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Original Investigations

Some Neurochemical and Neuropharmacological Studies on the Interactions between Mescaline and 1-Methyl-1,2,5,6-Tetrahydropyridine-3-(N,N-Diethylcarboxamide) (THPC)

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Abstract. The effect of THPC was studied on some pharmacological and neurochemical changes induced in the rat by mescaline. The results show that THPC antagonizes the effect of mescaline on the calorigenic action of α methyl-m-tyrosine in reserpinized mice. THPC potentiated the depletion of brain dopamine caused by H77/77 in combination with mescaline. In none of the other pharmacological or neurochemical tests was there any evidence that THPC antagonized or potentiated the effects of mescaline.

Key words: Mescaline — THPC — Brain Amines and Amino Acids.

Smythies and coworkers (1966, 1968, 1970a) have studied the effects of a number of hallucinogenic phenylethylamines on the behaviour of rats using a Sidman avoidance schedule. The reported that, by using the Bovet-Gatti profiles on this avoidance schedule, it was possible to differentiate hallucinogenic from non-hallucinogenic drugs. In attempting to understand how hallucinogenic drugs act, these workers have extended their studies to the structure/activity relations of a number of phenylethylamines and tryptamines (Smythies, Benington and Morin, 1970b). As a result of such a study, Smythies has attempted to explain the hallucinogenic activity of such compounds in terms of their electronic structure (Smythies *et al.*, 1970b).

Smythies, Beaton, Benington and Morin (1970a) reported that THPC could potentiate the effects of mescaline in rats on the Sidman avoidance schedule. They speculated that the combined structures of THPC and mescaline would simulate the action of the more potent hallucinogen

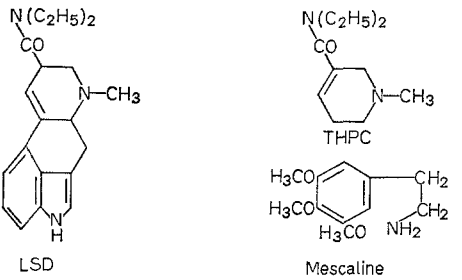

Fig. 1

d-LSD and found evidence to suggest that this did occur. The structural similarity between d-LSD and mescaline together with THPC is shown in Fig. 1.

Previous investigations have shown that hallucinogenic drugs produce changes in brain biogenic amines and their amino acid precursors which may enable them to be distinguished from non-hallucinogens (Leonard and Tonge, 1969; Tonge and Leonard, 1969; Tonge and Leonard, 1970; Tonge and Leonard, 1971; Leonard and Shallice, 1971). Because of the potential therapeutic importance of substances which modify the action of hallucinogenic drugs, the following study was undertaken to investigate the effects of THPC alone, and in combination with mescaline, on several neuropharmacological and neurochemical parameters.

Methods

In all experiments specific pathogen free albino (90—110 g) rats or mice (18—22 g) of either sex and of the Alderly Park strain were used.

Pharmacological

Reversal of Reserpine Hypothermia. This test was carried out as described by Somerville and Whittle (1968). Groups of 6 mice, kept in a room maintained at 21 $\pm$ 1°, were pretreated for 17 h with reserpine (2 mg/kg s.c.). The pharyngeal temperatures were then recorded and found to approximate to the ambient temperature. Groups of mice were then injected with physiological saline (control group) or with different doses of mescaline (10—80 mg/kg i.p.) alone, THPC (10—80 mg/kg i.p.) or with a combination of mescaline and THPC. Pharyngeal temperatures were recorded 1, 2 and 4 h later and the cumulative temperature rise (Sum of temperatures at 1, 2 and 4 h minus 3 $\times$ zero time temperature) calculated.

Prevention of Reserpine Hypothermia Test. This test was carried out according to the method of Brittain and Spencer (1964) and Spencer (1967). The doses of mescaline, THPC and mescaline together with THPC used were the same as those used in the reversal of reserpine hypothermia test.

