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FURTHER STUDIES ON THE MODE OF ACTION OF PSYCHOTOMIMETIC DRUGS: ANTAGONISM OF THE EXCITATORY ACTIONS OF 5-HYDROXYTRYPTAMINE BY METHYLATED DERIVATIVES OF TRYPTAMINE

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1 The actions of 5-methoxytryptamine (5-MeOT), *N,N*-dimethyltryptamine (DMT), 5-hydroxy-*N,N*-dimethyltryptamine (bufotenine, 5-HODMT) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT), and their interactions with 5-hydroxytryptamine (5-HT), acetylcholine, (−)-noradrenaline, and glutamate were studied by microiontophoresis on single neurones in the brain stem of rats anaesthetized with urethane or decerebrate cats.

2 Like D-lysergic acid diethylamide (LSD 25) the three psychotomimetic derivatives (DMT, 5-HODMT, 5-MeODMT) specifically antagonized 5-HT excitations of single neurones, but the non-psychotomimetic 5-MeOT had no antagonistic effects.

3 In contrast to LSD 25, the psychotomimetic tryptamines only rarely antagonized glutamate effects, indicating that the excitatory 5-HT receptors and the glutamate receptors on the same neurones may be closely related spatially, but are separate.

4 The methylated tryptamine derivatives were able to mimic the actions of 5-HT on neurones. The non-psychotomimetic 5-MeOT was most potent in this respect, while the other three derivatives which are psychotomimetic, were less active.

5 The 5-HT mimicking actions of 5-MeOT were the same in rats pretreated with *p*-chlorophenylalanine or reserpine as in untreated rats. It therefore seems that the 5-HT mimicking actions are unlikely to be due to release of 5-HT, but are due to direct actions on 5-HT receptors.

6 The evidence presented supports the hypothesis that LSD-like psychotomimetics act by an antagonism of 5-HT in the lower brain stem, and is not compatible with the suggestion that the psychotomimetic action of these drugs is related to 5-HT receptor stimulation.

Introduction

In a previous study of the actions of three derivatives of lysergic acid as antagonists to microiontophoretically applied 5-hydroxytryptamine (5-HT) and other putative transmitters on brain stem neurones (Boakes, Bradley, Briggs & Dray, 1970), evidence was obtained suggesting that the basis for the psychotomimetic action of D-lysergic acid diethylamide (LSD 25) might be related to its antagonism to the excitatory effects of 5-HT and glutamate. Such an action by LSD 25 on the brain stem reticular formation, related to the afferent collateral input (Bradley & Key, 1958) which appears to be concerned with the filtering and integration of sensory information (Key, 1965), may account for the distortions of perception induced by this drug. On the other hand, evidence from other studies has been interpreted as indicating that the action of LSD 25 and other agents with LSD-like behavioural effects is to stimulate 5-HT receptors in the CNS, i.e. to mimic rather than block 5-HT effects (Andén, Corrodi, Fuxe & Hökfelt, 1968; Aghajanian, Foote & Sheard, 1968, 1970; Andén, Corrodi & Fuxe, 1971; Fuxe, Hölmstedt & Jonsson, 1972; Aghajanian, 1972).

Further evidence to elucidate these two possibilities seemed desirable and the data presented here represent the results of a study of the actions on single neurones, in the brain stem of both cats and rats, of four methylated tryptamine derivatives. In addition, in order to determine whether some of the effects observed might have been due to release of 5-HT from presynaptic sites, experiments were carried out on rats pretreated with either reserpine or *p*-chlorophenylalanine (PCPA).

Of the four methylated tryptamines studied, one, 5-methoxytryptamine (5-MeOT), is not psychotomimetic (Mashkovskii & Arutyunyan, 1964; Mashkovskii & Roshchina, 1964; Takeo & Himwich, 1967) while the other three are all reported to be psychotomimetic; they are *N,N*-dimethyltryptamine (DMT), 5-hydroxy-*N,N*-dimethyltryptamine (bufotenine, 5-HODMT) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) (Szara, 1957; Gessner, 1970; Shulgin, 1970). There are some doubts about the psychotomimetic activity of bufotenine (Fabing & Hawkins, 1956; Turner & Merlis, 1959) which may be related to the relatively low penetration of the drug into the brain (Sanders & Bush, 1967). However, it has been reported that bufotenine is at least as active as 5-MeODMT in certain animal behaviour tests when it is administered by intraventricular infusion, thus bypassing the blood brain barrier (Mandell, Buckingham & Segal, 1971).

