Psychotomimetic Drugs

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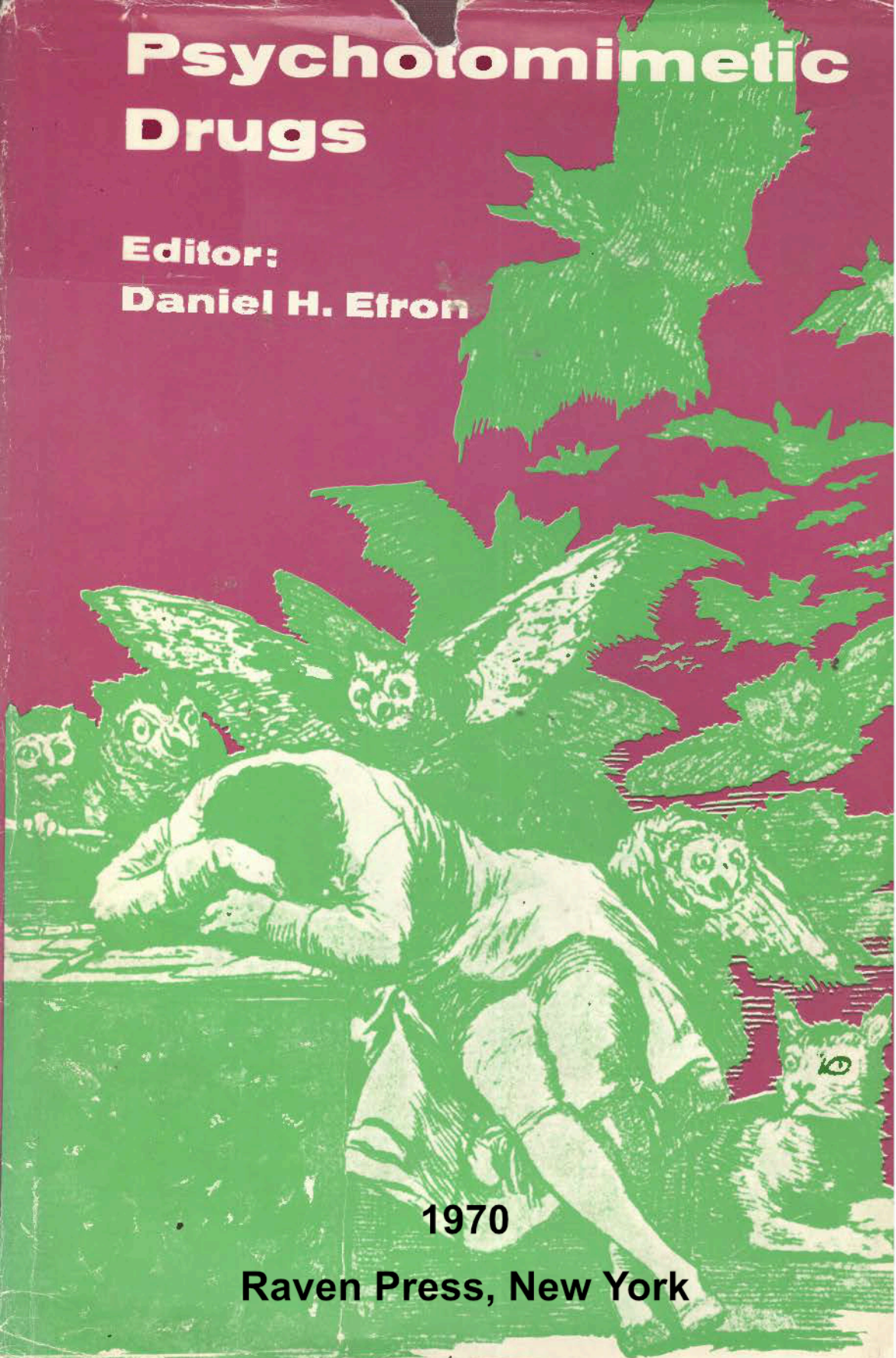

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PHARMACOLOGICAL STUDIES OF 5-METHOXY-N,N-DIMETHYLTRYPTAMINE, LSD AND OTHER HALLUCINOGENS