Hexobarbitone Sleeping Time. Groups of 10 mice were pretreated for 30 min with different doses of mescaline, THPC or mescaline + THPC. The doses used are shown in Results. The mice were then injected intravenously with 100 mg/kg sodium hexobarbitone; this dose caused the animals to lose their righting reflexes immediately following injection. The sleeping times, taken as the period (in sec) between the loss and regaining of the righting reflex, were recorded.

Neurochemical

Groups of 5 rats were treated with physiological saline (controls), mescaline, THPC or with mescaline together with THPC (at the doses shown in Results) and killed at 0, 60, 120, 180 and 240 min later. When serum amino acids were to be determined, blood was collected from the cut jugular veins and carotid arteries, allowed to clot and then centrifuged at approximately 800 $\times$ g for 10 min. The procedures used for the fluorimetric determination of tyrosine and tryptophan concentrations in the serum and brain, and of γ amino butyric acid (GABA), noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) in the brain have been described in greater detail elsewhere (Leonard and Shallice, 1971).

Effect on Depletion of Brain Biogenic Amines by 4α Dimethyl-m-Tyramine (H77/77) and 4-Methyl-α-Ethyl-m-Tyramine (H75/12). In some experiments the effects of mescaline, THPC and mescaline together with THPC on the depletion of brain catecholamines by H77/77 and on the depletion of brain 5-HT by H75/12 were studied.

For the experiment in which the effect of mescaline and THPC was studied on the depletion of brain catecholamines caused by H77/77, the following dosage schedule was used. Each group consisted of 5 rats.

Group 1 — physiological saline (control group).

Group 2 — H77/77 alone. The rats were injected at 0 and 2 h later with 12.5 mg/kg of the drug.

Group 3, 4 and 5 — H77/77 (2 $\times$ 12.5 mg/kg) in combination with mescaline (2 $\times$ 40 mg/kg), THPC (2 $\times$ 40 mg/kg) or mescaline + THPC. Mescaline and THPC were injected 30 min before each H77/77 treatment.

Two hours after the last injection of H77/77, the animals were decapitated and the catecholamines estimated in the whole brains by the solvent extraction method of Welch and Welch (1969).

In the H75/12 experiment, four groups of 5 rats were pretreated 2 and 4 h before sacrifice with 25 mg/kg H75/12. The experimental procedure

was similar to that described for the H77/77 experiment. Group 1 was also injected with physiological saline, group 2 with mescaline (2×20 mg/kg i.p.), group 3 with THPC (2×20 mg/kg i.p.) and group 4 with mescaline together with THPC. After the animals had been killed, brain 5-HT was estimated by the solvent extraction method of Welch and Welch (1969), as modified by Leonard and Shallice (1971).

Effect on the Depletion of Brain Catecholamines Caused by α-Methyl-p-Tyrosine (αMPT) and α Methyl-m-Tyrosine (αMMT). Groups of 5 rats were given either αMPT (300 mg/kg i.p.) or αMMT (400 mg/kg i.p.). Some of these groups were then given either mescaline (20 mg/kg i.p.), THPC (20 mg/kg i.p.) or mescaline + THPC. The rats were killed 3 h later and brain noradrenaline and dopamine estimated by the method of Welch and Welch (1969).

Effect on the Depletion of Brain 5-HT by p-Chlorophenylalanine (PCPA). Groups of 5 rats were pretreated for 9 h with PCPA (400 mg/kg i.p.). Some of these groups were also injected at 9, 6 and 3 h before sacrifice with mescaline (20 mg/kg i.p.), THPC (20 mg/kg i.p.) or mescaline + THPC. The animals were killed by decapitation and the brain 5-HT content determined by the method of Bogdanski, Pletscher, Brodie and Udenfriend (1956).

