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8-Hydroxy-2-(Di-n-Propylamino)Tetralin, 8-OH-DPAT, a Potent and Selective Simplified Ergot Congener with Central 5-HT-Receptor Stimulating Activity*

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With 4 Figures

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Summary

It was demonstrated that the simplified ergot congener 8-hydroxy-2-(di-n-propylamino)tetralin, 8-OH-DPAT, is able to elicit pronounced biochemical and behavioural alterations indicative of central serotoninomimetic activity. Since these effects are resistant to prior monoamine depletion and/or synthesis inhibition by means of reserpine and α-propyldopacetamide (H22/54), respectively, they are most likely to be attributable to direct serotonin-receptor agonism by 8-OH-DPAT. With regard to central 5-HT neurotransmission the effects of 8-OH-DPAT—increased 5-HT levels, decreased 5-HIAA levels, 5-HT-synthesis rate and 5-HT utilization and inhibited 5-HT neuronal firing—are virtually identical, and comparable in potency, to those reported to result from the administration of lisuride or LSD. In contrast, however, to lisuride and LSD (included for comparative purposes in this study) as well as to several differently N-substituted, 5,6-dihydroxy, 6,7-dihydroxy and 5-,6- and 7-monohydroxy 2-aminotetralins, 8-OH-DPAT lacks appreciable effects on

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central catecholamine receptors. The compound may thus be regarded the most potent, selective centrally acting 5-HT agonist described to date. In accordance with this it was shown that the full-blown 5-HT-like behavioural syndrome induced by 8-OH-DPAT cannot be antagonized by reserpine, phenoxybenzamine, propranolol and haloperidol. In addition, of the three putative 5-HT-receptor blockers cyproheptadine, methergoline and methiothepin only the latter was able to counteract the 8-OH-DPAT-induced syndrome. The results are discussed in relation to the recent subclassification of central 5-HT receptor sites.

A comparison between the chemical structures and biological activities for different fragments of the ergot nucleus was also made. The data suggest that while the role of the A ring in the ergot structure for dopaminergic activity at present is unclear, this ring may be important for the 5-HT activity like in e.g. lisuride and LSD.

Moreover, based on the present results and literature reports, it is speculated that a selective 5-HT-receptor agonist such as 8-OH-DPAT would not be liable to induce hallucinations in man.

Key words: 8-hydroxy-2-(di-n-propylamino)tetralin, ergot congener, central 5-HT receptor stimulation.

Introduction

The suggested/established involvement of 5-hydroxytryptamine (5-HT) in a number of physiological functions (e.g. body temperature, sleep, pain, sexual behaviour) as well as its possible role in mental depression has in recent years prompted many efforts aimed at finding new compounds with a high selectivity for 5-HT systems. Moreover, much attention has lately been focused on the subclassification of central 5-HT-receptor sites based on the differential biochemical, electrophysiological and behavioural actions of putative 5-HT agonists and antagonists, frequently of ergot type (*Haigler* and *Aghajanian*, 1977; *Peroutka et al.*, 1981). Based on the structural relationships between the ergot skeleton and 5-HT and dopamine (DA) several attempts have been made to delineate what portions of the ergot molecule are implicated in the biological actions of agents such as lisuride and LSD (*Bach et al.*, 1980; *Cannon et al.*, 1981). In particular, the relation between 5-HT-/DA-ergic properties and ability to induce hallucinations has been discussed in this connection (*Nichols*, 1976).

As part of a programme directed at finding new monoamine-receptor active drugs we are currently synthesizing and investigating the pharmacological properties of 2-aminotetralins and related compounds. The 2-aminotetralin skeleton, which may be viewed as a

partial ergoline (as well as a partial apomorphine) structure, has previously been substituted in a number of ways yielding derivatives possessing various pharmacological actions. Among these compounds are the differently N-substituted 5,6-dihydroxy, 6,7-dihydroxy and the 5-, 6-, and 7-monohydroxy 2-aminotetralins, many of which have been shown to exhibit considerable DA-receptor stimulating activity (*McDermed et al.*, 1975; *McDermed et al.*, 1976; *Arvidsson et al.*, 1981; *Hacksell et al.*, 1979). In this report we present evidence that 8-hydroxy-2-(di-n-propylamino)tetralin, 8-OH-DPAT, in contrast to the above compounds, is a centrally acting, selective and direct 5-HT-receptor agonist, devoid of DA-receptor stimulating activity. The biochemical and behavioural profile of 8-OH-DPAT is compared to the profiles of lisuride and LSD and the structure-activity relationships are discussed with special reference to the relative importance of different fragments of the ergot skeleton for central DA- and 5-HT-receptor stimulation.

Methods and Materials

Male rats of Sprague-Dawley strain (Anticimex, Stockholm) weighing 200—300 g were used throughout the studies. The animals were kept at the department for at least a week until use in the experiments and were allowed food and water ad lib. The experimental procedures were all carried out during daytime (8 a.m.—5 p.m.). The brain dissections and the spectrophotofluorimetric determinations of amine and metabolite levels were carried out according to methods previously described (*Atack* and *Lindqvist*, 1973; *Kehr et al.*, 1972; *Bédard et al.*, 1972). The drugs used in the study were (±)-8-hydroxy-2-(di-n-propylamino)tetralin HBr (8-OH-DPAT; synthesized in these laboratories (*Arvidsson et al.*, 1981)), lisuride hydrogen maleate (Schering AG) d-lysergic acid diethylamide tartrate (LSD; Sandoz), 3-hydroxybenzylhydrazine HCl (NSD 1015; synthesized in these laboratories), reserpine (Ciba), α-propyldopacetamine (H22/54; Hässle), phenoxybenzamine HCl (Leo), propranolol chloride (ICI), haloperidol (Leo), cyproheptadine HCl (MSD), methergoline (Farmitalia) and methiothepin maleate (courtesy Drs. Neumann and Haefely, Hoffman—La Roche). Reserpine, phenoxybenzamine, haloperidol, cyproheptadine, methergoline and methiothepin were dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. All other drugs were dissolved in 0.9% saline, occasionally with gentle warming and stirring in order to obtain complete dissolution. Routes of drug administration, doses and time schedules are given in the figure and table legends. Control rats received the same number of injections at corresponding time intervals, with vehicle replacing drug. Injection volumes were 5 or 10 ml/kg.