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My interest in hallucinogens, and particularly hallucinogenic tryptamines, dates back to 1958, at which time I joined Irving Page and his research group at the Cleveland Clinic. This group had earlier isolated serotonin from blood (Rapport *et al.*, 1948), and this was shown by Rapport (1948) to be 5-hydroxytryptamine. Page and his group showed serotonin to be also a component of brain tissue (Twarog and Page, 1953), and therefore they were understandably excited by a report by Stromberg (1954) that bufotenine, the N,N-dimethyl derivative of 5-hydroxytryptamine, was a component of the seeds of *Piptadenia peregrina* Benth from which the South American Indians prepared a psychotropic snuff called cahoba. It was decided therefore that we should study the metabolic fate of bufotenine (Gessner *et al.*, 1960). However, upon review of the literature, the hallucinogenic effects of bufotenine did not appear to be very impressive (Fabing, 1956; Fabing and Hawkins, 1956; Turner and Merlis, 1959). Considering the structure of bufotenine and the presence of a rather hydrophilic hydroxy group in the molecule, it appeared rather likely that this compound would have poor lipid solubility, and hence would experience difficulty in crossing the blood-brain barrier. One way of rendering the compound more lipophilic while still retaining the oxygen moiety in the 5 position of the indole ring was to synthesize the 5-methoxy-N,N-dimethyltryptamine, and this we did. Using as a test system the conditioned avoidance response of trained rats, we obtained a measure of the potency of 5-methoxy-N,N-dimethyltryptamine (Gessner and Page, 1962). We found it to be somewhat more active in this test system than either N,N-diethyltrypta-

mine or N,N-dimethyltryptamine, tryptamines shown to be hallucinogenic in man by Szara (1957), and somewhat less active than LSD. Bufotenine, in this test system, appeared to have only marginal activity. These experiments provided us with quantitative data; they did not, however, provide a measure of the significance of the observed potency differences. Accordingly, after moving to Buffalo, I proceeded to design experiments that would yield this information. Again, the conditioned avoidance response of trained rats was used as the test system, but the design followed was that of a Latin square, such that in a group of, say, five rats, each rat would receive each of the drugs over a period of time. I also embarked at this time, together with Dr. Domodar D. Godse, on a synthetic program. We synthesized, in addition to the 5-methoxy, the 4-, 6- and 7-methoxy-N,N-dimethyltryptamines, and tryptamines with substituents other than dimethyl on the side chain nitrogen. On testing the relative potency of these compounds on our behavioral test system, we found (Gessner *et al.*, 1968) the 5-methoxy-N-methyl-N-ethyltryptamine to be significantly more potent than the 5-methoxy-N,N-dimethyltryptamine or the 4-methoxy-N,N-dimethyltryptamine, the activity of the latter compound approaching that of 5-methoxy-N,N-dimethyltryptamine. The 6- and 7-methoxy-N,N-dimethyltryptamines, on the other hand, proved to be significantly less potent than 4-methoxy-N,N-dimethyltryptamine. 5-Methoxy-N,N-dimethyltrpytamine proved significantly more potent than psylocin (4-hydroxy-N,N-dimethyltryptamine) or N,N-diethyltryptamine.

The similarity in the structure of the various tryptamines and 5-hydroxytryptamine leads to a working hypothesis that the observed effects of the various tryptamines are mediated by their acting on, or interfering with, the 5-hydroxytryptamine receptor. Accordingly, it appeared reasonable to Dr. Jerrold C. Winter and me to continue these structure-activity studies utilizing a tissue preparation in which the effects of these agents could be studied *in vitro*. To this end we selected Vane's (1957) rat stomach fundus preparation, a tissue which is contracted by 5-hydroxytryptamine but relaxed by catecholamines. Using this preparation, we compared not only a number of substituted tryptamines, but also compounds isosteric to these, in which the ring nitrogen of the indole moiety was substituted for by a methylene bridge or by a sulfur atom. We found that in terms of contracting the rat stomach fundus, these isosteric compounds were about as active as the tryptamines (Winter *et al.*, 1967). While doing this work, however, we made some observations which suggested to us that the tryptamines could perhaps contract the rat stomach fundus by acting on more than one type of receptor. Therefore, we undertook a pharmacological analysis using agents blocking the tryptamine sensitive receptors in the rat stomach fundus (Winter and Gessner, 1968). 5-Hydroxytryptamine itself contracts the rat stomach fundus by action on a

