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Effect of pergolide on MOPEG sulphate levels in rat brain regions

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Dopamine receptors located presynaptically on noradrenergic nerve terminals suppress noradrenaline release by peripheral sympathetic nerves (Starke et al 1977; Langer 1980; Dubocovich & Langer 1980). There is also evidence that noradrenergic neurons in brain may have presynaptic dopamine receptors that inhibit transmitter release (Dubocovich et al 1981). Galzin et al (1982) have shown that noradrenergic nerve endings in hypothalamus contain dopamine receptors that inhibit the stimulation-evoked overflow of tritiated noradrenaline previously taken up by the nerve endings. The most potent compound among dopamine agonists they studied as activators of these receptors was pergolide, which had an IC50 of 19 nM.

Central noradrenergic nerve terminals are known to possess inhibitory α_2-receptors, activation of which also suppresses stimulation-evoked overflow of tritiated noradrenaline (Langer 1980; Galzin et al 1982). Agents like clonidine stimulate these presynaptic α_2-receptors and lead not only to reduced overflow of labelled noradrenaline during in vitro stimulation (Galzin et al 1982) but also to a reduction in noradrenaline turnover in vivo, one manifestation of which is a decreased concentration of MOPEG sulphate (3-methoxy-4-hydroxyphenyl-ethylene glycol sulphate), the major metabolite of noradrenaline in rat brain (Braestrup & Nielsen 1976).

Although we had earlier reported that a high dose of pergolide *increased* whole brain levels of MOPEG sulphate (Fuller et al 1979), presumably due to blockade of α_2-receptors, we thought it possible that low doses of pergolide, by activating the presynaptic dopamine receptor, might *decrease* noradrenaline turnover and MOPEG sulphate concentrations. To examine this possibility, we measured MOPEG sulphate specifically in hypothalamus, the brain region in which the inhibitory dopamine receptors were demonstrated (Galzin et al 1982), and included other brain regions for comparison.

Method

Male Wistar rats, 190–220 g, obtained from Harlan Industries, Cumberland, IN, were housed in groups of 5 in a 24 °C room with 12 h light:dark cycles. Pergolide mesylate was injected i.p., and rats were killed 4 h later. The 4 h time was selected because this is when MOPEG sulphate levels are essentially at their minimum after α_2-agonists (Braestrup & Nielsen 1976; Fuller et al 1977) and dopamine metabolites are maximally lowered after pergolide (Fuller et al 1979). Brain regions were rapidly dissected and stored at −15 °C before analysis. MOPEG sulphate was isolated on an ion exchange column, then hydrolysed to MOPEG which was measured by high performance liquid chromatography with electrochemical detection (Perry 1982).

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Results

Table 1 shows the effects of 0·01, 0·1 and 1 mg kg^{-1} i.p. doses of pergolide mesylate on MOPEG sulphate levels in four regions of rat brain. At the highest dose of pergolide tested, 1 mg kg^{-1}, statistically significant increases in MOPEG sulphate were found in all brain regions. The increases ranged from 36% in cerebral hemispheres to 88% in the hypothalamus. At the 0·1 mg kg^{-1} dose, MOPEG sulphate was affected significantly only in hypothalamus, and the increase was small (18%). At the lowest dose, no changes in MOPEG sulphate concentration were found in any of the four brain regions.

Discussion

These data reveal that pergolide increases MOPEG sulphate in rat brain at doses substantially lower than that reported previously (20 mg kg^{-1}) (Fuller et al 1979). The increase in MOPEG sulphate concentration that occurred with the 1 mg kg^{-1} dose of pergolide probably results from blockade of α_2-receptors. Galzin et al (1982) reported that pergolide had a biphasic pattern of effects on tritiated noradrenaline release from hypothalamic slices in-vitro, and they attributed this to α_2-adrenoceptor antagonism by higher concentrations of pergolide counteracting the dopamine receptor-mediated decrease in noradrenaline overflow. Several α-blocking drugs have been shown to increase MOPEG sulphate concentration in rat brain, including phenoxybenzamine, yohimbine and aceperone (Meek & Neff 1973; Braestrup & Nielsen 1976; Baumann & Waldmeier 1978). Our in-vivo experiments reveal only this apparent α_2-blocking component of pergolide's action and fail to give evidence that dopamine receptor activation can lead to decreased noradrenaline turnover in brain.