Results

Effects of Transmitter Synthesis Rates in Different Brain Regions

8-OH-DPAT (0.04—0.32 mg/kg s.c.) produced a dose-dependent decrease in 5-HTP formation in all brain regions examined. A much smaller, though significant, decrease in the DOPA formation was observed in the limbic forebrain and corpus striatum; no effect on DOPA formation was found in the cortex. Weak changes (<25% from control levels) in tryptophan and tyrosine levels were obtained following 8-OH-DPAT administration. No clearcut relation to the dose used could, however, be demonstrated (results not shown). The above data refer to results from limbic forebrain, corpus striatum and cortical parts of the brain and are presented in Table 1. Results from

Table 1. *8-OH-DPAT: Effects on rat brain 5-HTP and DOPA formation*

8-OH-DPAT mg/kg s.c.	5-HTP (ng/g tissue)	DOPA[a] (ng/g tissue)	
	Limbic forebrain		
0	177 ± 27	404 ± 30	4
0.04	124 ± 6.3*(*)	375 ± 19	4
0.08	115 ± 11**	356 ± 15	4
0.16	92 ± 4.2***	346 ± 28	4
0.32	82 ± 4.6***	322 ± 10	4
	Corpus striatum		
0	78 ± 5.0	498 ± 13	4
0.04	49 ± 2.3***	505 ± 26	4
0.08	41 ± 0.9***	462 ± 7.1	4
0.16	42 ± 1.0***	468 ± 12	4
0.32	36 ± 0.7***	450 ± 8.3	4
	Hemispheres (cortex)		
0	65 ± 1.9	61 ± 3.0	4
0.04	41 ± 1.8***	62 ± 3.6	4
0.08	37 ± 1.0***	52 ± 2.1	4
0.16	32 ± 1.0***	54 ± 2.8	4
0.32	31 ± 0.7***	57 ± 3.5	4

Rats were given 8-OH-DPAT (0.04—0.32 mg/kg) or saline subcutaneously and NSD 1015 (100 mg/kg i.p.) at 60 and 30 minutes, respectively, before death. The animals were decapitated, their brains rapidly removed, dissected and taken for analysis of the 5-HTP and DOPA contents in the different brain regions. Shown are the means ± S.E.M. ($n = 4$). Statistics: Analysis of variance followed by *t*-test; *(*) $p < 0.025$, **$p < 0.01$, and *** $p < 0.001$ from the corresponding control value.

[a]Although analysis of variance gave no significant F value, a dose-dependent decrease in DOPA (linear correlation) was found in the limbic forebrain ($r = -0.55$; $p < 0.02$) and in the corpus striatum ($r = -0.53$; $p < 0.02$).

other regions of the CNS simultaneously taken for analysis (i.e. diencephalon, brain stem and spinal cord) were essentially the same (data not shown).

The selective, dose-dependent decrease in brain 5-HTP accumulation induced by 8-OH-DPAT was not affected by reserpine pretreatment (Fig. 1). Likewise, lisuride and LSD, included for comparative purposes in this study, dose-dependently decreased the brain 5-HTP formation in reserpine-pretreated animals. In addition, these agents elicited a dose-dependent reduction of the DOPA accumulation in limbic and striatal, but not cortical, parts of the rat brain. A comparison between the potencies of 8-OH-DPAT, lisuride and LSD with regard to 5-HTP and DOPA decreases in different parts of the rat brain is shown in Table 2.

It should be noted that 8-OH-DPAT caused no significant effect on DOPA formation in any brain region of animals pretreated with reserpine (Table 3).

Effects on Whole Brain 5-HT Utilization

8-OH-DPAT (0.16 mg/kg s.c.) markedly decelerated the disappearance of 5-HT following synthesis inhibition by means of α-propyldopacetamide (H 22/54) (*Carlsson et al.*, 1963) (Table 4).

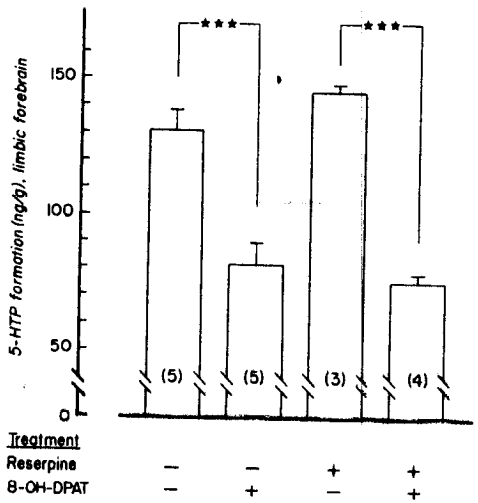

Fig. 1. 8-OH-DPAT (0.16 mg/kg s.c.) was given 60 min before death to non-pretreated or reserpine-pretreated (5 mg/kg i.p., 18 hours before) rats. All animals received NSD 1015 (100 mg/kg i.p.) 30 min before death. The 5-HTP formation in different brain parts was determined. Shown are the means ± S.E.M. ($n = 3-5$). Statistics: Analysis of variance followed by *t*-test; *** $p < 0.001$ from corresponding controls

Table 2. *8-OH-DPAT, lisuriae and LSD: Comparison of the effects on central monoamine synthesis rates in reserpinized rats*[a]. *Shown are the ED_{50} for inhibition of 5-HTP and DOPA formation, respectively (nmol/kg s.c.)*[b]

Compound \ Brain area	Limbic forebrain	Corpus striatum	Hemisph. (cortex)
		5-HTP formation	
8-OH-DPAT	48[c]	45[c]	68[c]
Lisuride	6	6	10
LSD[d]	36	35	36
		DOPA formation	
8-OH-DPAT	I[e]	I[e]	I[e]
Lisuride	8	9	ND[f]
LSD[d]	390	395	ND[f]

[a] For experimental details see *Arvidsson et al.* (1981) and *Hacksell et al.* (1979). [b] Separate dose-response curves (based on 4–8 levels [n = 3–6; standard error of the means were always less than 15%]) for each compound and brain area were constructed. From these curves the dose corresponding to a half-maximal decrease in the 5-HTP and/or DOPA formation was graphically determined as previously described (*Arvidsson et al.*, 1981; *Hacksell et al.*, 1979). [c] Taken from *Arvidsson et al.* (1981). [d] As the salt used was the tartrate ($[C_{20}H_{25}N_3O]_2 \times C_4H_6O_6 \times 2\,CH_3$; Molec. weight: 860), *i.e.* containing 2 units of LSD/molecule of salt, LSD was assigned an effective molecular weight of 860/2 = 430 from which the values in the table are calculated. [e] Inactive; no significant effect at doses approximately 40 times the ED_{50} for 5-HTP formation. From *Arvidsson et al.* (1981) (*cf.* also Table 3). [f] Not determined.

