α_1-adrenoceptors (Bradley *et al.,* 1986).

The disadvantage of "classical" 5-HT_{2A} receptor antagonists as tools for receptor classification is based on their lack of specificity and selectivity. For example, nonergoline 5-HT_{2A} receptor antagonists (e.g., ketanserin and mianserin) interact with α_1-adrenoceptors and histamine H_1 receptors, whereas ergoline 5-HT_{2A} receptor antagonists interact with dopamine receptors (e.g., LSD, metergoline, and mesulergine) and/or fail to discriminate between 5-HT_1 receptors and 5-HT_2 receptors (e.g., LSD, metergoline, and methysergide) (Closse *et al.,* 1984; Hoyer, 1989). Thus the search for more specific and selective 5-HT_{2A} receptor antagonists is of special interest.

Among the ergolines, derivatives with high antagonist activity for 5-HT_{2A} receptors and negligible α_1 adrenergic, histaminergic and dopaminergic blocking properties, include the isopropyldihydrolysergic acid esters LY53857 and sergolexole as well as the amides amesergide and LY215840, which have been developed by *Lilly Research Laboratories* (Garbrecht, 1971; Marzoni *et al.,* 1987; Garbrecht *et al.,* 1988; Misner *et al.,* 1990). It has been shown that LY53857, sergolexole, and amesergide potently block 5-HT_{2A} receptors on both blood vessels and platelets, thereby inhibiting 5-HT-stimulated platelet aggregation (McBride *et al.,* 1990). In addition, LY53857 and amesergide, respectively, inhibit 5-HT-amplified ADP-induced aggregation in rabbit platelets (Wilson *et al.,* 1991; Cohen *et al.,* 1994), and LY215840 in both rabbit and human platelets (Cohen *et al.,* 1992). This additional mechanism may contribute to the potential effectiveness of such 5-HT_{2A} receptor antagonists in the treatment of vascular disorders. On historical grounds

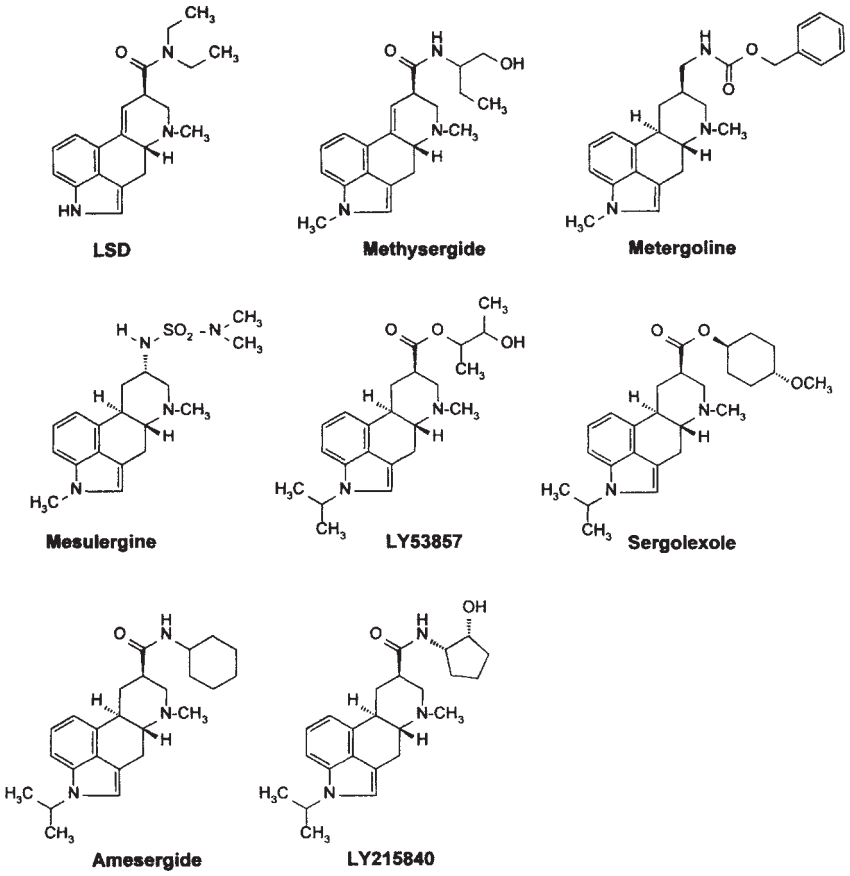


Figure 2 Structures of ergolines that show potent antagonist activity at receptors. LSD is a partial agonist at 5-$HT_{2A/2C}$ receptors. Additionally, mesulergine, methysergide, and LY53857 are potent antagonists at 5-$HT_{2B/2C}$ receptors, and metergoline is a potent antagonist at 5-HT_{2C} receptors. Ergotamine and dihydroergotamine (see Figure 1) are agonists at 5-$HT_{2B/2C}$ receptors