receptor which can be completely blocked by pretreatment with phenoxybenzamine. No matter how much phenoxybenzamine is used, however, other tryptamines still retain, in varying degrees, an ability to contract this tissue. This leads therefore to the conclusion that they must contract the rat stomach fundus by acting, at least in part, on a receptor other than that for 5-hydroxytryptamine. Furthermore, we found that these tryptamines, when present in bath concentrations necessary to obtain a maximal response, also occupied the 5-hydroxytryptamine receptor and are able to protect it against phenoxybenzamine block. Interesting as these observations were, they did indicate the complexity involved in using the rat stomach fundus for the investigation of the mechanism of action of tryptamines.

As Drs. Laties and Kornetsky have pointed out earlier in this meeting, one cannot expect a direct correlation between the psychic action of a hallucinogen in man and its effect on the randomly chosen behavioral parameter in animals. By definition, hallucinations are subjective phenomena and can be studied only in men. Nonetheless, hallucinogens do exert marked pharmacological effects in animals, be these behavioral or otherwise. These may be mediated by the same mechanism of action as the hallucinations in men. The likelihood of this being so is enhanced if a clear correlation can be empirically established between the known hallucinogenic potency of these compounds and their potency in bringing about certain effects in animals. One of the pharmacological parameters that Drs. Richard T. La Rosa, William J. Fiden and I became interested in was the ability of hallucinogens to alter body temperature. Jacob and Lafille (1963) in France have shown that there is a high degree of correlation between the hyperthermic effects of a variety of hallucinogens in animals and the hallucinogenic activity of these agents in man. Using mice at an ambient temperature of 29° centigrade, we were able to show (Fig. 1) that 5-methoxy-N,N-dimethyltryptamine does indeed cause a hyperthermia, the duration and extent of which are proportional to dose, but that this is followed by a hypothermic effect which is quite prolonged.

Another pharmacological parameter that Dr. Richard La Rosa and I became interested in was the ability of a number of hallucinogens to cause tremor. We had noticed in the behavioral work described above that rats, given various hallucinogens, exhibited a fine tremor. Investigation of the literature showed that a number of other hallucinogens have also been observed to cause tremor in small mammals (Lessin *et al.*, 1965; Jarvik, 1965; Cohen, 1967). We moved therefore to utilize this property, and did so by measuring the ballistographic activity of severely restricted mice.

Mice were placed in a cage such that their freedom of movement was rather limited (they could not scratch), and the mouse and its cage were hung from a force displacement transducer. The voltage output from the

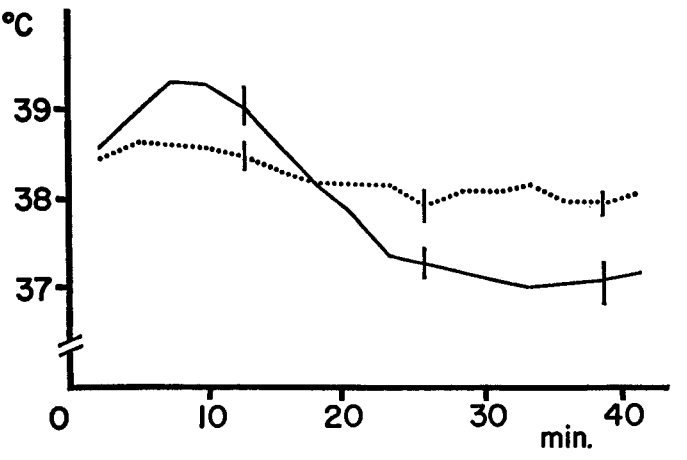

FIG. 1. Body temperature of mice kept at 29°C at various times following injection of 10 μmoles/kg of 5-methoxy-N,N-dimethyltryptamine (———) as compared to mice injected with saline (.....). Vertical lines are standard errors of the mean (N = 7).