Table 3. *Effect of 8-OH-DPAT on DOPA formation with or without reserpine pretreatment*

Treatment	Saline	Reserpine
	Limbic forebrain	
Saline	386 ± 8.3 (5)	627 ± 24 (3)
8-OH-DPAT	325 ± 18 (5)	613 ± 8.8 (4)
P	< 0.025	N.S.
	Corpus striatum	
Saline	461 ± 11 (5)	1424 ± 48 (3)
8-OH-DPAT	442 ± 13 (5)	1297 ± 90 (3)
P	N.S.	N.S.

Reserpine-pretreated (5 mg/kg i.p., 18 hours before) rats were given 8-OH-DPAT (0.16 mg/kg, s.c.) 60 min before death. Controls received saline injections. All animals were given NSD 1015 (100 mg/kg, i.p.) 30 min before death. The animals were decapitated, their brains rapidly removed, dissected and taken for analysis of the DOPA contents in the different brain regions. Shown are the means ± S.E.M. (n). Statistics: Student's *t*-test. Significant differences (P) are depicted in the table. N.S. = not significant.

Table 4. *8-OH-DPAT: Effect on rat brain 5-HT utilization*

Treatment	5-HT(ng/g)	n	P
A. Saline	181 ± 4.3	12	
B. 8-OH-DPAT	194 ± 8.1	8	
C. H 22/54	96 ± 2.0	12	< 0.001 vs. A
D. 8-OH-DPAT + H 22/54	143 ± 3.4	12	< 0.001 vs. A and C

8-OH-DPAT (0.16 mg/kg s.c.) and/or H 22/54 (an inhibitor of tryptophan hydroxylation; 500 mg/kg i.p.) were given 3.5 and 3 hours, respectively, before death. Controls received saline. Whole brain 5-HT levels were determined. Shown are the means ± S.E.M. (pooled data from three experiments, n = 8–12). Statistics: Analysis of variance followed by *t*-test. Significant differences are depicted in the table.

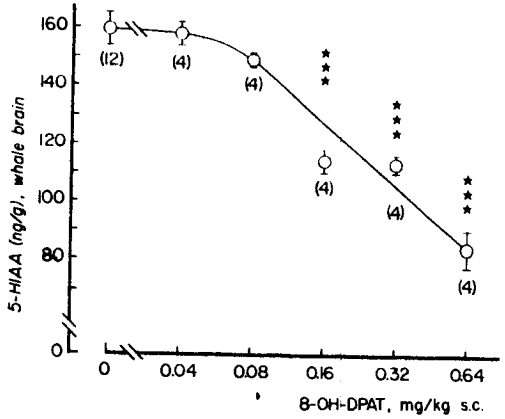

Fig. 2. 8-OH-DPAT (0.04–0.64 mg/kg s.c.) was given 60 min before death. Whole brain 5-HIAA levels were determined. Shown are the pooled means ± S.E.M. of data obtained in three separate experiments. Statistics: Analysis of variance followed by *t*-test; *** $p < 0.001$ from saline controls

Table 5. *8-OH-DPAT: Effect on rat brain 5-HT levels*

8-OH-DPAT dose, mg/kg s.c.	5-HT level, % control	n	p
0	100 ± 3.2	4	–
0.16	113 ± 3.6	4	< 0.05
0.32	113 ± 1.4	4	< 0.05
0.64	110 ± 5.7	4	< 0.1

8-OH-DPAT (0.16–0.64 mg/kg s.c.) was given 60 min before death. Whole brain 5-HT levels were determined. Shown are the means ± S.E.M., % of control values obtained in two separate experiments (exp. 1: 8-OH-DPAT 0.16 and 0.64 mg/kg: 5-HT control = 154 ± 5.0 ng/g [n = 4] and exp. 2: 8-OH-DPAT 0.32 mg/kg; 5-HT control = 191 ± 5.9 ng/g [n = 4]). Statistics: Student's *t*-test. Significant differences from controls are depicted in the table.

Effects on Whole Brain 5-HIAA and 5-HT Levels

8-OH-DPAT (0.16—0.64 mg/kg s.c.) produced a dose-dependent decrease in 5-HIAA accompanied by a small, yet significant ($p < 0.05$), increase in 5-HT levels (Fig. 2 and Table 5).

Duration of Action

A single dose (0.32 mg/kg s.c.) of 8-OH-DPAT produced a significant decrease ($p < 0.001$) in 5-HTP formation at 60 and 120 minutes, but not at 240 and 360 (not shown) minutes after administration. Similar time-courses were obtained in all brain parts (limbic forebrain, corpus striatum and hemispheres (cortex) investigated. The results from limbic forebrain are shown in Fig. 3.

8-OH-DPAT (0.32 mg/kg s.c.) also significantly ($p < 0.005$ or less) decreased whole brain 5-HIAA levels 5—90 minutes after administration (Fig. 3).

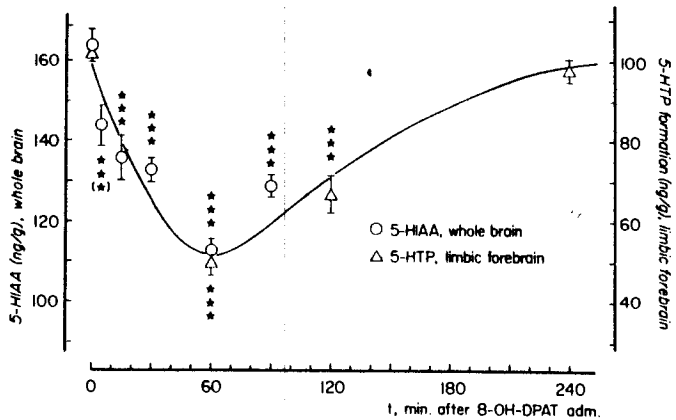

Fig. 3. The figure is constructed from two different experiments. In both experiments 8-OH-DPAT (0.32 mg/kg s.c.) was injected at various time intervals before death. In experiment one the animals were killed at 5 to 90 min after 8-OH-DPAT administration and the whole brain 5-HIAA level was determined. In experiment two, in addition to the 8-OH-DPAT injection, all animals received NSD 1015 (100 mg/kg i.p.) 30 min before death. The animals were killed at 1, 2, and 4 hours after 8-OH-DPAT, brains dissected into limbic, striatal and hemispheral (cortical) portions and subsequently taken for analysis of the 5-HTP levels. The results shown are the means ± S.E.M. and represent whole brain 5-HIAA levels 5—90 min and limbic forebrain 5-HTP formation 1—4 hours, respectively, after 8-OH-DPAT (0.32 mg/kg s.c.) administration. Statistics: Analysis of variance followed by *t*-test; ** $p < 0.005$; *** $p < 0.001$ from saline controls (5-HIAA: pooled controls 15 min and 60 min; 164 ± 4.0 ng/g (n = 8) and 5-HTP: pooled controls 1 and 4 hours; 102 ± 2.3 ng/g (n = 4)

Thus, taken together, it appears that the dose of 8-OH-DPAT used in these studies (0.32 mg/kg s.c.) is able to produce significant reductions in central 5-HT neuronal activity with a duration of action of more than 2 hours after administration.