Some of the results given in this paper have been presented in a communication at a meeting of the British Pharmacological Society (Briggs, 1972).

Methods

Both cats and rats were used in this investigation as experimental subjects. The initial experimental procedures were carried out on unanaesthetized decerebrate cats but later, rats were also used as this species was better able to tolerate drug pretreatment (e.g. reserpine and PCPA).

Adult cats of either sex were decerebrated, and the medial portions of the cerebellum removed under Fluothane anaesthesia (Bradley, Dhawan & Wolstencroft, 1966). Recording was begun 1-2 h after withdrawal of the anaesthetic. Male Wistar albino rats (250-450 g) were anaesthetized with urethane (ethyl carbamate, B.D.H.; 1.6-1.8 g/kg, i.p.) given in divided doses, and the medial portions of the cerebellum were removed by suction. Some rats were pretreated with D,L-*p*-chlorophenylalanine methyl ester HCl (H 69/17, AB Biotec; 150-200 mg/kg per day i.p.) in 0.9% w/v NaCl solution (physiological saline) for three days prior to the experiment, or with reserpine (5 mg/kg, i.p.) 20 h previously.

Glass five-barrelled micropipettes were inserted into the brain stem through the floor of the fourth ventricle, and used to record extracellular neuronal activity and to eject drugs in the vicinity of the cells. Only spontaneously active cells were studied, most of which were located in the region 2-6 mm rostral to the obex and up to 2.0 mm lateral to the midline in the cat, and 0.5-3.5 mm rostral to the obex and up to 2.0 mm lateral to the midline in the rat, avoiding the midline itself. Neuronal activity was amplified and counted conventionally and the firing rates were plotted as mean frequencies in spikes/s, in successive 5 s epochs. The micropipettes had overall tip diameters of 4-10 μm. The recording barrel contained 4 M NaCl and usually one other barrel contained 1 M NaCl to determine the effects of current alone. The other three barrels contained respectively aqueous solutions of one of the methylated tryptamines, 5-hydroxytryptamine, and another putative transmitter substance. The following drugs were used: 5-methoxytryptamine hydrochloride (Sigma); *N,N*-dimethyltryptamine bioxalate (Koch-Light); bufotenine oxalate hydrate (Ralph N. Emanuel); 5-methoxy-*N,N*-dimethyltryptamine (kindly donated by Dr A. Hofmann, Sandoz, Basel); 5-hydroxytryptamine bimaleinate (Koch-Light); acetylcholine chloride (Sigma); (−)-noradrenaline hydrochloride (Sigma); monosodium L-glutamate (Koch-Light). The methylated tryptamines were prepared as 0.5-2.0% solutions, and other drugs as 5-10% solutions, all being adjusted to pH 5.0-6.0. The micropipettes were filled 18-24 h before use and stored at 4°C in the dark.

Results

The four methylated derivatives of tryptamine, with differing behavioural effects and potencies were examined (a) for their direct effects on neuronal activity, in comparison with the effects of 5-HT applied to the same neurone, both in normal animals and in animals pretreated with reserpine or PCPA; and also in comparison with the effects of other putative transmitters, noradrenaline, acetylcholine and glutamate; (b) for their interactions with 5-HT, noradrenaline, acetylcholine and glutamate.

Results were obtained from 79 neurones in 14 cats and from 312 neurones in 72 rats. The two species showed little difference with respect to the effects of the compounds tested.

The actions of all four compounds were complex: on some neurones they had agonistic actions while on others they antagonized the actions of putative transmitters. All mimicked the actions of 5-HT, although the extent to which they did so varied considerably. The actions of the tryptamine derivatives, compared with the actions of 5-HT on the same neurones in the cat and rat, are shown in Tables 1 and 2 respectively and are illustrated in Figure 1. As mimickers of 5-HT, the compounds could be ranked in the following order of potency in both cat and rat, if neurones unaffected by 5-HT are discounted: 5-MeOT > 5-HODMT >5-MeODMT >DMT. No relationship was