The Effect on Changes in Brain Biogenic Amines Caused by Mebanazine. Groups of 5 rats were treated with mebanazine (Actomol—I.C.I. Trade Mark) and killed 4 h later. Some of these groups were also injected with mescaline (20 mg/kg i.p.), THPC (20 mg/kg) or mescaline + THPC, 4 and 2 h before sacrifice. The rats were decapitated and brain noradrenaline, dopamine and 5-HT determined by the method of Welch and Welch (1969).

Results and Discussion

Pharmacological

Effects on the Gross Behaviour of Rats and Mice. Doses of mescaline greater than 20 mg/kg (i.p.) significantly increased the motility of rodents. Some head shaking was also apparent, but the pharyngeal temperature was not affected by the doses of drug used. THPC alone, even at the highest dose used (100 mg/kg, i.p.) did not affect the behaviour of the rats nor did it modify that produced by mescaline.

Reversal of Reserpine Hypothermia Test. Neither mescaline nor THPC alone or in combination significantly affected the hypothermia induced by reserpine. The cumulative temperature increases for the highest dose (80 mg/kg) of the drugs used were:

Control (saline)	1.82 ± 0.44
Mescaline	1.62 ± 0.38
THPC	1.09 ± 0.25
Mescaline + THPC	0.93 ± 0.38

Each result represents the mean ± s.e.m. for at least 6 mice.

It may be presumed that antagonism of reserpine hypothermia is partly a result of a drug decreasing the turnover of brain catecholamines. Differences in the mode of action of mescaline and THPC may therefore result when these drugs are given to reserpinized mice which have also been treated with drugs affecting the synthesis or release of brain catecholamines. Experiments were therefore undertaken in which groups of mice which had been pretreated for 17 h with reserpine were given α-methyl-p-tyrosine (αMPT) or α-methyl-m-tyrosine (αMMT). αMPT was used because it has been shown that this drug reduces the concentration of brain noradrenaline by inhibiting its synthesis at the tyrosine hydroxylase stage (Spector, Sjoerdma and Udenfriend, 1965).

In contrast, αMMT reduces the concentration of this amine by forming a false transmitter substance, metaraminol, which displaces noradrenaline from its storage sites (Andén, 1964) thereby depleting it.

Experiments were therefore undertaken using α-MPT and α-MMT alone, and in combination with THPC and mescaline, in reserpinised mice. By such experiments it was hoped that more subtle interactions between these drugs might become apparent. In these experiments, mescaline, THPC or THPC + mescaline were injected at the same time as α-MPT or α-MMT.

Effect of α-MPT. αMPT alone or in combination with mescaline and THPC did not significantly antagonise the reserpine induced hypothermia: The cumulative rise in temperature for α-MPT alone in combination with mescaline and THPC was:

Controls (saline)	− 2.40 ± 0.5
α MPT (300)	− 2.25 ± 0.76
Mescaline (100)	− 3.68 ± 1.60
α MPT + Mescaline	− 2.60 ± 0.38
THPC (100)	− 2.10 ± 0.50
α MPT + THPC	− 2.18 ± 1.60
α MPT + THPC + mescaline	− 3.00 ± 1.40

Results expressed as Mean ± s.e.m. Figures in parenthesis give the doses of drugs used in mg/kg (i.p.).

Effect of α MMT. The effect of α MMT alone in combination with mescaline and THPC on reserpine induced hypothermia are summarised in Table 1.

These results show that mescaline and THPC alone have no significant effect on reserpine induced hypothermia. However, α MMT, unlike

Table 1. *Effect of mescaline and THPC on the reversal of reserpine induced hypothermia by α MMT in mice*

Treatment	Dose (mg/kg)	Cumulative temperature (Mean ± s.e.m.)	Significance from	
			Controls group	MMT group
Saline (controls)	—	2.35 ± 0.87		
α MMT	400	30.10 ± 1.21	***	—
Mescaline + α MMT	50 + 400	4.20 ± 0.98	n.s.	***
Mescaline + α MMT	100 + 400	2.25 ± 0.74	n.s.	***
THPC + α MMT	50 + 400	28.40 ± 0.63	***	n.s.
THPC + α MMT	100 + 400	29.62 ± 0.84	***	n.s.
Mescaline + THPC + α MMT	50 + 50 + 400	18.72 ± 1.46	***	**
Mescaline + THPC + α MMT	100 + 100 + 400	15.25 ± 0.80	***	**

Significance of the results (using Student's *t*-test) shown by n.s. = not significance: $**P < 0.01$, $***P < 0.001$. Each result represents the mean of at least 6 mice.