Behaviour

The full-blown 5-HT-like behavioural syndrome (flat body posture, forepaw extension and treading ("piano-playing"), abducted hindlimbs, tremor in the forebody and Straub tail) induced by 8-OH-DPAT was neither antagonized by pretreatment with reserpine (10 mg/kg i.p.) alone, nor by the combination of reserpine with the catecholamine-receptor blockers phenoxybenzamine (10 mg/kg i.p.), propranolol (10 mg/kg i.p.) or haloperidol (2 mg/kg i.p.) (see Table 6). In addition, three drugs claimed to possess 5-HT-receptor-blocking properties were tried. Of these, methiothepin (10 mg/kg i.p.) was the only drug able to antagonize the 8-OH-DPAT-induced syndrome whereas methergoline (10 mg/kg i.p.) and cyproheptadine (10 mg/kg i.p.) were ineffective in this respect. Moreover, pretreatment with reserpine (10 mg/kg i.p.) plus the 5-HT biosynthesis inhibitor α-propyldopacetamide (H 22/54; 500 mg/kg i.p.) also failed to counteract the behavioural syndrome induced by 8-OH-DPAT (cf. also *Arvidsson et al.*, 1981).

Table 6. *Effect of monoamine depletion and receptor blockade on the 8-OH-DPAT-induced 5-HT-like syndrome in rats*

Pretreatment	Antagonism of the 8-OH-DPAT-induced 5-HT-like syndrome		n
Reserpine (R), 10 mg/kg i.p.	No[a]	0/4	4
R + H 22/54, 500 mg/kg i.p.	No[a]	0/4	4
R + Phenoxybenzamine, 10 mg/kg i.p.	No	0/4	4
R + Propranolol, 10 mg/kg i.p.	No	0/4	4
R + Haloperidol, 2 mg/kg i.p.	No	0/4	4
R + Methergoline, 10 mg/kg i.p.	No	0/4	4
R + Cyproheptadine, 10 mg/kg i.p.	No	0/4	4
R + Methiothepin, 10 mg/kg i.p.	Yes	4/4	4

Rats were given the monoamine depletor reserpine (10 mg/kg i.p.), a monoamine receptor blocker (phenoxybenzamine, propranolol, haloperidol, methergoline, cyproheptadine or methiothepin; does used given in the table)/synthesis inhibitor (H 22/54; 500 mg/kg i.p.) and 8-OH-DPAT (0.5 mg/kg s.c.) at 6 hours, 1 hour and immediately before, respectively, start of the experiment. Fifteen min. later the 8-OH-DPAT-induced behavioural syndrome (for a description, see the text) was individually scored (present/absent) by three observers unaware of the pretreatment(s). [a] See also *Arvidsson et al.* (1981).

Discussion

The present data are consistent with the characterization of the 2-aminotetralin derivative 8-OH-DPAT as a potent and selective, centrally acting 5-HT receptor agonist of reasonable duration. Thus, in confirmation of previous observations (*Arvidsson et al.*, 1981) it was shown that 8-OH-DPAT causes a potent and dose-dependent reduction of brain 5-HT synthesis rate (5-HTP formation) comparable to that of lisuride and LSD (Table 2). The lowering of 5-HT synthesis rate was resistant to reserpine pretreatment, suggesting that the effect was direct and independent of intact monoamine storage and release mechanisms.

Interestingly, in contrast to the ergots lisuride and LSD (and most 2-aminotetralin derivatives so far reported), 8-OH-DPAT appears to lack significant direct effects on central catecholamine systems. This is indicated by previous (*Arvidsson et al.*, 1981) as well as present results, showing no significant effects of 8-OH-DPAT upon the DOPA formation in either the main DA-containing or the noradrenaline (NA)-predominated brain regions of rats pretreated with reserpine (i.e. limbic forebrain/corpus striatum and cortical parts, respectively, see Table 2). Taken together with the recent report by *Feenstra et al.* (1980) that this compound neither alters the DA nor decreases the DOPAC and HVA levels in rat striatum (also verified in our laboratories; data not shown), the above findings seem to confirm that 8-OH-DPAT lacks appreciable direct central DA- and NA-receptor stimulatory properties. Furthermore, the behavioural data (below) are in agreement with this suggestion. The demonstration that the brain 5-HT (Table 4), utilization is markedly retarded by 8-OH-DPAT also corroborates the concept of selective 5-HT-receptor stimulation by the compound. Since the transmitter utilization is known to be largely dependent on nerve-impulse flow (*Aghajanian et al.*, 1973) it may be assumed that the observed retardation of 5-HT disappearance following 8-OH-DPAT administration results from a reduction in 5-HT neuronal firing rate. In support of this contention there is evidence that 8-OH-DPAT, similarly to lisuride and LSD (*Rogawski* and *Aghajanian*, 1979), inhibits the rat dorsal raphe 5-HT cell body neuronal firing (*T. H. Svensson*, personal communication). The biochemical data showing a dose-dependent decrease in the principal 5-HT metabolite, 5-HIAA, accompanied by a small (10—13%) but significant rise in 5-HT level, are also in concert with the above findings. In addition, it was shown that 5-HT depletion induced by the displacer 4-methyl-α-ethylmetatyramine (H 75/12) (*Carlsson et al.*, 1969) was not appreciably (less than 10%)

counteracted by a high dose of 8-OH-DPAT (0.64 mg/kg s.c.), indicating absence of significant reuptake blocking properties (unpublished data from these laboratories). Thus, with regard to central 5-HT neurotransmission the effects of 8-OH-DPAT—increased 5-HT levels, decreased 5-HIAA levels, 5-HT synthesis rate and 5-HT utilization and inhibited 5-HT neuronal firing—are virtually identical to those reported to result from the administration of lisuride or LSD (*Rogawski* and *Aghajanian,* 1979; *Freedman,* 1961; *Rosecrans et al.,* 1967; *Carlsson* and *Lindqvist,* 1972; *Andén et al.,* 1968; *Kehr,* 1977; *Pieri et al.,* 1978). A potency comparison shows that, although being roughly 8 times less potent than lisuride, 8-OH-DPAT was only slightly less potent than LSD in reducing central 5-HT synthesis rate (Table 2). In addition, the report by *Rogawski* and *Aghajanian* (1979) that lisuride is approximately 5—10 times more potent than LSD in suppressing the firing rate of the rat dorsal raphe serotoninergic units appears to correlate well with the biochemical data obtained in this study (Table 2).