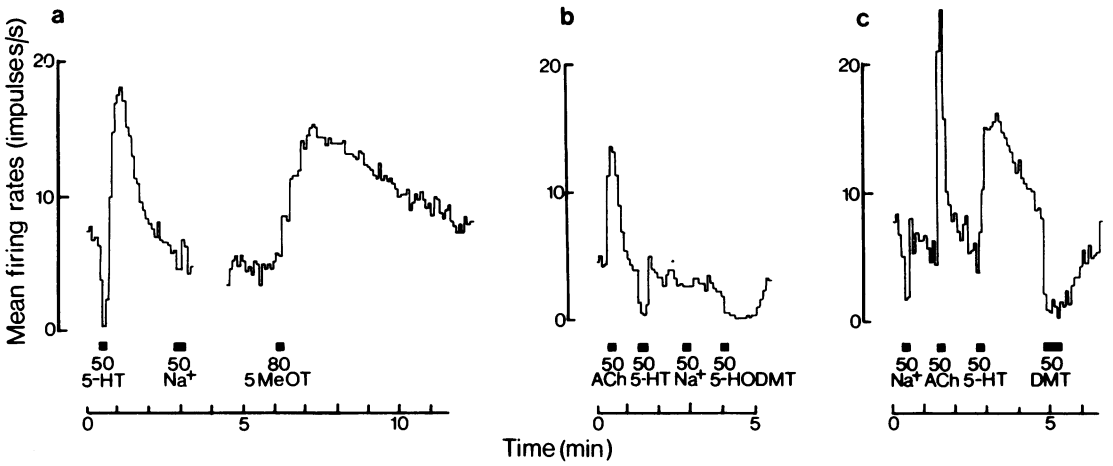

Fig. 1 Examples of the effects of methylated tryptamine derivatives compared with the effects of 5-hydroxytryptamine (5-HT) on the same neurones. The mean firing rates in impulses/s in successive 5 s epochs are plotted against time in minutes. Iontophoretic applications of drugs are indicated by bars, with the expelling currents shown in nA. (a) Excitatory effects of 5-hydroxytryptamine (5-HT) and 5-methoxytryptamine (5-MeOT); (b) inhibitory effects of 5-HT and 5-hydroxy-*N,N*-dimethyltryptamine (5-HODMT), with excitation by acetylcholine (ACh); (c) excitations by 5-HT and ACh with inhibition by *N,N*-dimethyltryptamine (DMT).

observed between the effects of the methylated tryptamines and the effects of other putative transmitters applied to the same neurone. The actions of these compounds in mimicking 5-HT were usually weaker than those of 5-HT; that is, larger iontophoretic currents or longer application times were needed to produce a similar change in firing rate (Figures 1a and 2). Furthermore, the time courses of the effects were usually longer than those of 5-HT effects. However, the transport numbers of these tryptamine derivatives have not been determined, and the observed differences in apparent potencies and time courses may reflect differences in transport numbers and diffusion rates.

Table 1 Comparison of the effects of methylated tryptamines with those of 5-hydroxytryptamine (5-HT) applied to the same neurones in the brain stem of the cat

		5-HT			*Responses same*	
		+	*0*	*–*		*(%)*
5-MeOT	+	15	0	0		
	0	6	1	0	19/25	76
	–	0	0	3		
5-HODMT	+	8	0	0		
	0	2	2	0	13/17	76
	–	2	0	3		
5-MeODMT	+	8	0	0		
	0	11	0	0	9/31	29
	–	11	0	1		
DMT	+	0	0	0		
	0	6	1	0	3/20	15
	–	8	3	2		

5-MeOT = 5-methoxytryptamine.
5-HODMT = 5-hydroxy-*N,N*-dimethyltryptamine.
5-MeODMT = 5-methoxy-*N,N*-dimethyltryptamine.
DMT = *N,N*-dimethyltryptamine.

5-Methoxytryptamine (5-MeOT)

The effects of this substance were tested on 25 neurones in the cat and 120 in the rat. As with 5-HT, excitation was the predominant effect, although some selection bias is likely, since excitations were easier to study. The actions of 5-MeOT closely followed those of 5-HT (Tables 1 and 2, Fig. 1); 18 of 24 cat neurones and 35 of 37 rat neurones affected by 5-HT were affected in the same way by 5-MeOT, and only one neurone unaffected by 5-HT was affected by 5-MeOT. The actions of 5-MeOT were also studied in rats which had been pretreated with either PCPA or reserpine. Table 3 shows the responses to 5-MeOT obtained in these animals, compared with responses to 5-HT. The proportions of responses are similar to those observed in untreated animals (Table 2). The slight differences are probably due to sampling variability. In PCPA-pretreated rats, 34 of 38 neurones affected by 5-HT were similarly affected by 5-MeOT, and in reserpine-pretreated rats, 33 of 38 effects were similar.