Table 2
Effect of mescaline and THPC alone on the hexobarbitone sleeping times of mice

Treatment	Dose (mg/kg)	Mean sleeping time (sec)	Treatment	Dose (mg/kg)	Mean sleeping time
Saline (control)	—	425	Saline (control)	—	660
Mescaline	6.25	567	THPC	6.25	892*
Mescaline	12.5	610*	THPC	12.5	860*
Mescaline	25.0	872**	THPC	25.0	859*
Mescaline	50.0	877**	THPC	50.0	872*
Mescaline	100.0	987**	THPC	100.0	1088*

Each result represents the mean of at least 6 mice. The significance of the difference between the control and experimental groups is by $*P < 0.05$; $** P < 0.01$.

α MPT, significantly antagonizes the hypothermic effect of reserpine. Previous studies have shown that this is due to the formation of metaraminol (Leonard and Stonier, 1971). This effect of α-MMT is antagonized by mescaline but not by THPC; other hallucinogenic drugs have a similar effect to mescaline (Leonard and Stonier, 1971).

Although THPC alone has no significant effect on the reversal of hypothermia by α-MMT, it significantly reduces the effect of mescaline in mice which have been reserpined and treated with α MMT.

Prevention of Reserpine Hypothermia. Neither mescaline nor THPC, in doses of up to 100 mg/kg i.p., alone or in combination significantly antagonised the decrease in body temperature which followed the intravenous administration of reserpine.

Hexobarbitone Sleeping Time. The results of this experiment are shown in Table 2. It is apparent that mescaline produces an increase in the hexobarbitone sleeping time of mice, which is approximately related to the dose of drug given. On the other hand, the effect of THPC on the hexobarbitone sleeping time did not appear to be related to the dose of drug given.

When mescaline was given in combination with THPC to mice which were then injected with hexobarbitone, the resulting increase in the sleeping time was intermediate between those produced by either drug alone. Thus the mean sleeping time for the control group was 325 sec. Mescaline (25 mg/kg i.p.) caused a significant increase to 688 sec ($P < 0.05$) whereas THPC (50 mg/kg i.p.) alone increased the sleeping time to 1062 sec ($P < 0.01$). In combination, mescaline and THPC produced a sleeping time of 920 sec ($P < 0.01$).

From the results of the pharmacological studies, it can be concluded that in most of experiments, THPC neither antagonizes nor potentiates the action of mescaline. The only exception is in the reversal of reserpine induced hypothermia by α MMT. In this experiment THPC significantly antagonized the effect of mescaline on the α MMT reversal. The mechanism whereby this antagonism occurs is uncertain but it may be speculated that as mescaline reduces brain noradrenaline possibly by increasing its intraneuronal metabolism (Leonard and Tonge, 1969), THPC could be producing its effect either by reducing the release of noradrenaline from its bound form or by affecting the metabolism of this amine. The effect of these drugs on brain amines and their amino acid precursors were therefore studied in order to investigate these possibilities further.

Neurochemical

Effect on Brain Catecholamine and 5-HT Concentrations. A dose response curve was first obtained for the effect of mescaline and THPC on the concentration of these biogenic amines in the brain. The results showed that both mescaline and THPC were producing their maximal effect at a dose of approximately 20 mg/kg. All subsequent studies were therefore undertaken using these doses.