LY53857 justifies special mention as a prototype in this series of ergoline 5-HT_{2A} receptor antagonists (Cohen *et al.,* 1983). The compound represents a mixture of 4 diastereomers, all of which individually display nearly equal affinity for the 5-HT_{2A} receptor (Cohen *et al.,* 1985). Although LY53857 antagonizes central as well as peripheral 5-HT_{2A} receptors, it does not lower the blood pressure in the spontaneously hypertensive rat (Cohen *et al.,* 1983). Similarly, no marked effect on blood pressure has been found with sergolexole (Cohen *et al.,* 1988), amesergide (Foreman *et al.,* 1992), and LY215840 (Cohen *et al.,* 1992). Thus 5-HT_{2A} receptor bockade *per se* appears to be

not sufficient to cause a reduction in blood pressure. Sergolexole has recently been shown to be ineffective for migraine prophylaxis (Chappell *et al.,* 1991). Since sergolexole equipotently blocks 5-HT_{2A} and 5-HT_{2C} receptors (Tfelt-Hansen and Pedersen, 1992), this would speak against the previously postulated theory that 5-HT_{2C} receptors are involved in the initiation of migraine (Fozard and Gray, 1989; Fozard, 1992) *(vide infra)*. Amesergide which proved to be 10–100 times more potent than LY53857 and sergolexole, respectively, in augmenting sexual responses of male rats might be useful in the treatment of sexual dysfunctions (Foreman *et al.,* 1989, 1992). Since amesergide shows nearly equal affinity than LY53857 and sergolexole, respectively, for 5-HT_{2A} receptors (Nelson *et al.,* 1993), the amplification of male rat sexual behaviour caused by amesergide may be attributed to its interaction with 5-HT_{2C} receptors.

The ergoline 5-HT_{2A} receptor antagonists LY53857, sergolexole, amesergide, and LY215840 share the structural property to be substituted with an isopropyl group at the indole nitrogen (N1) (see Figure 2). It has recently been shown that ergolines with an N1-isopropyl group have higher affinity for the rat versus the human, monkey, and pig 5-HT_{2A} receptor, whereas the corresponding N1-unsubstituted ergolines have higher affinity for the human, monkey, and pig versus the rat 5-HT_{2A} receptor (Nelson *et al.,* 1993; Johnson *et al.,* 1993). The findings are consistent with the higher affinities of mesulergine and methysergide, which both are N1-methylergolines, for the rat versus the human and pig 5-HT_{2A} receptor (Pazos *et al.,* 1984a). The affinity profile of further ergoline-based compounds confirms this pattern: the rat 5-HT_{2A} receptor prefers Nl-methylergolines such as metergoline and nicergoline, whereas the human 5-HT_{2A} receptor prefers N1-unsubstituted ergolines such as ergotamine, dihydroergotamine, ergometrine, LSD, lisuride, and pergolide (Hagen *et al.,* 1994). Mutational studies have shown that a single amino acid difference at position 242 in TMH 5 of the 5-HT_{2A} receptor protein accounts for species variability. Point mutation of the Ser242 in the human 5-HT_{2A} receptor to alanine resulted in an affinity for mesulergine that closely resembled that at the rat 5-HT_{2A} receptor (Kao *et al.,* 1992). Similarly, the change from alanine to serine in the rat 5-HT_{2A} receptor explained all of the affinity differences seen for a large number of N1-alkylated ergolines and their N1-unsubstituted analogues in different species (Johnson *et al.,* 1994). Hence it has been concluded that the amino acid 242 seems to be in close proximity to the N1-position of the indole nucleus of the ergolines and may serve as an important contact point in the 5-HT_{2A} receptor by allowing a favourable hydrogen-bonding interaction of N1-unsubstituted ergolines with Ser242 of the human 5-HT_{2A} receptor and a favourable Van der Waals interaction of N1-alkylated ergolines with the Ala242 of the rat 5-HT_{2A} receptor (Johnson *et al.,* 1994). It has additionally been shown by alignment of the TMH 5 of the cloned 5-HT_{2A} and 5-HT_{2C} receptors that the locus which corresponds to Ser/Ala in the 5-HT_{2A} receptor is characterized by an alanine in the 5-HT_{2C} receptor of both humans and rats. As a consequence,