Electrophysiological and biochemical investigations have also shown that lisuride and LSD may interact with pre- and postsynaptic DA (and at high doses, NA (α) receptors) (*Kehr,* 1977; *Pieri et al.,* 1978; *Walters et al.,* 1979). In line with these findings it was confirmed that, apart from their strong serotoninergic activities, lisuride and (to a lesser extent) LSD exhibited clearcut DA-receptor (autoreceptor; cf. *Hacksell et al.,* 1979) stimulatory effects in the reserpinized rat. In contrast, 8-OH-DPAT appears essentially devoid of direct catecholaminergic properties (cf. above). Consequently, 8-OH-DPAT may be regarded the most potent, selective centrally acting 5-HT agonist described to date.

In animals not pretreated with reserpine 8-OH-DPAT caused a moderate decrease in DOPA formation in the DA-rich brain regions. Since this effect was absent after reserpine pretreatment, it was probably indirect and mediated via a change in serotoninergic activity.

Besides causing profound biochemical perturbations of central 5-HT systems (cf. above) the administration of 8-OH-DPAT elicits a clearcut behavioural syndrome most conspicuously consisting of flat body posture, forepaw extension and treading ("piano-playing"), abducted hindlimbs, occasionally tremor in the forebody and (at higher doses) Straub tail reaction. This syndrome is considered characteristic for central 5-HT-receptor activation (*Jacobs,* 1976; *Gerson* and *Baldessarini,* 1980) and can thus be induced by all known directly (or indirectly) acting 5-HT agonists including e.g. lisuride and LSD (*Trulson et al.,* 1976; *Silbergeld* and *Hruska,* 1979). Accord-

ingly, attempts to antagonize the 8-OH-DPAT-induced syndrome by the NA-receptor blockers phenoxybenzamine (α) or propranolol (β) were unsuccessful. Moreover, the demonstration that pretreatment with reserpine only, or reserpine plus α-propyldopacetamide (H 22/54; an inhibitor of 5-HT biosynthesis), does not attenuate the expression of the 5-HT-like syndrome (present data and *Arvidsson et al.*, 1981) suggests that it is not caused by 8-OH-DPAT interacting with presynaptic compartmentation, intraneuronal metabolism or reuptake processes (cf. also the biochemical data referred to above) in the central 5-HT neurons. Hence, these data corroborate the concept of direct 5-HT-receptor stimulation by 8-OH-DPAT as its major mechanism of action.

It should also be noted that the 8-OH-DPAT-induced 5-HT-like syndrome, though clearly present in non-pretreated rats, becomes more prominent in animals depleted of their monoamine stores by means of reserpine. This implies that, under physiological conditions, the neuronal outputs responsible for expression of the syndrome may be modulated by the activity in, i.a. catecholaminergic systems so as to render the behavioural effects of 5-HT-receptor stimulation less marked. In accordance with this view is also the report by *Silbergeld* and *Hruska* (1979) showing that the serotonin syndrome produced by lisuride or LSD is not antagonized by metoclopramide or haloperidol but rather, at least for LSD, the effects are significantly potentiated. They suggest that blocking of the dopaminergic actions (of lisuride and LSD) allows a more clearcut expression of serotoninergically related behaviours.

On the basis of neuropharmacological, biochemical, and electrophysiological data a number of drugs have been claimed to possess central 5-HT-receptor blocking capacity (*Fuxe et al.*, 1975; *Cerrito* and *Raiteri*, 1979; *Lloyd* and *Bartholini*, 1974; *Tebecis*, 1972; *Sastry* and *Phillis*, 1977; *Clineschmidt* and *Lotti*, 1974). Three of these drugs—methergoline, cyproheptadine, and methiothepin—were therefore investigated for their ability to antagonize the behavioural syndrome elicited by 8-OH-DPAT. Methergoline, as well as cyproheptadine, claimed to be fairly selective 5-HT-receptor blocking agents (*Fuxe et al.*, 1975; *Clineschmidt* and *Lotti*, 1974), even in large dosage failed to modify, whereas methiothepin completely abolished the behavioural signs of 5-HT-receptor activation by 8-OH-DPAT. Methiothepin is also a potent blocker of central DA- and NA-receptors (*Lloyd* and *Bartholini*, 1974). However, blocking of these receptors does not appear to be a very likely explanation for the antagonism of the 8-OH-DPAT-induced syndrome by methiothepin since the classical neuroleptic agent haloperidol in a dose that blocks both DA- and

NA-receptors in the CNS (*Carlsson,* 1978) was not effective in antagonizing the 8-OH-DPAT behavioural effects. In addition, as already mentioned (above), the syndrome was not affected by α- or β-adrenergic blockade by means of phenoxybenzamine and propranolol, respectively.

A growing body of evidence indicates the presence of multiple 5-HT-receptor sites with distinct pharmacological properties and varying distribution in the mammalian central nervous system (*Haigler* and *Aghajanian,* 1977; *Peroutka et al.,* 1981; *Peroutka* and *Snyder,* 1981). Thus, the differential ability of the three putative 5-HT-receptor blockers (methergoline, cyproheptadine, and methiothepin) to antagonize the 8-OH-DPAT-induced syndrome may be interpreted in terms of the type(s) of 5-HT receptor involved. Using the nomenclature of *Peroutka* and coworkers (1981) methergoline is a very potent ligand at the 5-HT_1 (or agonist) as well as the 5-HT_2 (or antagonist) site, whereas methiothepin and cyproheptadine display preferential 5-HT_2 binding. Moreover, *Peroutka et al.* (1981) suggest that central 5-HT excitatory synaptic actions are mediated by the 5-HT_2 receptors and are linked to the induction of the serotonin behavioural syndrome. Although the subclassification of central 5-HT-receptor sites could serve as an argument for the effectivity of methiothepin it does not, however, seem to sufficiently explain why methergoline and cyproheptadine are ineffective in counteracting the behavioural syndrome elicited by 8-OH-DPAT. It appears also difficult to reconcile the (agonistic) ability of LSD to induce the 5-HT syndrome with its antagonistic activity on central excitatory 5-HT synapses, as both effects are suggested to involve 5-HT_2-receptor interactions. Unfortunately, it is impossible to arrive at definite conclusions of these problems in view of the fact that no specific and efficient 5-HT receptor antagonists capable of blocking the motor syndrome induced by *e.g.* 5-HTP or LSD are presently available (see *e.g. Andén et al.,* 1968; and *Silbergeld* and *Hruska,* 1979). The correlation between behavioural observations and in vitro receptor binding data is thus not satisfactory (*cf. Peroutka et al.,* 1981).

