delivered to the patient and this demand was fulfilled with the device used.

As the intention was to study absorption in the nasal cavity, the volunteers were asked not to inhale whilst being dosed to avoid significant aspiration of drug into the pharyngeal, laryngeal and tracheal regions. It is also feasible that some of the drug delivered intranasally may have entered the digestive tract by mucociliary clearance to be largely inactivated by first pass metabolism. From the intranasal t_{max}, the drug is rapidly absorbed from the intranasal mucosa thereby avoiding most such losses, although it is probably impossible to eliminate them. This may account for some of the variations in the amount of drug absorbed seen in this study. Individual variations in the nasal mucosa and/or nasal cavity anatomy may contribute to variability, as may the size of droplets given by the spray. The pharmacokinetics after intranasal buprenorphine were similar in profile to those achieved after intramuscular administration (Bullingham et al 1980) rather than to those after sublingual administration (Bullingham et al 1982). The mean t_{max} after the intranasal administration was about 30 min compared with average peak plasma concentrations in 5–10 min after intramuscular injection and a t_{max} of about 200 min after sublingual administration. The mean, within-patient relative systemic bioavailability after an intranasal dose averaged 48·2%, varying from 33·0% to 86·5%. As calculated from the mean AUC of each group this was 52%. The corresponding values for the intramuscular and sublingual administration according to Bullingham et al (1980, 1981, 1982) were 40–90% and 31–57·7%, respectively. Although 24 h blood samples were taken, the AUC values were only calculated to 12 h as plasma concentrations after this time were barely above the detection limit of the assay and thus unreliable as would have been an extrapolation of the curves to yield $AUC_{0-\infty}$ values. In practice, the comparison of $AUC_{0-12\,h}$ data were considered well justified.

In conclusion, intranasal administration of buprenorphine may represent a new delivery route approaching the effectiveness of the intramuscular route but without the problems associated with invasive techniques.

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Decreased 5-hydroxytryptamine turnover in striatum and other brain regions after administration of 5-methoxy-3-(di-n-propylamino)-chroman to rats

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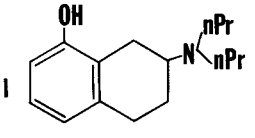
Abstract—5-Methoxy-3-(di-n-propylamino)chroman (5-MeO-DPAC) caused a dose-dependent decrease in the accumulation of 5-hydroxytryptophan after decarboxylase inhibition in rat striatum, hippocampus and frontal cortex. The decreased 5-hydroxytryptamine (5-HT) turnover may have resulted from activation of 5-HT receptors on cell bodies of 5-HT neurons that project to the striatum and other brain regions, since 5-MeO-DPAC had earlier been reported to lack affinity for striatal binding sites.

5-Methoxy-3-(di-n-propylamino)chroman (5-MeO-DPAC, II) is a structural analogue of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, I) and shares with the latter compound a high and selective affinity for $5\text{-}HT_{1A}$-binding sites (Cossery et al 1987). When tritiated 5-MeO-DPAC was used as a radioligand, it labelled sites in hippocampal and cortical membranes from rat brain apparently identical to those labelled by tritiated 8-OH-DPAT. In contrast to tritiated 8-OH-DPAT, tritiated 5-MeO-DPAC did not bind to striatal membranes. 8-OH-DPAT, like other 5-hydroxytryptamine (5-HT) agonists, decreases 5-HT turnover in rat brain (Arvidsson et al 1981; Hjorth et al 1982; Fuller 1985). 8-OH-DPAT has been shown to decrease 5-HT turnover in the striatum just as in hippocampus and other brain regions in rats (Hjorth et al 1982). The current study was undertaken to see if 5-MeO-DPAC affected 5-HT turnover in the striatum, where binding sites for it were not present, and in other brain regions.



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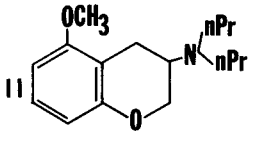
8-OH-DPAT



II

5-MEO-DPAC

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Materials and methods

Male Sprague-Dawley rats, 150-170 g, were from Charles River Breeding Laboratories, Portage, MI. The turnover of 5-HT was measured as the accumulation of 5-hydroxytryptophan (5-HTP) following decarboxylase inhibition by NSD 1015 (m-hydroxybenzylamine hydrochloride, Aldrich Chemical Company, Milwaukee, WI). 5-MeO-DPAC was synthesized in the Lilly Research Laboratories. NSD 1015 was dissolved in distilled water and injected i.p. at a dose of 100 mg kg^{-1} 40 min before the rats were killed. 5-MeO-DPAC was dissolved in distilled water and injected s.c. at various doses 2 min before NSD 1015. Rats were decapitated, and brain regions were quickly excised, frozen on dry ice, and stored at −60°C before determination of 5-HTP by liquid chromatography with electrochemical detection.