N1-alkylated ergolines such as mesulergine displayed higher selectivity for human 5-HT_{2C} versus 5-HT_{2A} receptors, whereas N1-unsubstituted ergolines such as LSD, lisuride, and ergometrine displayed higher affinity for human 5-HT_{2A} versus 5-HT_{2C} receptors (Almaula *et al.,* 1996). Thus, N1-unsubstituted ergolines and those with suitable substituents (methyl or isopropyl) are useful tools not only for unmasking species differences among 5-HT_{2A} receptors but for determining subtype selectivity between human 5-HT2A and 5-HT_{2C} receptors. Additional loci within the 5-HT_{2A} receptor necessary for high affinity receptor binding have been detected with the use of several ergolines: the conserved aspartic acid residue at position 155 which has been found to be essential for LSD binding (Wang *et al.,* 1993) and the conserved phenylalanine residue at position 340 of which the phenyl moiety may allow a specific aromatic-aromatic interaction (e.g., π-π or hydrophobic) with the aromatic ring of the ergoline nucleus of non-peptide ergolines such as mesulergine, metergoline, methysergide, lisuride, LY53857, ergometrine, lergotrile, and amesergide (Choudhary *et al.,* 1995). By means of the potent 5-HT2A receptor antagonism of 1-isopropylelymoclavine, the parent drug of a series of ergoline reverse esters, and some other simple clavines such as 1-isopropylagroclavine and 1-isopropylfestuclavine of which the tetracyclic skeleton represents more or less the complete molecule, it has recently been demonstrated in the rat that the ergoline nucleus plays a crucial role in determining 5-HT_{2A} receptor affinity and not the substituent at position 8 (Pertz *et al.,* 1995).

Insurmountable antagonists of 5-HT at vascular 5-HT_{2A} receptors such as the ergolines LSD, methysergide, and LY53857 have been reported to bind to an allosteric site of this receptor, thereby inducing a conformational change of the receptor protein which is responsible for the depression of the 5-HT maximum response (Kaumann, 1989). The model of the allosteric 5-HT_{2A} receptor system was supported by the pharmacological properties of 9, 10didehydro-6-methyl-8*ß*-ergolinylmethyl *R, S*-2-methylbutyrate, a derivative of the naturally occurring clavine lysergol, which was able to reverse the depressent effect of the insurmountable 5-HT_{2A} receptor antagonist methysergide (Pertz and Eich, 1992).

14.2.5. The Complexity of the Interaction of the Ergolines with 5-HT_{2B} and 5-HT_{2C} Receptors

Based on their pharmacological profile, 5-HT_{2B} receptors are closely related to 5-HT_{2A} and even more to 5-HT_{2C} receptors (Bonhaus *et al.,* 1995). The 5-HT_{2B} receptor is the receptor that mediates the contractile response to 5-HT in the rat stomach fundus. Although this tissue has been used as a bioassay for 40 years (Vane, 1957), the classification of the fundal contractile receptor within the 5-HT receptor family has proven difficult. Its exact characterization as a 5-HT_{2B} receptor could be established only after the successful cloning of this subtype in the early 1990s (Foguet *et al.,* 1992; Kursar *et al.,* 1992). Ergolines

such as methysergide, metergoline, mesulergine, 2-Br-LSD, LY53857, and amesergide possessed high affinity for the cloned rat 5-HT_{2B} receptor in radioligand binding studies (Wainscott *et al.,* 1993). On the other hand, mesulergine, LY53857, and methysergide displayed complex behaviour as antagonists of 5-HT at the cloned rat 5-HT_{2B} receptor and in rat stomach fundus. Mesulergine acted as a potent and surmountable antagonist, while LY53857 and methysergide showed potent but insurmountable antagonism of the effects of 5-HT (Wainscott *et al.,* 1993; Baxter *et al.,* 1995).