Brain noradrenaline levels were reduced by both mescaline and THPC, the maximal reduction (14%) occurring 80 min after the drugs had been administered. These changes were not statistically significant ($P < 0.1 > .05$). The small reduction in brain noradrenaline by mescaline was surprising as previous experiments, using rats obtained from other

Table 3. *Effect of mescaline and THPC on brain 5-HT levels*

Treatment	Time after administration (mins)				
	0	20	40	80	180
Mescaline	0.77 ± 0.05	0.84 ± 0.08	$*0.88 \pm 0.06$	$**0.85 \pm 0.08$	0.80 ± 0.05
THPC	0.72 ± 0.04	0.74 ± 0.06	0.72 ± 0.04	0.73 ± 0.07	0.67 ± 0.09
Mescaline + THPC	0.74 ± 0.06	—	—	0.96 ± 0.06	—

Mescaline and THPC were given at a dose of 20 mg/kg. All results (as μ g/g) represent the mean $\pm$ s.e.m. for at least 5 rats. The significance of the results, assessed by the students t-test, shown by * $P < 0.05$; ** $P > 0.02$.

sources, had shown that mescaline produces a highly significant fall in brain noradrenaline (Leonard and Tonge, 1969). The combination of THPC with mescaline did not produce any change in brain noradrenaline levels. Brain dopamine levels were slightly elevated following mescaline; the maximum rise (10%; $P < 0.1 > 0.05$) occurred 80 min after administration. In contrast, THPC caused a slight (15%) decrease in the concentration of this amine 40 min after administration but this change was not statistically significant ($P < 0.1 > 0.05$). In combination, THPC and mescaline did not cause any significant change in the concentration of dopamine.

Mescaline caused a highly significant increase in total brain 5-HT 40 and 80 min after administration (Table 3), whereas THPC had no significant effect. When THPC was administered together with mescaline and the animals killed 80 min later, the concentration of brain 5-HT increased by 10%. This change was not statistically significant.

Changes in blood and brain tyrosine following the administration of mescaline and THPC are summarised in Table 4. THPC caused a slight rise in brain tyrosine (5%) whereas mescaline produced a significant rise followed by a compensatory fall 120 mins later. In combination, THPC and mescaline caused a 5% increase in the concentration of this amino acid. Both mescaline and THPC produced a fall in the serum level of this amino acid 160 min after administration.

Brain tryptophan levels were increased by THPC but decreased by mescaline. When given in combination, THPC and mescaline had no significant effect. Both mescaline and THPC reduced serum tryptophan levels significantly but only mescaline had a significant effect on brain γ-amino butyric acid.

Effect on the Depletion of Noradrenaline and Dopamine by 4-α Dimethyl-m-Tyramine (H 77/77). Neither mescaline nor THPC alone or in combination significantly affected the depletion of brain noradrenaline caused by

Table 4. *Effect of mescaline and THPC on brain and amino acids*

Treatment	Time after administration (mins)				
	0	20	40	80	160
			Brain tyrosine		
		*	*		*
Mescaline	23.0 ± 1.9	27.3 ± 1.6	27.6 ± 0.9	21.1 ± 1.7	20.2 ± 1.2
THPC	23.7 ± 2.03	25.0 ± 1.7	24.1 ± 1.9	21.3 ± 2.0	21.5 ± 1.7
Mescaline + THPC	23.5 ± 1.8	—	25.2 ± 1.6	—	—
			Blood tyrosine		
				*	*
Mescaline	28.7 ± 0.59	17.8 ± 0.7	17.3 ± 0.85	20.2 ± 0.3	15.8 ± 0.6
					*
THPC	18.2 ± 0.40	17.6 ± 0.48	17.5 ± 0.50	17.2 ± 0.3	15.7 ± 0.4
			Blood tyrosine		
Mescaline + THPC	18.6 ± 0.70	—	—	19.1 ± 0.60	—
			Brain tryptophan		
				**	**
Mescaline	1.82 ± 0.06	1.73 ± 0.04	1.80 ± 0.05	1.44 ± 0.03	1.36 ± 0.05
				**	
THPC	1.80 ± 0.03	2.18 ± 0.05	2.00 ± 0.04	2.14 ± 0.03	1.96 ± 0.05
Mescaline + THPC	1.84 ± 0.07	—	—	1.80 ± 0.06	—
			Blood tryptophan		
				**	**
Mescaline	15.7 ± 1.75	17.0 ± 1.62	14.6 ± 1.70	11.2 ± 0.95	11.4 ± 1.25
THPC	15.6 ± 1.60	11.78 ± 1.30	13.4 ± 1.40	15.7 ± 1.65	15.8 ± 0.97
Mescaline + THPC	16.0 ± 1.82	14.8 ± 2.0	—	—	—
			Brain γ-amino butyric acid		
			**		
Mescaline	416 ± 20.2	425 ± 18.4	500 ± 17.6	458 ± 19.3	450 ± 20.0
THPC	418 ± 18.6	422 ± 12.4	430 ± 20.2	426 ± 17.2	413 ± 19.2
Mescaline + THPC	412 ± 22.4	—	438 ± 21.6	—	—