Results

Table 1 shows the amount of 5-HTP accumulated during 40 min after injection of the decarboxylase inhibitor, NSD 1015. 5-MeO-DPAC significantly decreased 5-HTP accumulation in all three brain regions studied—striatum, cortex and hippocampus—at doses of 0·3 and 1 mg kg^{-1} s.c. In the cortex, the small

Table 1. Effect of 5-MeO-DPAC, 5-methoxy-3-(di-n-propylamino)chroman, on the accumulation of 5-hydroxytryptophan (5-HTP) in rat brain regions after decarboxylase inhibition. NSD 1015 (100 mg kg^{-1} i.p.) was injected 40 min before rats were killed and 2 min after 5-MeO-DPAC. Mean values ± standard errors for 5 rats per group are shown.

Dose of 5-MeO-DPAC mg kg^{-1} (s.c.)	Accumulated 5-HTP, nmol g^{-1}		
	Striatum	Cortex	Hippocampus
0	1·31 ± 0·07	0·62 ± 0·02	0·94 ± 0·07
0·03	1·11 ± 0·14	0·57 ± 0·05	0·78 ± 0·06
0·1	1·09 ± 0·10	0·49 ± 0·03* (−21%)	0·86 ± 0·04
0·3	0·82 ± 0·04* (−37%)	0·35 ± 0·01* (−44%)	0·60 ± 0·02* (−36%)
1	0·67 ± 0·06* (−49%)	0·31 ± 0·01* (−50%)	0·58 ± 0·04* (−38%)

* Significant decrease ($P < 0·05$).

Discussion

The decrease in 5-HT turnover produced by 5-MeO-DPAC suggests that the compound acts as an *agonist* at 5-HT_{1A}-receptors, since 8-OH-DPAT, LY165163 and other 5-HT_{1A}-agonists cause this characteristic effect (Hjorth et al 1982; Fuller 1985; Fuller et al 1986; Fuller & Snoddy 1987). 5-MeO-DPAC is less potent than 8-OH-DPAT, which has decreased 5-HTP accumulation significantly at s.c. doses as low as 0·01 mg kg^{-1} in our laboratory (unpublished data) and at s.c. doses as low as 0·01–0·02 mg kg^{-1} in the studies of Arvidsson et al (1984). Cossery et al (1987) had inferred that 5-MeO-DPAC was probably an agonist at 5-HT_{1A}-receptors in rat brain based on modulation of its binding sites by GTP and manganese ion.

5-MeO-DPAC and 8-methoxy-2-(di-n-propylamino)tetralin (8-MeO-DPAT) are similar in potency in decreasing 5-HT turnover, based on a comparison of our data on 5-MeO-DPAC to those of Arvidsson et al (1984) for 8-MeO-DPAT. Both are less potent than 8-OH-DPAT in producing this effect. Also, 5-MeO-DPAC and 8-MeO-DPAT have similar low nanomolar affinity for 5-HT_{1A}-binding sites, based on data of Naiman et al (1989) and of Cossery et al (1987). Thus it appears that the decrease in 5-HTP was statistically significant at the 0·1 mg kg^{-1} s.c. dose of 5-MeO-DPAC.

chroman ring substitutes readily for the tetralin ring vis-a-vis activation of 5-HT_{1A}-receptors.

Despite the fact that Cossery et al (1987) found that 5-MeO-DPAC did not label striatal receptors and had low affinity for tritiated 8-OH-DPAT binding sites in the striatum relative to those in hippocampus, we found that 5-MeO-DPAC decreased 5-HTP accumulation in striatum essentially the same as in hippocampus and cortex. These observations need not be considered paradoxical. The striatum may lack 5-HT_{1A}-receptors, and the binding sites there for 8-OH-DPAT may be associated with 5-HT uptake carriers as suggested by Schoemaker & Langer (1986). 5-MeO-DPAC may lack affinity for 5-HT uptake carriers, which would explain its poor affinity for tritiated 8-OH-DPAT binding sites in striatum and its lack of binding to striatum. Autoreceptors that decrease 5-HT turnover may be mainly 5-HT_{1A}-receptors on the cell bodies and mainly 5-HT_{1B}-receptors on nerve terminals (Engel et al 1986; Hoyer 1988). The decreased 5-HT turnover after administration of 5-HT_{1A}-agonists may result from activation of cell body autoreceptors. The decreased 5-HT turnover in striatum after 8-OH-DPAT or 5-MeO-DPAC administration may reflect activation of 5-HT_{1A}-receptors on 5-HT cell bodies in raphe nuclei which project to the striatum rather than an interaction with binding sites present in the striatum. Both 8-OH-DPAT and 5-MeO-DPAC would thus be expected to cause the same decrease in striatal 5-HT turnover.

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