Interestingly, the human stomach does not contain a contractile 5-HT_{2B} receptor. Thus, after the successful cloning of the human 5-HT_{2B} receptor (Schmuck *et al.,* 1994) the question arose what function could be ascribed to this receptor type in humans. There are some facts that speak at that time for an involvement of 5-HT_{2B} receptors in the onset of migraine attacks, although 5-HT_{2C} receptor activation has previously been suggested to be a key step in the initiation of migraine. It has been shown that *m*-chlorophenylpiperazine (*m*-CPP), originally characterized as a potent 5-HT_{2C} receptor agonist, acts as an inducer of migraine-like headache (Fozard and Grey, 1989; Fozard, 1992). Since *m*-CPP also stimulates 5-HT_{2B} receptors in concentrations which induce headache, it has been suggested that drugs that prevent migraine may do so by blocking 5-HT_{2B} receptors. Indeed, the most consistently effective drugs in migraine prophylaxis, lisuride, methysergide, pizotifen, and propranolol have in common antagonist effects at 5-HT_{2B} receptors (Kalkman, 1994; Roos and Glusa, 1998). Also of interest is that methylergometrine, the major metabolite and active principle of methysergide in man (Müller-Schweinitzer and Tapparelli, 1986; Bredberg *et al.,* 1986) has found to be a potent antagonist at 5-HT_{2B} receptors (Fozard and Kalkman, 1994). A further argument that supports the idea of an involvement of 5-HT_{2B} receptors in the initiation of migraine is the finding that 5-HT_{2B} receptors which are present on endothelial cells, including those lining the cerebral blood vessels (Ullmer *et al.,* 1995), mediate vascular relaxation by the release of nitric oxide (NO). Clinical evidence points to a key role for NO in the initiation of migraine (Olesen *et al.,* 1994). In agreement with the findings in the rat stomach fundus, mesulergine acted as a potent and surmountable antagonist at endothelial 5-HT_{2B} receptors in rat jugular vein, while methysergide and LY53857 produced insurmountable antagonism in this tissue (Bodelsson *et al.,* 1993). In contrast, ergopeptines such as ergotamine and dihydroergotamine which proved to be highly efficient as anti-migraine drugs were potent agonists at endothelial 5-HT_{2B} receptors in porcine pulmonary artery (Glusa and Roos, 1996). Therefore, the relevance of 5-HT_{2B} receptor antagonists as efficient drugs in migraine seems to be a point of controversy, although the agonist activity of ergotamine and dihydroergotamine does not rule out a role for 5-HT_{2B} receptors in the initiating event of migraine. The therapeutic benefit of ergotamine and dihydroergotamine in the acute migraine attack and *not* in migraine prevention is based on the potent agonist activity of these drugs at 5-HT_1-like 5-$HT_{1B/1D}$ receptors *(vide supra)*.

Based on similarities between the former "5-HT_{1C} receptor" and the5-HT_{1A} receptor according to structural, transductional and operational criteria, the 5-HT_{1C} receptor has been suggested to be a member of the 5-HT_2 class and is now termed 5-HT_{2C} (Hoyer *et al.,* 1994). 5-HT_{2C} receptors have definitely been detected only in the CNS, where they are localized with high density in the choroid plexus (Hoyer, 1988). [^{3}H]5-HT and [^{3}H]mesulergine have been used as high affinity radioligands for labelling 5-HT_{2C} receptors (Pazos *et al.,* 1984b). The lack of selective agonists and antagonists at the 5-HT_{2C} receptor has hampered elucidation of its pharmacological effects for a long time. Ergolines such as mesulergine, methysergide, and LY53857, originally characterized as 5-HT_{2A} receptor antagonists, and the nonselective ergot derivative metergoline, show high affinity for the 5-HT_{2C} receptor (Hoyer, 1989). LSD has found to be a partial agonist at this site (Sanders-Bush *et al.,* 1988). In the CNS nonselective 5-$HT_{2C/2A}$ receptor antagonists display an anxiolytic profile, whereas selective 5-HT_{2A} receptor antagonists fail to produce anxiolysis. Consequently, it has been suggested that anxiolysis is mediated via the blockade of 5-HT_{2C} receptors (Kenneth, 1992). Further evidence for the involvement of 5-HT_{2C} receptors in anxiety has been provided by means of LY53857, of which a 5-fold selectivity for 5-HT_{2C} versus S-HT_{2A} receptors may be responsible for its marked anxiolytic effect (Kenneth *et al.,* 1994).

The pharmacological profile of ergotamine and dihydroergotamine at 5-HT_{2C} receptors resembles that of these drugs at 5-HT_{2B} receptors. Both drugs behaved as powerful 5-HT_{2C} receptor agonists in piglet choroid plexus (Brown *et al.,* 1991). It is worth mentioning in this connection that the ability of ergotamine and dihydroergotamine to produce headache when taken in excess, may result from sufficient brain penetration at high doses followed by the activation of cerebral 5-HT_{2C} receptors (Brown *et al.,* 1992). On the other hand, headache as an adverse reaction seen with bromokryptine (antiparkinsonian drug) and dihydroergotoxine (used in the treatment of senile dementia), is due to vasodilatation rather than to 5-HT_{2C} receptor stimulation (Brown *et al.,* 1992).

14.2.6. No Role for Ergolines at 5-HT_3 and 5-HT_4 Receptors

With the exception of LY53857 which possesses moderate affinity for 5-HT_3 receptors (Kennett *et al.,* 1994), only few informations exist about the interaction of ergolines with these sites. Similarly, ergolines play no role as ligands for 5-HT_4 receptors. It has been shown that ergolines such as metergoline, mesulergine, and methysergide possess low affinity for 5-HT_4 receptors (Dumuis *et al.,* 1988).