5-Hydroxy-N,N-*dimethyltryptamine (bufotenine, 5-HODMT)*

This compound was tested on 17 neurones in cats and 55 neurones in rats. In the cat, 11 of 15 neurones, which were affected by 5-HT, were similarly affected by 5-HODMT, and in the rat 27 of 54 effects were similar. The effects of 5-HODMT are summarized in Tables 1 and 2, and examples are shown in Figures 1b and 2.

5-Methoxy-N,N-*dimethyltryptamine (5-MeODMT)*

The effects of this derivative were similar to those of 5-HT on 9 of 31 neurones in the cat, and 11 of 58 in the rat. The two compounds had opposite effects on about half of the neurones on which mimicking effects were not observed, and 5-MeODMT did not affect the rest. The effects of 5-MeODMT in cat and rat are compared with those of 5-HT in Tables 1 and 2, respectively.

Table 2 Comparison of the effects of methylated tryptamine derivatives with those of 5-hydroxytryptamine (5-HT) applied to the same neurones in the brain stem of the rat

		5-HT			*Responses same*	
		+	*0*	*–*		*(%)*
5-MeOT	+	32	0	0		
	0	0	1	0	36/39	92
	–	2	1	3		
5-HODMT	+	17	0	0		
	0	6	1	1	28/55	51
	–	20	0	10		
5-MeODMT	+	9	0	2		
	0	25	0	2	11/59	17
	–	18	1	2		
DMT	+	2	1	1		
	0	8	1	0	9/73	12
	–	54	0	6		

5-MeOT = 5-methoxytryptamine.
5-HODMT = 5-hydroxy-*N,N*,dimethyltryptamine.
5-MeODMT = 5-methoxy-*N,N*,dimethyltryptamine.
DMT = *N,N*-dimethyltryptamine.

N,N-*Dimethyltryptamine (DMT)*

In the cat, applications of DMT produced no excitatory effects; of 14 cat neurones excited by 5-HT, 8 were inhibited by DMT. The main effects of DMT were also inhibitory in the rat: 60 neurones were inhibited out of 71 affected by 5-HT, including 54 inhibitions by DMT of 64 neurones excited by 5-HT.

All the four tryptamine derivatives usually mimicked the inhibitory actions of 5-HT, but not always: in the rat, DMT and 5-MeODMT excited some neurones inhibited or unaffected by 5-HT. However, the number of neurones tested which were inhibited by 5-HT was small and comparisons are therefore difficult.

At the maxima of the 5-HT mimicking effects of these compounds, the effects of 5-HT were often reduced, and those of noradrenaline were sometimes reduced; acetylcholine and glutamate effects were not reduced (Figure 2).

The four compounds had widely differing properties as antagonists. 5-MeOT did not antagonize the actions of any of the putative transmitters tested except, as has already been described, during its 5-HT-mimicking actions. The other compounds did have antagonistic effects in the absence of mimicking actions, and Fig. 3 shows examples of antagonism of 5-HT excitation, which was the strongest, most frequent and most consistent antagonistic effect observed; acetylcholine excitation, glutamate excitation, noradrenaline excitation and inhibition are shown as parallel control responses on four different neurones. In the rat, the excitatory effects of 5-HT were

Table 3 Comparison of the effects of 5-methoxytryptamine (5-MeOT) with those of 5-hydroxytryptamine (5-HT) on the same neurones in the brain stem of rats pretreated with either *p*-chlorophenylalanine (PCPA) or reserpine

		5-HT			*Responses same*	
		+	*0*	*–*		*(%)*
5-MeOT (PCPA-pretreated rats)	+	34	0	0		
	0	1	3	1	37/41	90
	–	2	0	0		
5-MeOT (reserpine-pretreated rats)	+	26	0	0		
	0	2	2	2	35/40	88
	–	1	0	7		