transducer was fed into a Grass polygraph equipped with a unit integrator. In this manner it became possible to obtain a quantitative measure of the ballistic movements of the mouse in its restraining cage. By determining the amount of activity in the six minutes following intraperitoneal injection of various doses of a hallucinogen, we were able to obtain dose-response curves for a number of these compounds. These showed, for instance, that 5-methoxy-N,N-dimethyltryptamine was less potent in this system than LSD and more potent than N,N-dimethyltryptamine, which in turn was more potent than N,N-diethyltryptamine (Fig. 2).

Using this system Dr. La Rosa and I undertook a pharmacological investigation designed to cast some light on the possible mechanism of action of these compounds in producing this type of activity. The experimental design used was to select three groups of five mice, each chosen at random, and to pretreat two of these groups with a drug designed to alter monoamine function in the CNS. Then, after an appropriate lapse of time, one of the pretreated groups and the group given no pretreatment would be dosed with the hallucinogen, and the ballistographic activity of each animal would be recorded. An analysis of variances was applied to activity observed during the first six minutes following injection of the hallucinogen to determine whether the pretreatment had any significantly synergistic or inhibitory effect upon the action of the hallucinogen. In this manner it was possible to show (Table I), for instance, that pretreatment with *p*-chlorophenylalanine brings

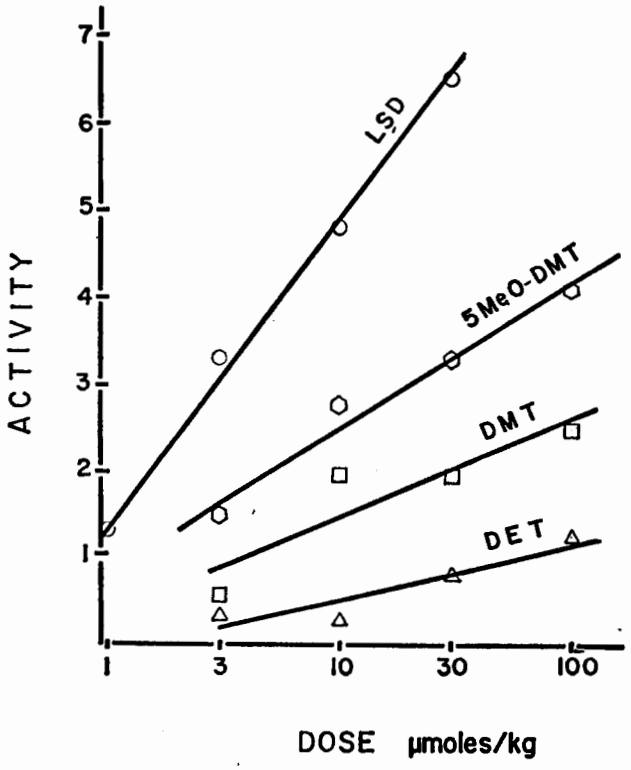

FIG. 2. Ballistographic activity (see text) of mice injected with various doses of LSD, 5-methoxy-N,N-dimethyltryptamine (5 MeO-DMT), dimethyltryptamine (DMT) and diethyltryptamine (DET).

about a significant increase in the activity observed following administration of 5-methoxy-N,N-dimethyltryptamine (Fig. 3) or LSD. A distinction should be drawn between the results of our interaction experiments and the conclusions that can be drawn from them. Thus, there is little doubt of the statistical significance of our findings and the high degree of correlation between the results obtained with two different hallucinogens. On the other hand, only one pretreatment time interval and, in most instances, a fixed dose of the pretreatment agent was employed. These times and doses were arrived at by review of the effects of these agents on monoamine function in the CNS as reported in the literature. It is possible that the use of different pretreatment times or doses would have led to somewhat different results. For instance, *p*-chlorophenylalanine in the pretreatment schedule used by us has been

TABLE I

The effect of pretreatment with various agents, considered to have an effect on brain 5-hydroxytryptamine function, on the increase in ballistographic activity (see text) is observed following administration of either LSD or 5-methoxy-N,N-dimethyltryptamine (5 MeO-DMT) to restrained mice.