14.2.7. Ergolines as Useful Tools for the Characterization of 5-ht_5, 5-ht_6, and 5-ht_7 Receptors

Two G-protein coupled 5-HT receptors from both mouse and rat brain, designated 5-ht_{5A} and 5-ht_{5B}, have recently been cloned, of which the amino

acid sequence and the pharmacological profile is sufficiently distinct from those of the well characterized receptors 5-HT_1—5-HT_4. Due to its high affinity for both 5-ht_{5A} and 5-ht_{5B} receptors, 2-[^{125}I]LSD has been used as radioligand for these sites. 5-ht_{5A} and 5-ht_{5B} receptors display high affinity for ergotamine and methysergide (Matthes *et al.,* 1993). The functional role of 5-ht_5 receptors remains to be established.

The recently cloned rat 5-ht_6 receptor is exclusively localized in the CNS (especially in the corpus striatum and various limbic and cortical systems). Competition for 2-[^{125}I]LSD binding by a number of drugs revealed high affinity for 5-ht_6 receptors not only for ergolines such as lisuride, dihydroergotamine, 2-Br-LSD, pergolide, metergoline, and lergotrile but for tricyclic antipsychotic and antidepressant drugs such as clozapine, amoxipine, and amytriptyline. This suggests a possible role for 5-ht_6 receptors in several neuropsychiatric disorders that involve serotoninergic systems (Monsma *et al.,* 1993).

5-ht_7 receptors showed high affinity for ergolines (e.g., lisuride, metergoline, pergolide, mesulergine, bromokryptine, and methysergide) and antipsychotic/antidepressant drugs (e.g., clozapine, loxapine, and amitriptyline). In this regard 5-ht_7 receptors resemble 5-ht_6 receptors, although their transmembrane regions exhibit homology of only 44% (Shen *et al.,* 1993). Second messenger coupling, pharmacological profile, and tissue distribution suggest a possible role for 5-ht_7 receptors in relaxation of smooth muscle systems (Bard *et al.,* 1993). For example, the precontracted guinea-pig ileum can be relaxed by 5-HT receptor agonists, including 5-CT and 5-HT, due to activation of 5-ht_7 receptors. The relaxant effect of 5-CT has most potently been blocked by ergolines, including LSD, mesulergine, and methysergide, followed by nonergolines, including spiperone and clozapine (Carter *et al.,* 1995). Among structurally related ergolines such as LY53857, sergolexole, amesergide, and LY215840 which have originally been characterized as potent S-HT_{2A} receptor antagonists *(vide supra),* LY215840 has recently been identified as a high-affinity 5-ht_7 receptor antagonist of 5-HT-induced relaxation in canine coronary artery (Cushing *et al.,* 1996).

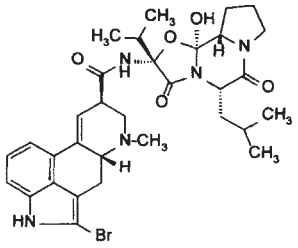
14.3. ERGOLINES AS LIGANDS FOR DOPAMINE RECEPTORS

Dopamine receptors are targets for antipsychotic drugs, antiparkinsonian drugs, and agents that affect the activity of the hypothalamic-pituitary system, particularly the release of prolactin from the pituitary gland. Antipsychotic agents (neuroleptics) specifically block dopamine receptors, whereas antiparkinsonian and prolactin-lowering agents stimulate dopamine receptors. Due to their agonist activity at dopamine receptors, a number of ergolines are widely used as antiparkinsonian drugs (e.g., bromokryptine, lisuride, and pergolide) and as inhibitors of prolactin release (e.g., bromokryptine, cabergoline, and lisuride) (Figure 3).

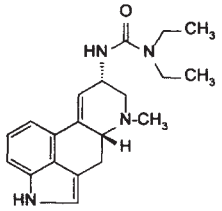
The knowledge of the existence of multiple dopamine receptors and their localization in different tissues is important for understanding how dopaminergic agents achieve their therapeutic effects and how adverse reactions may arise. Biochemical and pharmacological studies led to the identification of two native dopamine receptors, designated D_1 and D_2 (Kebabian and Calne, 1979). In the early 1990s, molecular biology techniques have corrected the oversimplified picture of two dopamine receptors and defined five different isoforms D_1—D_5 which may be divided into D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) subfamilies on the basis of their structural and pharmacological properties (Sibley and Monsma, 1992; Strange, 1993). The D_1-like and D_2-like subfamilies of cloned receptor isoforms correspond to the D_1 and D_2 receptors of the former receptor classification. D_1 and D_5 (both positively coupled to adenylyl cyclase) and D_2 (negatively coupled to adenylyl cyclase) belong to the superfamily of G-protein coupled receptors. Within the neostriatum, the brain region where dopamine is important for control of motor function, the principal receptor subtypes are D_1 and D_2. In addition D_2 receptors are localized at high levels in the pituitary gland. The preferential localization of D_3 receptors is in limbic regions of the brain. This suggests an important role for D_3 receptors in the control of aspects of behaviour, emotion, motivation, and cognition (Strange, 1991). The D_4 receptor appears to be distributed at lower levels in the brain and at higher levels in the CV system (Van Tol *et al.,* 1991). Therefore, the D_4 receptor may be considered as a peripheral D_2-like receptor (O'Malley *et al.,* 1992).

