suppository bases after rectal administration even suggesting spreading into intestinal regions (Rutten-Kingma et al 1979). However, in three reports, suppositories were mistaken for renal calculi on abdominal radiographs (Spitzer et al 1976; Lesher & Scott 1979; Brown & Gould 1982). In all of the reports, the radiopacity was confined to the rectum of the patient for extended periods of time after the administration of the suppository, as much as 5 h in one case.

In summary, the data obtained supports the conclusion that the absorption of drugs administered in suppository dosage forms is confined to the lower rectum. Therefore, the metabolism of drugs sensitive to the first-pass effect may be partially avoided by their rectal administration.

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Pergolide elevation of MHPG sulphate concentration in rat hypothalamus blocked by spiperone and mimicked by other dopamine agonists

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Pergolide increased the concentration of MHPG sulphate (3-methoxy-4-hydroxy-phenylethylene glycol sulphate) in rat hypothalamus, and the increase was prevented by pretreatment with spiperone, a dopamine antagonist. An increase in hypothalamic MHPG sulphate concentration similar to that caused by pergolide was found after injection of quinpirole, a 'partial ergoline' that is a selective D_2 agonist not affecting α-adrenoceptors, and by (−)-*N*-propylnorapomorphine, a dopamine agonist not related to the ergolines. Although the increase in MHPG sulphate concentration produced by pergolide had earlier been assumed to result from blockage of α-adrenoceptors, the present data indicate that it is an effect produced by dopamine D_2 receptor stimulation.

Pergolide and lergotrile, two ergolines that are dopamine agonists, have been reported to increase brain concentrations of MHPG sulphate (3-methoxy-4-hydroxy-phenylethyleneglycol sulphate), the metabolite of noradrenaline (Fuller et al 1979; Fuller & Perry 1983). The ergolines, like many other ergot-related drugs, have relatively high affinities for α-adrenoceptors (McPherson & Beart 1983). Since α-adrenoceptor antagonists increase noradrenaline turnover and MHPG sulphate concentration in brain (Braestrup & Nielsen, 1976; Fuller et al 1978; Baumann & Waldmeier 1978), we had supposed that the increase in MHPG sulphate caused by pergolide and lergotrile might be due to blockage of central α-receptors by those drugs. In fact, an increase in MHPG sulphate concentration or other measures of noradrenaline turnover by bromocriptine, lisuride and other ergot drugs that are dopamine agonists, has been interpreted as due to block of α-adrenoceptors (Kehr 1977; Burki et al 1978). We describe here evidence that the increase in MHPG sulphate produced by pergolide is instead a result of its activation of dopamine receptors. The evidence consists of the findings that spiperone, a dopamine antagonist, blocks the effect of pergolide completely and that quinpirole, a 'partial ergoline' much less potent than pergolide in interacting with α-adrenoceptors (McPherson & Beart 1983), as well as (−)-*N*-n-propylnorapomorphine (NPA), a potent dopamine agonist unrelated chemically to the ergolines (Neumeyer et al 1973), mimics the effect of pergolide in elevating brain levels of MHPG sulphate.

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Methods

Male Wistar rats (HSD/[WI]BR), 150–200 g, were obtained from Harlan Sprague-Dawley, Inc., Cumberland, IN. Pergolide mesylate and quinpirole hydrochloride were synthesized at Eli Lilly and Company. Quinpirole hydrochloride (LY171555) is the active enantiomer (Titus et al 1983; Wong et al 1983) that accounts for the D_2 dopamine agonist properties of LY141865 (Tsuruta et al 1981; McPherson & Beart 1983). The (−)-tartrate salt of quinpirole has been referred to as LY156258 (Wong et al 1983). SKF 38393A (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-benzazepine) was a gift from Smith Kline & French Laboratories, Philadelphia, PA, and spiperone was a gift from Janssen Pharmaceutica, Beerse, Belgium. NPA hydrochloride was purchased from Research Biochemicals, Wayland, MA. Drugs were injected i.p. or s.c. in aqueous solutions. Rats were decapitated and brains quickly removed, and dissected, the sections being frozen on dry ice and stored at −15 °C before analysis. MHPG sulphate, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were measured by high performance liquid chromatography with electrochemical detection (Perry & Fuller 1979; Fuller & Perry 1983). Statistical comparisons between groups were done using Student's *t*-test. The affinities for α_1- and α_2-receptors were determined by radioligand binding studies with tritiated WB-4101 (2-(*N*-[2,6-dimethoxyphenyl-oxyethyl])-aminomethyl-1,4-benzodioxane), and clonidine and rat frontal cortex membranes according to previously published procedures (Fuller et al 1981).

Results

Fig. 1 shows the effect of spiperone pretreatment on the elevation of MHPG sulphate in rat hypothalamus by pergolide. Pergolide caused a 65% increase in MHPG sulphate concentration, an effect that was highly significant statistically ($P < 0.001$). Spiperone itself did not significantly affect MHPG sulphate concentration, but spiperone pretreatment completely prevented the increase caused by pergolide. The dopamine metabolites, DOPAC and HVA, were measured in the cerebral hemispheres of these rats to verify the dopamine agonist activity of pergolide and the dopamine antagonist activity of spiperone. Pergolide decreased DOPAC and HVA from 0·78 ± 0·05 and 0·58 ± 0·01 nmol g^{-1}, respectively, in controls to 0·51 ± 0·03 and 0·42 ± 0·01 nmol g^{-1}, respectively. Spiperone increased DOPAC and HVA to 1·56 ± 0·23 and 2·40 ± 0·40 nmol g^{-1}, respectively. Rats pretreated with spiperone before pergolide, had increased, rather than decreased, concentrations of these dopamine metabolites; DOPAC was 0·80 ± 0·11 nmol g^{-1}, and HVA was 1·70 ± 0·29 nmol g^{-1}.