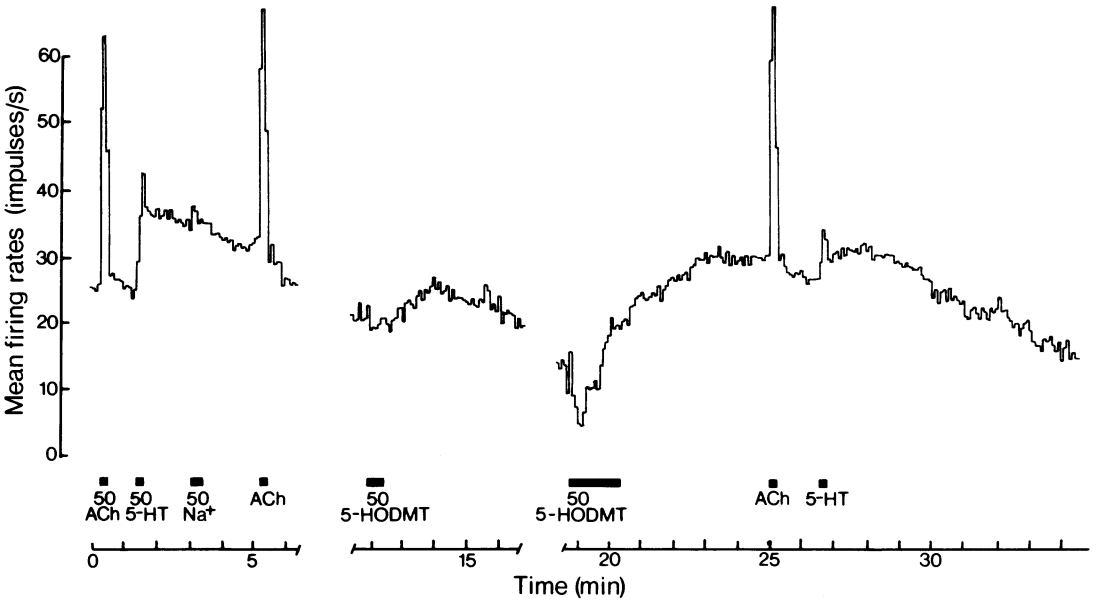

Fig. 2 Excitatory effect of bufotenine (5-hydroxy-*N,N*-dimethyltryptamine, 5-HODMT) on a neurone excited by 5-hydroxytryptamine (5-HT) and also by acetylcholine (ACh). During the effect of 5-HODMT the action of 5-HT is reduced, but that of ACh is not.

reduced by DMT on 80% of neurones tested, by 5-HODMT on 87% of neurones tested, and by 5-MeODMT on 85% of neurones tested. Sometimes the effects of the other transmitters were reduced at the same time as those of 5-HT, but antagonism of these effects was much less frequent than antagonism of 5-HT, and was less consistent among the three derivatives with antagonistic properties. The excitatory effects of glutamate were antagonized only infrequently. The actions of DMT, 5-HODMT and 5-MeODMT as antagonists are summarized in Table 4. In the cat only 5-HODMT and 5-MeODMT were studied on sufficient neurones to include in the Table (numbers in parentheses). Neurones which showed responses to the methylated tryptamine derivatives similar to the responses to 5-HT (5-HT-mimicking responses) are not included in this table.

Table 4 Antagonistic actions of tryptamine derivatives towards putative transmitter substances

		DMT		*5-HODMT*		*5-MeODMT*	
		Blocked	*Not blocked*	*Blocked*	*Not blocked*	*Blocked*	*Not blocked*
5-HT	+	32	8	21 (4)	3 (1)	33 (15)	6 (3)
	–	1	2	0	5	2	3
Acetylcholine	+	4	7	1 (0)	12 (4)	3 (1)	11 (4)
Noradrenaline	+	1	9	2 (0)	4 (4)	3 (0)	9 (3)
	–	5	6	2	4	0	7
Glutamate	+	3	11	1	12	0 (3)	12 (6)

Unbracketed figures refer to numbers of rat neurones; bracketed figures to cat neurones. + indicates excitation; – indicates inhibition.
DMT = *N,N*-dimethyltryptamine.
5-HODMT = 5-hydroxy-*N,N*,dimethyltryptamine.
5-MeODMT = 5-methoxy-*N,N*,dimethyltryptamine.