Results, as the mean ± s.e.m. of at least 5 rats per group, shown as μg/g wet weight brain or μg/ml serum. Significance of difference between the control (0 time) and experimental groups as $*P < 0.05$; $**P < 0.01$.

H77/77 (Table 5). However, when given in combination, mescaline and THPC significantly potentiated the reduction of brain dopamine caused by H77/77. These results suggest that whereas mescaline and THPC

Table 5. *Effect of Mescaline and THPC on the depletion of brain catecholamines by H77/77*

	Saline (control)	H77/77	H77/77 + mescaline	H77/77 + THPC	H77/77 + mescaline + THPC
		**	**	**	**
Noradrenaline	0.59 ± 0.03	0.37 ± 0.03	0.36 ± 0.03	0.36 ± 0.01	0.39 ± 0.02
			*	*	**
Dopamine	0.61 ± 0.01	0.53 ± 0.06	0.44 ± 0.09	0.45 ± 0.07	0.35† ± 0.03

Results expressed as μg/g wet weight. Significance of difference between the control and experimental groups shown as * $P < 0.05$; ** $P < 0.01$. Difference between groups treated with H77/77 alone and those treated with H77/77 + mescaline + THPC significant at †$P < 0.02$.

alone have little effect on the mechanism of action of H77/77, in combination they potentiate the action of this compound on dopaminergic neurones. Carlsson and coworkers (1969) reported that H77/77 displaces brain catecholamines and utilizes the reserpine resistance uptake mechanism to bring about this displacement. These results therefore suggest that THPC in combination with mescaline specifically affects the reserpine resistant uptake mechanism.

Effect on the Depletion of Brain 5-HT Caused by 4-Methyl-α-Ethyl-m-Tyramine (H75/12). H75/12 caused a 48% decrease in brain 5HT. In combination with mescaline and THPC, H75/12 caused a 50% and a 47% depletion respectively of brain 5-HT. Mescaline in combination with THPC caused a 52% depletion of brain 5-HT. The control values (saline treated) were 0.48 ± 0.04 μg/g. From these results it is apparent that neither mescaline nor THPC alone or in combination, significantly affect the depletion of brain 5-HT caused by H75/12. This compound is thought to act specifically on the 5-HT granule membrane in a manner similar to that for H77/77 on catecholamine containing granules (Carlsson, Corrodi, Fuxe and Hökfelt, 1969). There is no evidence from these studies that mescaline or THPC affect this mechanism for the depletion of brain 5-HT.

Effect on the Depletion of Brain Catecholamines Caused by α-Methyl-p-Tyrosine (αMPT) and α-Methyl-m-Tyrosine (αMMT). Neither mescaline nor THPC alone or in combination significantly affected the depletion of brain noradrenaline caused by αMPT. The concentration of noradrenaline in the brains of the saline treated (control) rats was 0.57 ± 0.06 μg/g; this decreased to 0.32 ± 0.05 μ/g in those animals treated with αMPT alone.