Ergolines presumably exert their antiparkinsonian effect *via* stimulation of neostriatal D_1 and D_2 receptors (Strange, 1993), whereas their inhibitory effect on prolactin release from the anterior pituitary may be mediated *via* stimulation of D_2 or D_4 receptors (Sokoloff *et al.,* 1993). Parkinson's disease is caused by a loss of dopaminergic neurones innervating the striatum (Strange, 1992). The treatment of Parkinson's disease with mixed D_1/D_2 receptor agonists which lack D_3, D_4, and D_5 receptor affinity may lead to a facilitation of motor function by maintaining the balance between D_1 receptor activation *via* a direct neostriatal pathway and D_2 receptor inhibition *via* an indirect neostriatal pathway in favour of the direct pathway (Strange, 1993). The improved efficiency of D_2-like receptor agonists such as bromokryptine and lisuride, when used in association with L-DOPA as a prodrug of dopamine which stimulates both D_1 and D_2 receptors in the neostriatum, provides some support for the need of D_1 and D_2 receptor occupancy in the treatment of Parkinson's disease (Agnoli *et al.,* 1985).

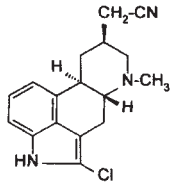
Ergolines with dopaminergic activity that have been most widely studied include bromokryptine, lisuride, lergotrile, pergolide, and cabergoline. Prior to molecular cloning of dopamine receptor subtypes, the dopaminergic profile of these drugs had been established on the basis of the existence of two native dopamine receptors, D_1 (i.e. D_1-like) and D_2 (i.e. D_2-like) *(vide supra)*. For example, bromokryptine seemed to be relatively selective at D_2 (i.e. D_2-like) receptors, whereas lisuride and lergotrile acted as a D_2



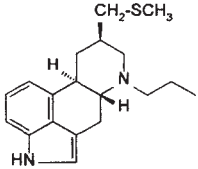
Bromokryptine



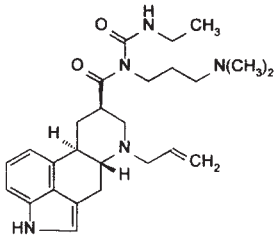
Lisuride



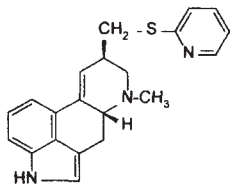
Lergotrile



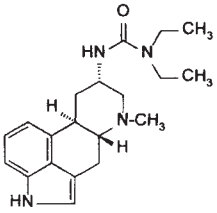
Pergolide



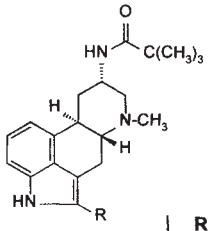
Cabergoline



CF 25-397



Terguride



	R
SDZ208911	CH_3
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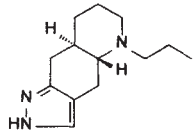
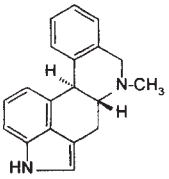


Quinpirole



CY 208-243

Figure 3 Structures of ergolines that show (partial) agonist activity at D_2-like receptors. CY 208–243 is an agonist at D_1-like receptors, and pergolide shows mixed D_1-like and D_2-like receptor agonist activity

(i.e. D_2-like) receptor agonists with antagonist activity at D_1 (i.e. Di-like) receptors (Kebabian and Calne, 1979; Cote *et al.,* 1985). It should be mentioned that lisuride lacks specificity for dopamine receptors due to its high affinity for 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors (Hoyer, 1989; Roos and Glusa, 1998). On the other hand, pergolide showed increased specificity for dopamine receptors and behaved as an agonist at both D_1 (i.e. D_1-like) and D_2 (i.e. D_2-like) receptors (Fuller and Clemens, 1991). Due to its mixed D_1-like and D_2-like receptor agonist activity, pergolide appears to be more suitable to treat parkinsonism than pure D_2-like receptor agonists *(vide supra)*. Cabergoline, another ergoline with enhanced specificity for dopamine receptors, showed marked D_2 (i.e. D_2-like) receptor agonist activity and long duration of action (Pontiroli *et al.,* 1987). Due to its poor brain penetration, the clinical application of cabergoline was restricted to the inhibition of prolactin release from the anterior pituitary, which is not protected by the blood-brain barrier. Unfortunately, only few informations are available about the interaction of ergolines with the cloned receptor isoforms D_1-D_5. Bromokryptine has been shown to possess comparably high affinity for both D_2 and D_3 receptors with marginal affinity for D_1, D_4, and D_5 receptors, while pergolide seems to be an equipotent ligand for D_1, D_2, and D_3 receptors (Seeman and Van Tol, 1994). It is worth mentioning that the interaction of bromokryptine and pergolide with D_3 receptors may be responsible for unwanted psychic side effects (e.g., confusion, hallucination) observed in the treatment of Parkinson's disease with these drugs.