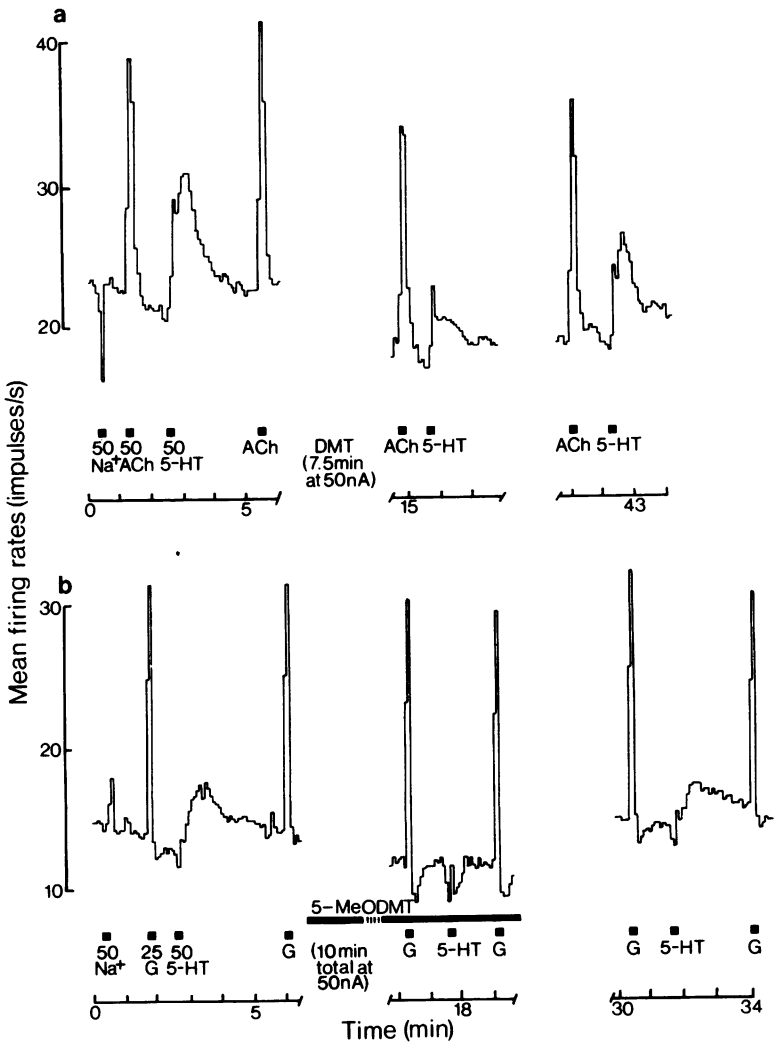

Fig. 3 Actions of methylated tryptamine derivatives as antagonists of 5-hydroxytryptamine (5-HT). (a) Antagonism by *N,N*-dimethyltryptamine (DMT) of the excitatory effect of 5-HT while acetylcholine (ACh) excitation was not reduced; (b) antagonism by 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) of 5-HT excitation while excitation by glutamate (G) was not reduced; (c) antagonism by DMT of 5-HT excitation while noradrenaline (NA) excitation was not reduced; (d) antagonism by DMT of 5-HT excitation while NA inhibition was not reduced. (Fig. 3 continued on opposite page.)

Discussion

Certain effects of LSD and other drugs with LSD-like actions (including DMT, bufotenine and 5-MeODMT) appear to be due to actions in the pons and medulla (Bradley & Key, 1958; Schweigerdt & Himwich, 1964; Key, 1965; Schweigerdt, Stewart & Himwich, 1966; Takeo & Himwich, 1967). In this part of the brain, 5-HT has mainly excitatory effects, both in the raphé nuclei (Couch, 1970) and in the reticular formation (Boakes *et al.*, 1970; Bradley & Dray, 1972; present investigation); more rostrally, in the mesencephalon, the effects of 5-HT are mainly inhibitory, both in the raphé nuclei (Aghajanian, Haigler & Bloom, 1972) and in the reticular formation (Straschill & Perwein, 1971).

Only the excitatory effects of 5-HT were found to be antagonized by LSD. Antagonism of 5-HT excitation by LSD has been observed in the cortex