Previous studies have shown that pergolide mesylate at doses in the range of 0·01–0·1 mg kg^{-1} activate presynaptic dopamine autoreceptors leading to decreased dopamine turnover in rat brain (Fuller et al 1979; Rabey et al 1981; Haubrich & Pflueger 1982), as measured by a decrease in brain concentrations of 3,4-dihydroxyphenylacetic acid (DOPAC) or decreased accumulation of dopa after decarboxylase inhibition in

Table 1. Effect of pergolide on MOPEG sulphate levels in brain regions.

Dose of pergolide mesylate (mg kg^{-1} i.p.)	MOPEG sulphate, nmol g^{-1} wet weight of tissue			
	Cerebral hemispheres	Hypothalamus	Brain stem	Midbrain
0	0·45 ± 0·02	0·73 ± 0·03	0·54 ± 0·03	0·75 ± 0·03
0·01	0·40 ± 0·02	0·78 ± 0·03	0·65 ± 0·05	0·79 ± 0·03
0·1	0·45 ± 0·02	0·86 ± 0·02*	0·58 ± 0·02	0·74 ± 0·03
1	0·61 ± 0·05*	1·37 ± 0·12*	0·92 ± 0·06*	1·11 ± 0·07*

* Significant change from control ($P < 0·05$).
Pergolide mesylate was injected 4 h before rats were killed. Mean values ± s.e. for 5 rats per group are shown.

γ-butyrolactone-treated rats. The decrease in brain DOPAC persisted for at least 18 h after a 0·3 mg kg^{-1} dose of pergolide mesylate (Fuller et al 1979). The in-vitro concentration at which pergolide inhibits stimulated overflow of tritiated noradrenaline from hypothalamic slices (IC50 19 nM) (Galzin et al 1982) resembles those at which pergolide inhibits stimulated overflow of tritiated dopamine from striatal slices (3–10 nM) (Lehmann et al 1981). One might then expect that pergolide would reduce noradrenaline turnover in hypothalamus in-vivo at doses similar to those required for reducing dopamine turnover, if presynaptic dopamine receptors on hypothalamic noradrenergic nerve terminals have the physiological role of suppressing noradrenaline formation and release. Galzin et al (1982) suggested that inhibitory presynaptic dopamine receptors were present on noradrenaline terminals in brain regions other than hypothalamus as well, since they found effects of dopamine agonists in limited studies on noradrenaline release from cerebral cortex. However, we found no reduction in MOPEG sulphate concentration by pergolide in any brain region. Decreased MOPEG sulphate concentration in brain has been reported to occur in rats following treatment with α_2-agonists, including clonidine and guanabenz (Braestrup & Nielsen 1976; Fuller et al 1977). These agents also inhibit tritiated noradrenaline release by electrical stimulation of brain slices in vitro (Galzin et al 1982). The inability of pergolide to decrease MOPEG sulphate concentration may mean that dopamine receptors on hypothalamic noradrenaline neurons do not reduce noradrenaline turnover. On the other hand, it is conceivable that such receptors are already maximally activated under normal physiological conditions so that an exogenous agonist has no added effect. The fact that numerous neuroleptic drugs known to block dopamine receptors do increase MOPEG sulphate concentrations in brain (Keller et al 1973; Berridge & Sharman 1974; Ader et al 1980) would be consistent with that possibility, though it has generally been assumed that their elevation of MOPEG sulphate results from block of α-noradrenergic receptors. The in-vitro studies of Galzin et al (1982) were done with hypothalamic slices from rabbits, so our in-vivo studies are in a different species. That species difference could be a factor in the nature of the results obtained.

Pergolide at low doses causes hypomotility in rodents as does apomorphine, effects that have been attributed to selective activation of presynaptic autoreceptors on dopamine neurons (Strombom 1976; Fuller et al 1982). Galzin et al (1982) suggested that sedative effects of low doses of dopamine agonists (apomorphine in particular) and sedative effects of clonidine might occur through a common mechanism, namely reduction of noradrenergic neurotransmission by activation of presynaptic receptors on noradrenaline neurons (dopamine receptors in the case of apomorphine and α_2-receptors in the case of clonidine). Although clonidine decreases noradrenaline turnover and MOPEG sulphate concentration in brain at doses causing sedation (Strombom 1976; Braestrup & Nielsen 1976), this is not true with pergolide. Pergolide causes hypomotility in rats between doses of 0·01–0·1 mg kg^{-1} (Fuller et al 1982), but pergolide did not decrease MOPEG sulphate concentration at these doses (Table 1). These data would argue against the possibility that Galzin et al (1982) suggested.

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