A phenomenon not directly related to subtypes deals with the partial D_2-like receptor agonism of ergolines such as CF 25–397 and terguride (*trans*-dihydrolisuride), respectively. Partial agonists have the advantage of being recognized as full agonists by dopamine receptors when neostriatal dopaminergic neurones are relatively low or absent as in Parkinson's disease. On the other hand, D_2-like receptors of non-striatal systems mediating nausea and emesis may remain untouched due to the antagonist properties of partial agonists. Thus, the use of partial agonists may lead to a better balance between therapeutic actions and unwanted side effects (Carlsson, 1993). Further examples for partial dopamine receptor agonists within the family of ergolines are SDZ208911 and SDZ208912. Whereas SDZ208912 is a potent D_2-like receptor antagonist with only marginal intrinsic activity, SDZ208911 exhibits higher intrinsic activity and less D_2-like receptor blockade. Based on their reduced parkinsonian side effects, SDZ208911 and SDZ208912 may be useful drugs in the treatment of schizophrenia (Coward *et al.,* 1990). It has recently been shown that non-addictive dopamine receptor agonists such as bromokryptine, lisuride, and pergolide may ameliorate some of the symptoms of psychostimulant withdrawal. It should be noted that partial agonists such as terguride, SDZ208911, and SDZ208912 are of special importance as candidates for the treatment of psychostimulant dependence due to their normalizing effect on dopamine neurotransmission during the various phases

of psychostimulant addiction. The therapeutical benefit of partial agonists can be ascribed to their antagonist activity under conditions of dopamine hyperactivity following the exposure to psychostimulants and to their agonist activity during psychostimulant withdrawal which is characterized by a low dopamine tone (Pulvirenti and Koob, 1994).

Early studies with lergotrile and pergolide suggested that the indole NH group of the ergoline nucleus is bioisosteric with the *m*-hydroxy group of dopamine, and that the rigid pyrrolethylamine portion of the molecule might be the pharmacophoric constituent of the ergolines (Bach *et al.,* 1980). Potent D_2-like receptor agonism of linear tricyclic analogues of ergolines confirmed the hypothesis. Tricyclic ergoline partial structures such as LY141865 were comparable in potency with the highly active ergoline pergolide (Bach *et al.,* 1980). It could be demonstrated that dopamine receptor agonist activity of racemic LY141865 is a property of its *R, R*-(—)enantiomer quinpirole (Titus *et al.,* 1983) which showed high affinity for D_2 receptors and somewhat lower affinity for D_3 and D_4 receptors (Seeman and Van Tol, 1994). On the other hand, enhanced D_1-like receptor selectivity could be induced by fusion of a benzene ring across the 8,9-bond of the ergoline skeleton. Benzo-fused pentacyclic ergolines ("benzergolines") such as CY 208–243 represent the first structural class of potent and selective non-catechol D_1-like receptor agonists which allow efficient penetration into the CNS (Seller *et al.,* 1991, 1993).

14.4. ERGOLINES AS LIGANDS FOR ADRENOCEPTORS

Since the end of the 1940s structure-activity relationship studies by means of natural and synthetic ligands have led to the detection of an increasing number of distinct adrenoceptor subtypes. Drugs interacting with these subtypes have proven useful in a variety of diseases such as hypertension, angina pectoris, congestive heart failure, cardiac arythmia, asthma, depression, prostatic hypertrophy, and glaucoma (Bylund *et al.,* 1994).

From a historical point of view ergot alkaloids are closely linked to the classification of adrenoceptors into two major subtypes (α and β). The discrimination between α- and β-adrenoceptors was based on the insensitivity of the latter to ergot alkaloids or β-haloalkylamines (Nickerson, 1949). On the basis of structural, transductional, and operational criteria it became apparent that the existence of two subtypes of α-adrenoceptors, the α_1-adrenoceptor, sensitive to blockade by prazosin, and the α_2-adrenoceptor, sensitive to blockade by yohimbine or rauwolscine, makes it more appropriate to classify adrenoceptors into three major subtypes: the α_1-adrenoceptors, α_2-adrenoceptors, and β-adrenoceptors (Bylund, 1988).