Pretreatment			Hallucinogen		Effect of pretreatment on observed activity	
Agent	Dose mg/kg	Time hours	Compound	Dose μmoles/kg	Direction	Percent
p-Chlorophenylalanine	100	24, 48, 72	5 MeODMT	30	Potentiation	+ 67.0*
			LSD	3.3	Potentiation	+ 15.8*
5-Hydroxytryptophan	100	1	5 MeODMT	3	Inhibition	− 32.6*
			5 MeODMT	30	Inhibition	− 3.2
			LSD	3.3	Inhibition	− 25.4*
			LSD	10	Inhibition	− 24.3*
Reserpine	2	4	5 MeODMT	30	Inhibition	− 27.5*
			LSD	3.3	Inhibition	− 60.0*
			LSD	10	Inhibition	− 28.5*
Morphine	0.5	4	LSD	3.3	Inhibition	− 24.02*

* $P < 0.05$

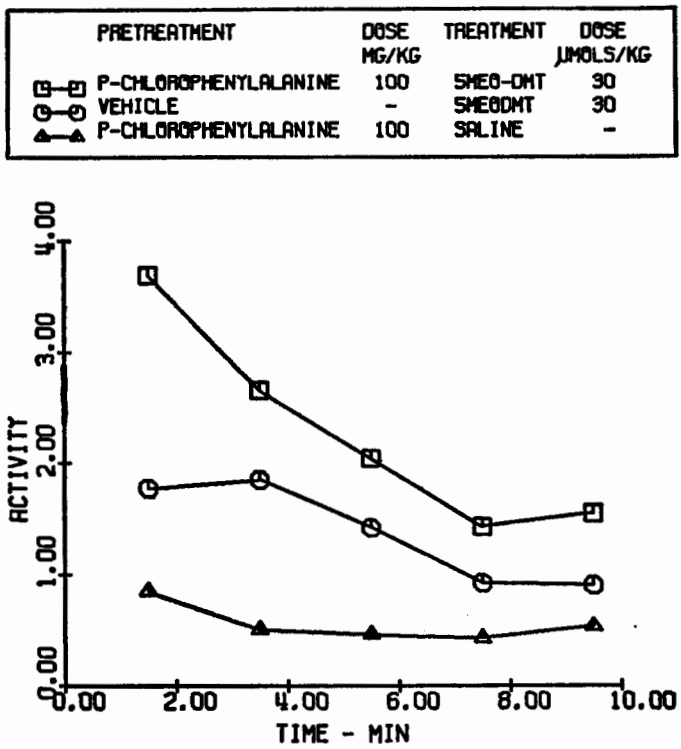

FIG. 3. Effect of pretreatment with *p*-chlorophenylalanine (100 µg/kg 24, 48 and 72 hours prior) on the ballistographic activity (see text) of mice injected with 5-methoxy-N,N-dimethyltryptamine (5 MeO-DMT).

shown by Koe and Weissman (1966) to deplete significantly brain 5-hydroxytryptamine in mice. This depletion results from a block of tryptophan hydroxylase, and thus an inhibition of 5-hydroxytryptamine synthesis (Jequier, 1967). It could therefore be postulated that *p*-chlorophenylalanine reduces the amount of 5-hydroxytryptamine reaching the receptor. Accordingly, the synergistic effect of this pretreatment on the action of the two hallucinogens could be considered to suggest that these may also act to reduce the amount of 5-hydroxytryptamine reaching its receptor. This possibility is enhanced by the results we obtained (Table I) upon pretreating animals with 5-hydroxytryptophan. Mice were pretreated with 100 mg/kg of 5-hydroxytryptophan one hour prior to the administration of the hallucinogen. This pretreatment brings about an increase in brain 5-hydroxytryptamine (Prockop *et al.*, 1959),

while the activity exhibited by mice thus pretreated was significantly lower than that of controls. This pretreatment resulted in a significant reduction in the activity seen following administration of 5-methoxy-N,N-dimethyltryptamine or LSD (Fig. 4). Here it could be argued that 5-hydroxytryptophan, by in-