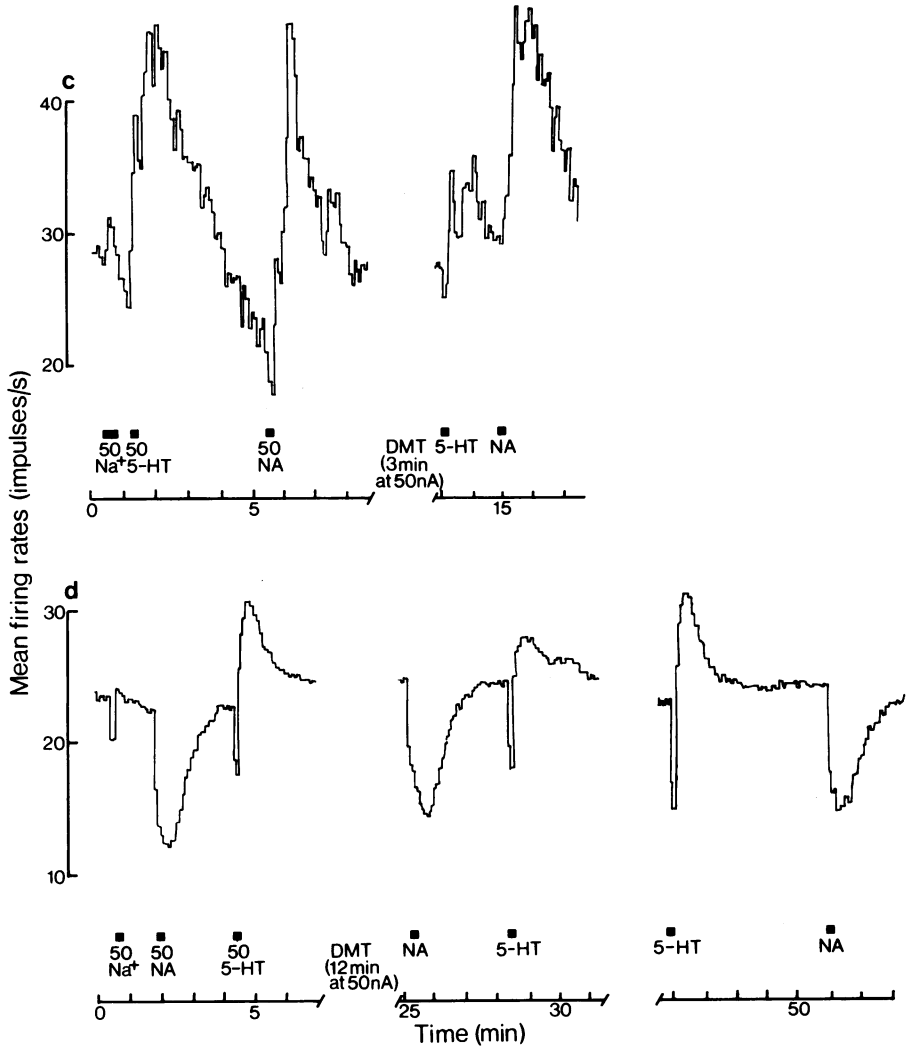

Fig. 3 (continued).

(Roberts & Straughan, 1967), the reticular formation of the pons and medulla (Boakes *et al.*, 1970), and the pontine raphé nuclei (Couch, 1970). There is evidence for a serotoninergic excitatory synaptic input to the pontine raphé, and LSD blocks both synaptic excitation and the excitations produced by microiontophoretically applied 5-HT (Couch, 1970; Bloom, Hoffer, Siggins, Barker & Nicoll, 1972).

The results presented here offer further support to the hypothesis that the mode of action of drugs with psychotomimetic actions similar to those of LSD is related to an ability to antagonize the excitatory effects of 5-HT. The three tryptamine derivatives which have been reported to have LSD-like psychotomimetic activity, DMT, 5-HODMT, and 5-MeODMT, were found to antagonize 5-HT excitations (Table 4), whereas the non-psychotomimetic 5-MeOT did not. The antagonism of 5-HT excitations by these compounds was less specific than that observed previously with LSD; other agents were also antagonized, but the 5-HT antagonism was greater, both on individual neurones and in terms of the proportions of neurones affected, and was also the most consistent effect of the three active derivatives.

The most striking difference between the

psychotomimetic tryptamine derivatives and LSD is in the effect on glutamate excitation of neurones which 5-HT excites. LSD always antagonized glutamate excitation of neurones which 5-HT also excited (Boakes *et al.*, 1970), but the tryptamine derivatives only rarely affected the action of glutamate. This difference may mean that the receptors for 5-HT and glutamate on these neurones are different but are closely related spatially, so that LSD, in occupying 5-HT excitatory receptors, overlaps the glutamate receptor sites, whereas the tryptamines do not. The ability of LSD to antagonize two excitant transmitters on the 5-HT sensitive neurones may contribute to its much higher psychotomimetic potency than those of the tryptamine derivatives.

LSD rarely, if ever, antagonizes specifically the inhibitory effects of 5-HT, whether it is iontophoretically applied (Krnjević & Phillis, 1963; Bloom, Costa & Salmoiraghi, 1964; Legge, Randić & Straughan, 1966; Roberts & Straughan, 1967; Boakes *et al.*, 1970) or released from presumed serotoninergic synapses (Bloom *et al.*, 1972).