The interaction of ergolines with these three major subtypes (α_1, α_2, β) appears to be highly complex even if newer developments considering the existence of further subtypes are neglected *(vide infra)*. Therefore, we will only mention some

general aspects of the effects of ergolines on adrenoceptors, particularly since this subject has been excellently reviewed years ago (MüllerSchweinitzer, 1978). In radioligand binding studies ergopeptines such as ergotamine, dihydroergotamine, dihydroergotoxine, α-dihydroergokryptine, and dihydroergocristine generally displayed higher affinity for α_2- than for α_1-adrenoceptors (Closse *et al.,* 1984). Functional studies showed that dihydroergotamine, dihydroergotoxine, and dihydroergocristine acted as partial agonists at α_2-adrenoceptors and antagonists at α_1-adrenoceptors in the peripheral vascular system and in vas deferens (Roquebert and Grenié, 1986; Roquebert *et al.,* 1983, 1984, 1985). Slightly higher affinity for α_2-adrenoceptors than for α_1-adrenoceptors has been obtained *in vivo* and *in vitro* for ergotamine (Megens *et al.,* 1986). Moreover, a combined 5-HT_{1D}/α_2-receptor agonist activity has been reported for ergotamine in dog saphenous vein (Müller-Schweinitzer, 1992). In contrast simple lysergic acid amides such as ergometrine, methylergometrine, and methysergide are only weakly active at α_1-adrenoceptors (Müller-Schweinitzer, 1978). However, this is not always the case. For example, LSD exhibits a highly complex pharmacology which is the result of its interference not only with 5-HT receptors and dopamine receptors but also with α_1-, α_2-, and ß-adrenoceptors (Closse *et al.,* 1984; MaronaLewicka and Nichols, 1995; Dolphin *et al.,* 1978). In addition, ergolines such as bromokryptine, lisuride, lergotrile, and pergolide, which play an important role in the treatment of Parkinson's disease and as inhibitors of prolactin secretion due to their dopaminergic activity *(vide supra),* also display high affinity for α_1- and α_2-adrenoceptors (Closse *et al.,* 1984; Ruffolo *et al.,* 1987). This may be taken as a further evidence for the lack of ergolines to interact specifically with monoamine receptor systems.

With the rapid development of additional pharmacological tools which displayed improved selectivity for either α_1, α_2- or ß-adrenoceptors in functional and radioligand binding studies, and the advent of molecular biological techniques by cloning of distinct adrenoceptor subtypes being in accord with their native correlates, the existence of additional subtypes became apparent. At present, the family of adrenoceptors comprises three α_1-adrenoceptor subtypes (α_{1A}, α_{1B}, α_{1D}), four α_2-adrenoceptor subtypes (α_{2A}, α_{2B}, α_{2C}, α_{2D}), and three ß-adrenoceptor subtypes ($ß_1$, $ß_2$, $ß_3$).

The present study makes it clear that ergolines as ligands of low specificity and selectivity generally play a limited role in the characterization of so many closely related subtypes of adrenoceptors. A worth-mentioning exception is BAM-1303 (8ß[(2-phenylimidazol-l-yl)methyl]-6-methylergoline) which represents a useful pharmacological tool in this field due to its ability to discriminate between the closely related α_{2A}- and α_{2D}-receptors on the one hand, and α_{2B}- and α_{2C}-receptors on the other hand (Simmoneux *et al.,* 1991). The relatively high affinity of methysergide, originally characterized as a 5-HT_{1D} receptor partial agonist and as a 5-$HT_{2A/2B/2C}$ receptor antagonist, for a_{2B}-adrenoceptors should be mentioned as a further evidence for the extremely complex activity profile of the ergolines (Brown *et al.,* 1990).

14.5. CONCLUSION

Despite their low specificity and selectivity, ergot alkaloids and their derivatives are highly efficient tools for the characterization of serotonin (5-HT) receptors, dopamine receptors, and adrenoceptors, where they display complex behaviour as agonists, partial agonists or antagonists. Analysis of the interaction at these sites shows that ergolines are "dirty" drugs of which the therapeutical benefit as well as the unwanted side effects can be related to the involvement of a variety of different receptor subtypes. Predominant targets for therapeutically used ergolines are 5-HT_{1D} receptors in the treatment of the acute migraine attack (ergotamine, dihydroergotamine), 5-HT_{2B} receptors in migraine prophylaxis (methysergide), 5-HT_{2A} receptors in the control of postpartum bleeding (ergometrine, methylergometrine), D_2-like receptors in the inhibition of prolactin release from the anterior pituitary (e.g., cabergoline), and D_2-like (e.g., bromokryptine) or D_1-like and D_2-like receptors (e.g., pergolide) in the treatment of parkinsonism. The vasoactive properties of certain ergolines (e.g., dihydroergotamine, dihydroergotoxine) involve partial α_2-adrenoceptor activation and α_1-adrenoceptor blockade in the peripheral vascular system. Their interaction with further subtypes of adrenoceptors remains to be established.

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