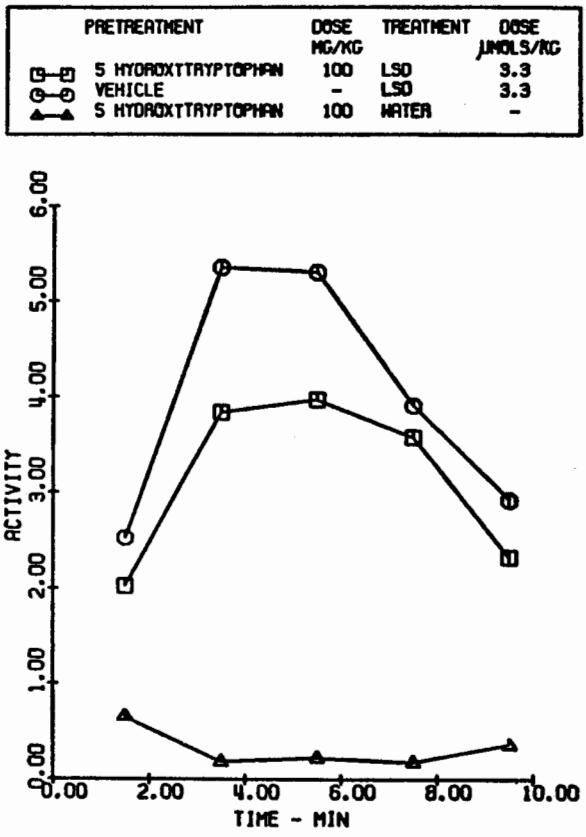

FIG. 4. Effect of a 1 hour pretreatment with 5-hydroxytryptophan on the ballistographic activity (see text) of mice injected with LSD.

creasing the local concentration of 5-hydroxytryptamine, may counteract an ability of the hallucinogen to reduce the amount of 5-hydroxytryptamine reaching the receptor. Similar arguments could be used to explain the ability of reserpine pretreatment to reduce the activity observed following administration of the hallucinogens (Fig. 5), since it has been postulated that reserpine acts

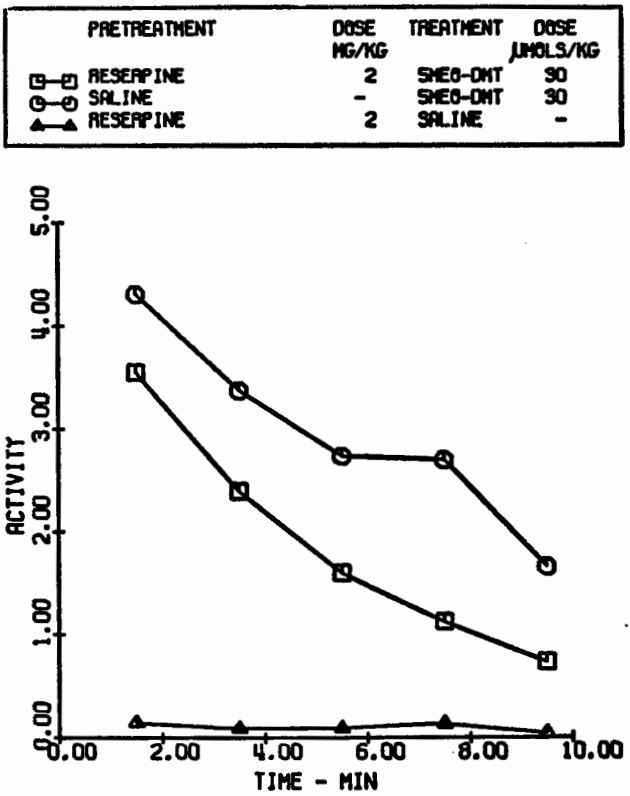

FIG. 5. Effect of a 4 hour pretreatment with reserpine on the ballistographic activity (see text) of mice injected with 5-methoxy-N,N-dimethyltryptamine (5 MeO-DMT).

by increasing the turnover of 5-hydroxytryptamine at its receptor (Brodie *et al.*, 1966). Finally, in view of a report by Way *et al.* (1968) that morphine enhances the turnover rate of brain 5-hydroxytryptamine, it is of interest that pretreatment with this agent also decreases significantly the activity seen following LSD administration (Table I).