Evidence from fluorescence histochemical studies has indicated that LSD and methylated tryptamine psychotomimetics may act by mimicking the actions of 5-HT (Andén *et al.*, 1968, 1971; Fuxe *et al.*, 1972). The reduced turnover of 5-HT in 5-HT containing neurones was suggested to be due to an inhibitory feedback loop, activated when these hallucinogens stimulate 5-HT receptors. An inhibitory feedback acting on raphé neurones, activated by stimulation of 5-HT receptors, has also been suggested as a mechanism for the inhibitory action of LSD on raphé neurones (Aghajanian *et al.*, 1968, 1970; Aghajanian, 1972; Samanin, Valzelli & Gumulka, 1972). More recently, LSD has been shown to have a direct inhibitory action on midbrain raphé neurones (Aghajanian *et al.*, 1972) and also to block the excitatory actions of 5-HT on pontine raphé neurones (Couch, 1970). Both of these actions would presumably reduce turnover of 5-HT by reducing raphé cell activity, but the possibility of negative feedback following 5-HT receptor stimulation cannot yet be excluded. Mimicking of 5-HT excitatory effects has not been observed with LSD (Roberts & Straughan, 1967; Boakes *et al.*, 1970), and in the present study, the most potent mimicker of 5-HT excitation was the non-psychotomimetic 5-MeOT, while the other compounds, with psychotomimetic effects, were less active in mimicking 5-HT excitation. The lack of correlation between mimicking of 5-HT excitation and psychotomimetic activity appears to exclude this effect as a possible mode of action. LSD and LSD-like drugs do, however, appear to have some effects which are similar to the effects of increasing 5-HT activity in the CNS (Andén *et al.*, 1968, 1971; Fuxe *et al.*, 1972). LSD has frequently been reported to inhibit neurones which 5-HT inhibits (Curtis & Davis, 1962; Phillis & Tebēcis, 1967; Phillis, Tebēcis & York, 1967; Aghajanian *et al.*, 1972), although the 'mimicking' of 5-HT inhibitory effects by LSD and psychotomimetic tryptamines is not a universal finding (Boakes *et al.*, 1970; present investigation). Nevertheless, mimicking of 5-HT inhibitory effects on neurones in some brain areas may explain some of the actions of these drugs; this possibility is not incompatible with the findings of antagonism of 5-HT excitation in other areas.

It seemed possible that the 5-HT-mimicking effects of the tryptamine derivatives observed in the present study might be due to release of 5-HT from terminals around the neurones being studied. The responses to the most potent 5-HT mimicker, 5-MeOT, were therefore examined in rats, which had been pretreated with reserpine or PCPA to deplete 5-HT levels. In both these groups the actions of 5-MeOT were the same as in untreated rats, and it thus appears that these actions were unlikely to be due to release of 5-HT, but were due to a direct action on 5-HT receptors.

We would suggest that the effects of indole-type psychotomimetics on perception and arousal levels depend at least partly on their ability to antagonize the excitatory actions of 5-HT in the pons and medulla.

Methylated derivatives of tryptamine and 5-hydroxytryptamine, including those whose actions are described in this paper, have been suggested as possible endogenous psychotogenic agents. DMT, bufotenine and 5-MeODMT have been detected in higher levels in blood and urine samples from cases of acute schizophrenia than in samples from non-schizophrenics or chronic schizophrenics (Fischer & Spatz, 1970; Tanimukai, Ginther, Spaide, Bueno & Himwich, 1970; Narasimhachari, Heller, Spaide, Haskovec, Fujimori, Tabushi & Himwich, 1971; Narasimhachari, Heller, Spaide, Haskovec, Meltzer, Strahilevitz & Himwich, 1971). An enzyme capable of synthesizing *N,N*-dimethylated tryptamines from tryptamine or 5-HT has been demonstrated in rat brain and in human brain (Mandell, Buckingham & Segal, 1971; Saavedra & Axelrod, 1972); the *O*-methylation of 5-hydroxytryptamine in the pineal body is well known (Axelrod & Weissbach, 1961), and recently, Green, Koslow & Costa (1973) demonstrated the presence in rat hypothalamus of 5-MeOT, apparently originating outside the pineal, since pinealectomy had little effect on the brain concentrations. 5-MeOT may also be the compound present in the B-type monoamine neurones described by Björklund, Falck & Steveni

(1971). It therefore seems possible that the hallucinogenic compounds studied in this investigation may be produced in the brain, and may be of importance in the aetiology of schizophrenia.

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