In this context it should also be mentioned that methiothepin has been reported to exhibit strong antagonistic activity at 5-HT autoreceptors involved in the control of serotonin release and turnover, whereas *e.g.* cyproheptadine is inactive (*Pieri et al.,* 1978; *Cerrito* and *Raiteri,* 1979). Even if the possibility is considered that 8-OH-DPAT, as well as lisuride and LSD (*Rogawski* and *Aghajanian,* 1979; *Pieri et al.,* 1978), has predominant 5-HT autoreceptor activating properties (*cf. Ahlenius et al.,* 1980) it is difficult to envisage the methiothepin-induced blockade of the 8-OH-DPAT behavioural

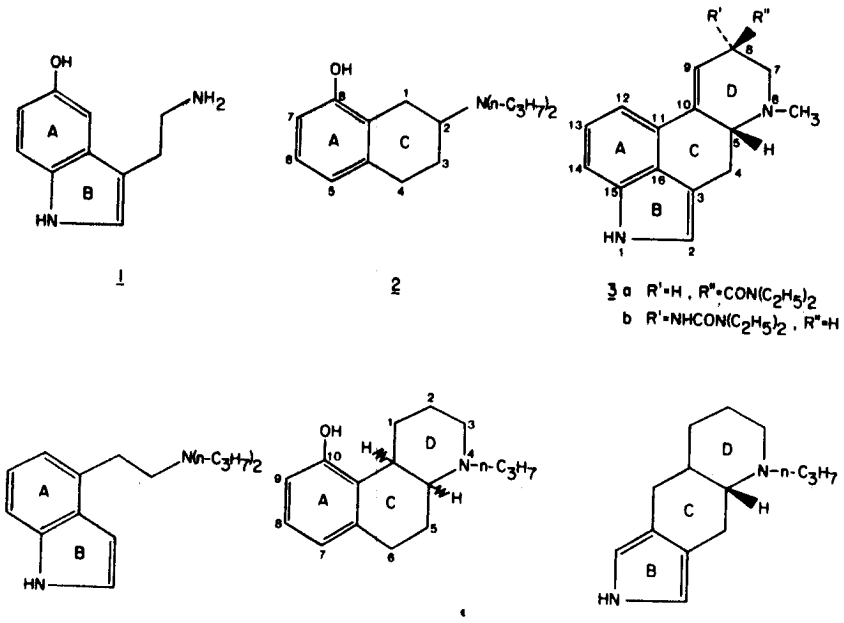

Fig. 4. Chemical structures of 5-HT (1), 8-OH-DPAT (2), lisuride (3 a), LSD (3 b), 4-(2-[di-n-propylamino]ethyl)indole (DPAI; 4), 10-OH-octahydrobenzo(f)quinoline (5) and "debenzergoline" (6)

syndrome in the reserpine-pretreated rat as being the result of agonist-antagonist interactions at 5-HT autoreceptor sites. Thus, available data would appear to suggest the possibility of several dissimilar postsynaptic 5-HT receptor sites but also that presynaptic (autoreceptor?) sites may differ from their postsynaptic counterparts. Obviously, further investigations are needed to clarify these matters.

Very interestingly, the structure of 5-HT (Fig. 4; 1) can be excellently fitted on the 2-aminotetralin skeleton of 8-OH-DPAT (Fig. 4; 2) with the hydroxy groups and the basic nitrogen atoms overlapping and with the aliphatic side chain of 5-HT matching the 2-, 3-, and 4-carbon atoms in the aliphatic ring of 2-aminotetralin. Curiously, when superimposed in this manner, the 2-aminotetralin and the tryptamine moieties construct the A, B, and C ring system of the ergot alkaloids with a hydroxy group placed so as to correspond to the 12-position in the ergot structure. The above fitting is not possible for the DA-receptor active 5-, 6-, and 7-monohydroxy 2-dipropylaminotetralins. It has been reported that ergot derivatives

can be hydroxylated *in vivo* in *i.a.* position 12 (*Slaytor* and *Wright*, 1962) (*i.e.* corresponding to the 8-position in the 2-aminotetralins), a finding that might also be worth noting in this context. In addition, it appears that the structural integrity of the D ring is not necessary for retained dopaminergic of serotonergic effects although if the D ring is present the stereochemical position and nature of the substituent attached to the 8-position may significantly contribute to the resultant activity (*Bach et al.*, 1980; *Pieri et al.*, 1978, and present results).

The original suggestion by *Nichols* (1976), that the pyrroleethylamine moiety of the ergots confers dopaminergic properties to drugs of this class was recently experimentally substantiated by *Bach et al.* (1980), showing that "debenzergoline" (Fig. 4; 6) is a potent dopaminergic stimulant which appears to lack the 5-HT agonistic (or antagonistic) effects seen with many of the ergot derivatives. However, on the basis of results obtained with 4-(2-[di-n-propylamino] ethyl) indole (DPAI) (Fig. 4; 4) containing the A and B rings of the ergots, *Cannon et al.* (1981) have challenged the view as to which is the dopaminergic pharmacophore of drugs belonging to the ergot class. No effects of DPAI on 5-HT systems have so far been reported. Recently, we reported a series of isomeric monohydroxylated 4-n-propyl substituted 1,2,3,4,4 a,5,6,10 b-octahydrobenzo(f)quinolines and their effects upon central DA and 5-HT receptors (*Wikström et al.*, 1982). These compounds construct the A, C, and D ring systems of the ergots (but lack the double-bond between carbon atoms 9 and 10 and the substituent in position 8 present in the D ring of *e.g.* lisuride and LSD). It was demonstrated that hydroxy-substitution in different positions of the aromatic ring in the octahydrobenzo(f)quinolines resulted in the same changes in the pattern of biological activity as did hydroxy substitution in the corresponding positions of the 2-aminotetralins previously described by us (*Arvidsson et al.*, 1981). That is, whereas the 7-, 8-, and 9-OH octahydrobenzo(f)quinolines, corresponding to the 5-, 6-, and 7-OH-2-aminotetralins, respectively, are dopaminergic stimulants lacking serotoninergic activity, the 10-OH-octahydrobenzo(f)quinolines (Fig. 4; 5), corresponding to 8-OH-2-aminotetralin (8-OH-DPAT; Fig. 4; 2) show no DA-receptor effects but instead marked 5-HT-receptor stimulatory properties. Thus, taken together, the above mentioned data indicate that while the role of the A ring in the ergot stucture for dopaminergic activity at present is unclear (see also *Camerman* and *Camerman*, 1981), this ring may be important for the 5-HT activity like in *e.g.* lisuride and LSD (*cf.* however, *Nichols et al.*, 1977).