We have also investigated the effect of pretreatment with agents known to influence brain catecholamine function. Thus disulfiram, a drug shown to inhibit dopamine-β-hydroxylase (Goldstein *et al.*, 1964; Musacchio *et al.*, 1964) and to cause an elevation in brain dopamine levels and a decrease in brain norepinephrine level (Goldstein and Nakajima, 1967), was also shown (Table II) by us to decrease significantly the activity observed following

TABLE II

The effect of pretreatment with various agents, considered to have an effect on brain catecholamine function, on the increase in ballistographic activity (see text) observed following administration of either LSD or 5-methoxy-N,N-dimethyltryptamine to restrained mice.

Pretreatment			Hallucinogen		Effect of pretreatment on observed activity	
Agent	Dose mg/kg	Time hours	Compound	Dose μmoles/kg	Direction	Percent
Disulfiram	400	12	5 MeODMT	30	Inhibition	− 24.4*
			LSD	10	Inhibition (trend)	− 11.4
Dihydroxyphenylalanine	200	0.25	5 MeODMT	30	Inhibition	− 30.1*
	600	0.25	5 MeODMT	30	Inhibition	− 83.4*
			LSD	3.3	Inhibition	− 71.2*
			LSD	10	Inhibition	− 70.0*
Dihydroxyphenylserine	1000	1	5 MeODMT	30	Potentiation	+ 52.6*
			LSD	3.3	N.S.	

* $P < 0.05$

5-methoxy-N,N-dimethyltryptamine administration. Fifteen minute pretreatment with *l*-dihydroxyphenylalanine (*l*-DOPA) also leads to a significant decrease in the activity observed following administration of either 5-methoxy-N,N-dimethyltryptamine (Fig. 6) or LSD. Everett and Wiegand (1962) have

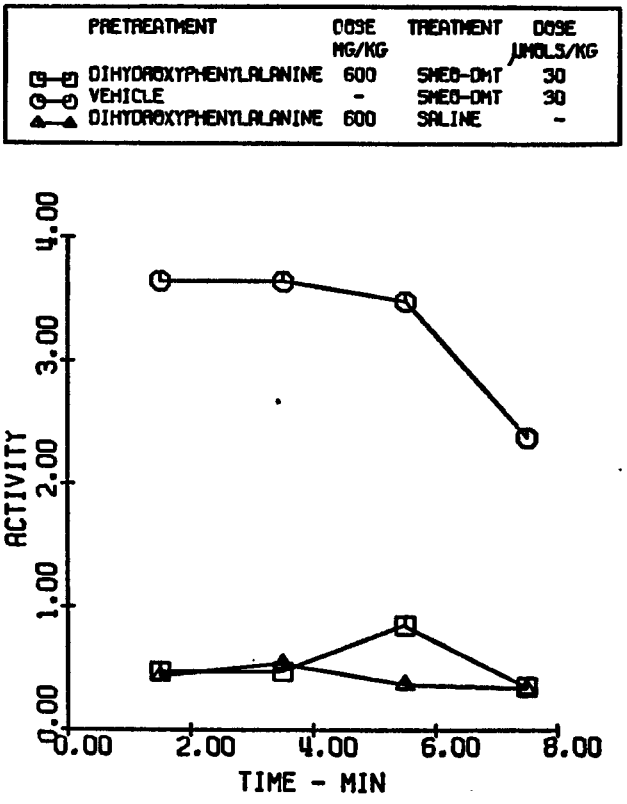

FIG. 6. Effect of a 15 minute pretreatment with dihydroxyphenylalanine on the ballistographic activity (see text) of mice injected with 5-methoxy-N,N-dimethyltryptamine (5 MeO-DMT).