Table 6. *Effect of mescaline and THPC on the depletion of brain noradrenaline by αMMT*

	Saline (control)	αMMT	αMMT + mescaline	αMMT + THPC	αMMT + THPC + mescaline
Brain noradrenaline μg/g ± s.e.m.)	0.60 ± 0.03	*** 0.33 ± 0.02	*** 0.27† ± 0.013	*** 0.28 0.012	*** 0.27† ± 0.016

Results expressed as μg/g wet weight. Significance of difference between the control and experimental groups shown as *** $P < 0.001$. Difference between the groups treated with αMMT and those treated with αMMT + mescaline and αMMT + mescaline + THPC significant at † $P < 0.05$.

Table 7. *Effect of mescaline and THPC on the depletion of brain 5-HT by PCPA*

	Saline (control)	PCPA	PCPA + mescaline	PCPA + THPC	PCPA + THPC + mescaline
		***	***	***	***
Brain 5-HT (mg/g ± s.e.m.)	0.53 ± 0.021	0.32 ± 0.016	0.31 ± 0.018	0.27† ± 0.017	0.31 ± 0.023

Significance of difference between the control and experimental groups shown as *** $P < 0.001$. Difference between the group treated with PCPA and that treated with PCPA + THPC significant at † $P < 0.05$.

Following the administration of αMMT however, mescaline significantly increased the depletion of brain noradrenaline whereas THPC had no significant effect (Table 6). The finding that mescaline potentiates the action of αMMT is confirmation of the previous study of Leonard and Tonge (1969).

Effect on the Depletion of 5-HT by p-Chlorphenylalanine (PCPA). The results show that THPC significantly increases the depletion of brain 5-HT following the blockade of its synthesis by PCPA (Table 7). Mescaline had no effect alone, nor in combination with THPC, on the depletion of this amine after PCPA administration. This result was surprising as previous studies have shown that lower doses of mescaline (10 mg/kg) reduce the depletion of 5-HT following PCPA (Tonge and Leonard, 1969) which suggested that the hallucinogen decreases the turnover of this amine.

The Effect on Changes in Brain Biogenic Amines Following the Administration of Mebanazine. Neither mescaline and THPC alone or in combination significantly affected the increase in brain noradrenaline, dopamine

or 5-HT which occurred after the administration of mebanazine. The concentration of brain noradrenaline after mebanazine was increased by 30%, dopamine by 20% and 5-HT by 110%. The absolute levels of these amines in the control group was 0.48 ± 0.06 μg/g, 0.87 ± 0.05 μg/g and 0.51 ± 0.08 μg/g for noradrenaline, dopamine and 5-HT respectively.

Drugs such as mescaline undoubtedly have a number of different loci of action. The amphetamine-like and cholinergic properties of mescaline and other hallucinogens are well known and complicate attempts to understand the mechanisms of action of these drugs at the subcellular level.

In the present investigation there are only 2 findings which suggest that THPC may modify the actions of mescaline. From the pharmacological studies it was found that THPC can reverse the effect of mescaline in reserpinized mice which have also been treated with αMMT. In the neurochemical studies, THPC in combination with mescaline potentiates the depletion of brain noradrenaline following the administration of H 77/77. Apart from these findings, there was no evidence that THPC specifically antagonized or potentiated the actions of mescaline.

The differences between the results of this investigation and those found by Smythies and coworkers (1970a) could be due to the different ways in which the problem has been approached. Thus the behavioural effects of mescaline and THPC reported by Smythies *et al.* (1970a) have been ascribed to the drugs having a specific action on central serotonin receptors (see Smythies, Benington and Morin, 1970b) whereas our experiments probably monitor the effects of the drugs on amine storage, release and metabolism. Clearly there is a need to extend the present investigation to study the actions of mescaline and THPC on central serotonin receptors and to extend it to investigate the reported antagonism of the central action of LSD by THPC.

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