Surprisingly, both enantiomers of 8-OH-DPAT have proven to be efficient 5-HT agonists separated only by a slight, yet significant, difference (~2 times) in potency (*Arvidsson et al.*, 1981). It was, however, predicted that the more active of the two enantiomers has the absolute configuration R, *i.e.* the same absolute configuration as the 2-aminotetralin fragment of the pharmacologically active form of LSD. That this is indeed the case has recently been established in our laboratories (*Arvidsson et al.*, to be published). Since both enantiomers of 8-OH-DPAT (*Arvidsson et al.*, 1981) as well as the trans-, and (to a lesser extent) cis-isomers of the 10-OH-octahydrobenzo(f)quinoline (not yet resolved) (*Wikström et al.*, 1982) mentioned above have considerable 5-HT-receptor stimulatory capacity, it may be that the 5-HT receptor has less pronounced sterical requirements for drug interaction than has the DA receptor, which shows marked specificity in this respect for *e.g.* agonists of the 2-aminotetralin class (*McDermed et al.*, 1976). Taken together, however, the close similarities between drugs acting at central DA and 5-HT receptors may lend support to the proposal that, though being distinct entities, the DA and 5-HT receptors structurally resemble each other.

The concept of an association between central 5-HT-receptor (autoreceptor) activation and hallucinogenesis in humans has recently been disputed by *Pieri et al.* (1978), who showed qualitatively similar effects on brain monoamine systems of the reportedly non-hallucinogenic ergot lisuride and the hallucinogenic ergot LSD. They concluded that central 5-HT autoreceptor stimulation is not a prerequisite for the hallucinogenic actions by *e.g.* LSD. At present it is not known whether 8-OH-DPAT (or related compounds) can induce hallucinations in man. However, despite inducing qualitatively and quantitatively similar effects on the 5-HT systems (*cf.* above), the non-hallucinogenic ergot derivative lisuride and 8-OH-DPAT differ markedly from LSD in their effects on male rat sexual behaviour. In this behavioural model, considered very sensitive to manipulation of central serotoninergic systems (*Ahlenius et al.*, 1980a), 8-OH-DPAT and lisuride have profound stimulatory actions whereas LSD is completely devoid of effects (*Ahlenius et al.*, 1980a; 1980b; 1981). (In addition, another hallucinogen, DOM (2,5-dimethoxy-4-methylamphetamine) has similarly been shown to lack effects on the copulatory behaviour (*Ahlenius et al.*, 1981)). Thus, taking these observations as well as the differences in biochemical specificity (*cf.* above), into account, it appears that hallucinatory properties are incompatible with retained (or even enhanced) sexual performance in the rat model and it is therefore tempting to speculate that a

selective 5-HT-receptor agonist such as 8-OH-DPAT would not be liable to induce hallucinations in man. On the other hand, it can, of course, not be excluded that the discrepancies in biological activity between the closely related serotoninergic compounds could be the result of different degrees of interaction with distinct types of 5-HT receptors in different regions of the brain as discussed above.

In conclusion, the data presented are consistent with the characterization of the simplified ergot congener 8-OH-DPAT as a potent and selective centrally acting 5-HT-receptor agonist. Thus, apart from providing important clues to the delineation of ergot structure-biological activity relationships, the compound may prove useful for elucidating 5-HT-ergic functions and in the treatment of depression and other disease states possibly associated with disturbances in central 5-HT transmission.

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References

Aghajanian, G. K., Bunney, B. S., Kuhar, M. J.: Use of single unit recording in correlating transmitter turnover with impulse flow in monoamine neurons. In: New Concepts in Neurotransmitter Regulation (*Mandell, A. J.*, ed.), pp. 119–134 and refs. cited therein. New York: Plenum Publ. Corp. 1973.

Ahlenius, S., Larsson, K., Svensson, L.: Further evidence for an inhibitory role of central 5-HT in male rat sexual behaviour. Psychopharmacol. *68*, 217–220 (1980 a).

Ahlenius, S., Larsson, K., Svensson, L.: Stimulating effects of lisuride on masculine sexual behaviour of rats. Eur. J. Pharmacol. *64*, 47–51 (1980 b).

Ahlenius, S., Larsson, K., Svensson, L., Hjorth, S., Carlsson, A., Lindberg, P., Wikström, H., Sanchez, D., Arvidsson, L.-E., Hacksell, U., Nilsson, J. L. G.:

Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. Pharmacol. Biochem. Behav. *15*, 785–792 (1981).

Andén, N.-E., Corrodi, H., Fuxe, K., Hökfelt, T.: Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide. Br. J. Pharmacol. *34*, 1–7 (1968).

Arvidsson, L.-E., Hacksell, U., Nilsson, J. L. G., Hjorth, S., Carlsson, A., Lindberg, P., Sanchez, D., Wikström, H.: 8-hydroxy-2-(di-n-propylamino)tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist. J. Med. Chem. *24*, 921–923 (1981).

Atack, C. V., Lindqvist, M.: Conjoint native and orthophthaldialdehyde-condensate assays for the fluorimetric determination of 5-hydroxyindoles in the brain. Naunyn-Schmiedeberg's Arch. Pharmacol. *279*, 267–284 (1973).

Bach, N. J., Kornfeld, E. C., Jones, N. D., Chaney, M. O., Dorman, D. E., Paschal, J. W., Clemens, J. A., Smalstig, E. B.: Bicyclic and tricyclic ergoline partial structures. Rigid 3-(2-aminoethyl)pyrroles and 3- and 4-(2-aminoethyl)pyrazoles as dopamine agonists. J. Med. Chem. *23*, 481–491 (1980).

Bédard, P., Carlsson, A., Lindqvist, M.: Effect of a transverse cerebral hemisection on 5-hydroxytryptamine metabolism in the rat brain. Naunyn-Schmiedeberg's Arch. Pharmacol. *272*, 1–15 (1972).

Camerman, N., Camerman, A.: On the stereochemistry of dopaminergic ergoline derivatives. Mol. Pharmacol. *19*, 517–519 (1981).

Cannon, J. G., Demopoulos, B. J., Long, J. P., Flynn, J. R., Sharabi, F. M.: Proposed dopaminergic pharmacophore of lergotrile, pergolide, and related ergot alkaloid derivatives. J. Med. Chem. *24*, 238–240 (1981).

Carlsson, A., Corrodi, H., Waldeck, B.: α-Substituierte Dopacetamide als Hemmer der Catechol-O-methyl-transferase und der enzymatischen Hydroxylierung aromatischer Aminosäuren. Helv. Chim. Acta *46*, 2271–2285 (1963).