As a further test of whether dopamine receptor activation was involved in MHPG sulphate elevation by pergolide, we determined the effects of quinpirole, a

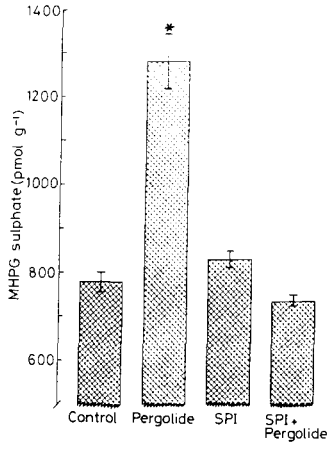

FIG. 1. Antagonism by spiperone of the pergolide-induced increase in MHPG sulphate concentration in rat hypothalamus. Pergolide mesylate (1 mg kg^{-1} i.p.) was injected 1 h before rats were killed and 1 h after spiperone (0·5 mg kg^{-1} i.p.). Mean values and standard errors for 5 rats per group are shown.

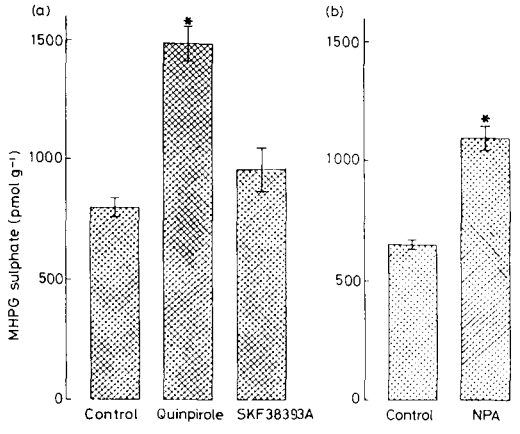

FIG. 2. Elevation of MHPG sulphate concentration in rat hypothalamus (a) by quinpirole not by SKF 38393A, and (b) by NPA. Quinpirole hydrochloride and SKF 38393A were injected at 2 mg kg^{-1} i.p. 2 h before rats were killed. NPA hydrochloride was injected s.c. at 0·1 mg kg^{-1} 2 h before rats were killed. Mean values and standard errors for 5 rats per group are shown.

dopamine agonist structurally related to pergolide but lacking affinity for α-adrenoceptors, and of NPA, a potent dopamine agonist not related chemically to the ergolines. Fig. 2 shows that quinpirole and NPA mimicked the effect of pergolide in causing an increase in MHPG sulphate concentration. In the first experiment, quinpirole, at a dose of 2 mg kg^{-1}, caused an 82% increase in MHPG sulphate concentration. Quinpirole and the racemate that contains it have been shown to be highly specific agonists of the D_2 subtype of dopamine receptors (Tsuruta et al 1981; Titus et al 1983; Kebabian et al 1984). A selective D_1 agonist, SKF 38393A (Setler et al 1978; Kebabian et al 1984), was included in this experiment and found not to mimic the effect of

quinpirole and pergolide in elevating MHPG sulphate concentration in rat hypothalamus. In the second experiment, NPA at a dose of 0·1 mg kg^{-1} caused a 69% increase in MHPG sulphate concentration.

The relative affinities of quinpirole and pergolide for α-adrenoceptors were assessed in separate experiments. Quinpirole had much lower affinity than pergolide for α-adrenoceptors studied by radioligand binding in-vitro. The IC50 values for pergolide were 330 nM and 47 nM for α_1- and α_2-receptors, respectively. In contrast, the IC50 values for quinpirole were >10 000 nM and 1200 nM for α_1- and α_2-receptors, respectively. Thus pergolide has more than 30 times the affinity of quinpirole for α_1-receptors and about 25 times the affinity of quinpirole for α_2-receptors. In contrast, quinpirole and pergolide have relatively similar potency in-vivo in producing dopaminergic effects such as reduction in dopamine turnover in brain (Rabey et al 1981) and elevation of serum corticosterone concentration (Fuller et al 1983). Hahn et al (1983) showed that quinpirole (studied as the racemate, LY141865) lacks α-agonist and antagonist activity at doses effective as a dopamine agonist in rats.

The increase in MPHG sulphate produced by pergolide (and other dopamine agonists) appears to be dopaminergic, but the exact mechanism is unknown. The increase might result from some stressful behavioural or physiological change that is caused by dopaminergic activation, since stress is known to increase MHPG sulphate concentration in brain (Tanaka et al 1982). The doses of pergolide required to increase MHPG sulphate are relatively high, higher than needed for some other dopaminergic effects such as lowering of serum prolactin concentration, lowering of DOPAC concentration in brain, and induction of turning behaviour in rats with unilateral nigrostriatal lesions (Fuller et al 1979).

In conclusion, although previously the elevation of MHPG sulphate concentration in brain by pergolide has been interpreted as probably indicative of α-receptor blockade by that ergoline-related drug (Fuller et al 1979; see McPherson & Beart 1983), the present data suggest that the elevation occurs secondarily to dopamine D_2 receptor activation. The effect of pergolide is blocked by a dopamine antagonist and is mimicked by dopamine agonists that are not ergolines and that have little affinity for α-receptors.

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