Carlsson, A., Corrodi, H., Fuxe, K., Hökfelt, T.: Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-α-ethyl-meta-tyramine. Eur. J. Pharmacol. *5*, 357–366 (1969).

Carlsson, A., Lindqvist, M.: The effect of L-tryptophan and some psychotropic drugs on the formation of 5-hydroxytryptophan in the mouse brain *in vivo*. J. Neural Transm. *33*, 23–43 (1972).

Carlsson, A.: Mechanism of action of neuroleptic drugs. In: Psychopharmacology: A Generation of Progress (*Lipton, M. A., Killam, K. F.*, eds.), pp. 1057–1070. New York: Raven Press. 1978.

Cerrito, F., Raiteri, M.: Serotonin release is modulated by presynaptic autoreceptors. Eur. J. Pharmacol. *57*, 427–430 (1979).

Clineschmidt, B. V., Lotti, V. J.: Indolamine antagonists: Relative potencies as inhibitors of tryptamine- and 5-hydroxytryptophan-evoked responses. Br. J. Pharmacol. *50*, 311–313 (1974).

Feenstra, M., Rollema, H., Dijkstra, D., Grol, C. J., Horn, A. S., Westerink, B. H. C.: Effect of non-catecholic 2-aminotetralin derivatives on dopamine metabolism in the rat striatum. Naunyn-Schmiedeberg's Arch. Pharmacol. *313*, 213–219 (1980).

Freedman, D. X.: Effects of LSD-25 on brain serotonin. J. Pharmacol. Exp. Therap. *134,* 160–168 (1961).

Fuxe, K., Agnati, L., Everitt, B.: Effects of methergoline on central monoamine neurones. Evidence for a selective blockade of central 5-HT receptors. Neurosci. Lett. *1,* 283–290 (1975).

Gerson, S. C., Baldessarini, R. J.: Motor effects of serotonin in the central nervous system. Life Sci. *27,* 1435–1451 (1980).

Hacksell, U., Svensson, U., Nilsson, J. L. G., Hjorth, S., Carlsson, A., Wikström, H., Lindberg, P., Sanchez, D.: N-Alkylated 2-aminotetralins: Central dopamine receptor stimulating activity. J. Med. Chem. *22,* 1469–1475 (1979).

Haigler, H. J., Aghajanian, G. K.: Serotonin receptors in the brain. Fedn. Proc. *36,* 2159–2164 (1977).

Jacobs, B. L.: An animal behavior model for studying central serotonergic synapses. Life Sci. *19,* 777–786 (1976).

Kehr, W., Carlsson, A., Lindqvist, M.: A method for the determination of 3,4-dihydroxyphenylalanine (DOPA) in brain. Naunyn-Schmiedeberg's Arch. Pharmacol. *274,* 273–280 (1972).

Kehr, W.: Effects of lisuride and other ergot derivatives on monoaminergic mechanisms in rat brain. Eur. J. Pharmacol. *41,* 261–273 (1977).

Lloyd, K. G., Bartholini, G.: The effect of methiothepin on cerebral monoamine neurons. In: Advances in Biochemical Psychopharmacology, Vol. 10, pp. 305–309. New York: Raven Press. 1974.

McDermed, J. D., McKenzie, G. M., Phillips, A. P.: Synthesis and pharmacology of some 2-aminotetralins Dopamine receptor agonists. J. Med. Chem. *18,* 362–367 (1975).

McDermed, J. D., McKenzie, G. M., Freeman, H. S.: Synthesis and dopaminergic activity of (±)-, (+)-, and (−)-2-dipropylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene. J. Med. Chem. *19,* 547–549 (1976).

Nichols, D. E.: Structural correlation between apomorphine and LSD: Involvement of dopamine as well as serotonin in the actions of hallucinogens. J. Theor. Biol. *59,* 167–177 (1976).

Nichols, D. E., Pfister, W. R., Yim, G. K. W., Cosgrove, R. J.: A new view of the structural relationship between LSD and mescaline. Brain Res. Bull. *2,* 169–171 (1977).

Peroutka, S. J., Snyder, S. H.: Two distinct serotonin receptors: Regional variations in receptor binding in mammalian brain. Brain Res. *208,* 339–347 (1981).

Peroutka, S. J., Lebowitz, R. M., Snyder, S. H.: Two distinct central serotonin receptors with different physiological functions. Science *212,* 827–829 (1981).

Pieri, L., Keller, H. H., Burkard, W., DaPrada, M.: Effects of lisuride and LSD on cerebral monoamine systems and hallucinosis. Nature *272,* 278–279 (1978).

Rogawski, M. A., Aghajanian, G. K.: Response of central monoaminergic neurons to lisuride: comparison with LSD. Life Sci. *24,* 1289–1298 (1979).

Rosecrans, J. A., Lovell, R. A., Freedman, D. X.: Effects of lysergic acid di-

ethylamide on the metabolism of brain 5-hydroxytryptamine. Biochem. Pharmacol. *16*, 2001–2021 (1967).

Sastry, B. S. R., Phillis, J. W.: Methergoline as a selective 5-hydroxytryptamine antagonist in the cerebral cortex. Can. J. Physiol. Pharmacol. *55*, 130–133 (1977).

Silbergeld, E. K. Hruska, R. E.: Lisuride and LSD: Dopaminergic and serotonergic interactions in the "serotonin syndrome". Psychopharmacol. *65*, 233–237 (1979).

Slaytor, M. B., Wright, S. E.: The metabolites of ergometrine and lysergic acid diethylamide in rat bile. J. Med. Pharmaceut. Chem. *5*, 483–491 (1962).

Tebecis, A.: Antagonism of 5-hydroxytryptamine by methiothepin shown in microelectrophoretic studies of neurones in the lateral geniculate nucleus. Nature (New Biol.) *238*, 63–64 (1972).

Trulson, M. E., Ross, C. A., Jacobs, B. L.: Behavioral evidence for the stimulation of CNS serotonin receptors by high doses of LSD. Psychopharmacol. Communic. *2*, 149–164 (1976).

Walters, J. R., Baring, M. D., Lakoski, J. M.: Effects of ergolines on dopaminergic and serotonergic single unit activity. In: Dopaminergic Ergot Derivatives and Motor Function (*Fuxe, K., Calne, D. B.*, eds.), pp. 207–221. Oxford: Pergamon Press. 1979.

Wikström, H., Sanchez, D., Lindberg, P., Arvidsson, L.-E., Hacksell, U., Johansson, A., Nilsson, J. L. G., Hjorth, S., Carlsson, A.: Monophenolic octahydrobenzo(f)quinolines–Central dopamine- and serotonin-receptor stimulating activity. J. Med. Chem. *25*, 925–931 (1982).

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