shown that 30 minutes after *l*-DOPA administration there is a three-fold increase in brain dopamine in mice, while brain norepinephrine levels are but slightly increased. It appears reasonable, therefore, to attribute these effects of pretreatment with *l*-DOPA to the dopamine formed from it by decarboxylation, rather than to any norepinephrine that might be formed by the subsequent

β-hydroxylation. To test this further, we pretreated the animals with threo-3,4-dihydroxyphenylserine (DOPS) which on decarboxylation yields norepinephrine directly, and which in the dose and time of pretreatment used by us has been shown (Carlsson, 1964) to increase brain norepinephrine levels. In contrast to pretreatment with *l*-DOPA, pretreatment with DOPS did not bring about any decrease in the activity observed following the administration of either hallucinogen, but instead actually significantly increased the activity observed following 5-methoxy-N,N-dimethyltryptamine administration (Table II).

The one agent which has been shown conclusively to counteract the psychic effects of LSD in man is chlorpromazine (Isbell *et al.*, 1957). It was of interest to us therefore to determine whether it would have a similar effect in our test system. We find (Table III) that a one hour pretreatment with

TABLE III

Effect of pretreatment with p-*chlorophenylalanine on the increase in ballistographic activity (see text) observed following administration of either LSD or 5-methoxy-N,N-dimethyltryptamine (5 MeO-DMT to restrained mice.*

Hallucinogen	Dose μmoles/kg	Direction	Percent
5 MeODMT	30	Inhibition	− 38.3*
LSD	3.3	Inhibition	− 69.2*
LSD	10	Inhibition	− 18.9*

* $P < 0.05$

chlorpromazine significantly decreases the activity observed following administration of either 5-methoxy-N,N-dimethyltryptamine or LSD.

Finally, we have explored the effect of pretreatment with 2-bromo-LSD (BOL). The antagonism exhibited by BOL towards 5-hydroxtryptamine in isolated tissues, coupled with its inability to mimic the central effects of LSD (Cerletti and Rothlin, 1955), constitutes a major objection to the hypothesis (Gaddum, 1953) that the central effects of LSD are related to its ability to antagonize 5-hydroxytryptamine. In our test system, BOL by itself causes a significant decrease in activity over saline treated controls. Furthermore, pretreatment with BOL significantly diminishes the activity observed following LSD administration (Table IV). Although the dose of BOL was ten times as large as that of LSD, these results are nonetheless rather striking, and suggest that it may be worthwhile to reevaluate the central pharmacology of BOL.

TABLE IV

The effect of pretreatment with 2-bromo-LSD (BOL) on the increase in ballistographic activity (see text) observed following administration of LSD to restrained mice.

Dose μmoles/kg	Hallucinogen	Effect of pretreatment on tremor activity	
		Direction	Percent
3	LSD	inhibition	-80.6*

* $P < 0.05$

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DISCUSSION

DR. LEHRER: I wonder if anyone could tell me what an effective dose of LSD for the mouse would be. The doses used in these experiments were 1 to 3 mg/kg; in terms of man they seem enormous.

DR. AGHAJANIAN: In rats 50 to 100 μg/kg i.v. is an effective dose in terms of the electrophysiological activity.

A VOICE: You have to consider what dose for what effect, and what systematic data you get thereby. The half-life of a drug varies sc vastly among animals that this is also significant.

DR. GESSNER: I might bring your attention to the fact that in 1962 a paper was published in *Science* stating that a dose which, on the basis of its effects in monkeys and cats wasn't all that large, when administered to an elephant proved rapidly fatal. As the size of the animal decreases the doses you have to give to observe similar effects are larger and larger.

DR. OSMOND: That was extrapolated on the basis of body weight. Not on the basis of body size.

DR. GESSNER: You mean body surface. If you extrapolate down to the mouse in terms of body surface, I don't think these doses are so high.

DR. DOMINO: I think Dr. Gessner's work emphasizes the fact that in addition to dose-effect and dose-duration problems, another important aspect is the end-point of hallucinogenic effects in animals. Thus, depression of tremor may not be a good end-point. I wonder if in some of these drug interactions we wouldn't be better off to ask clinical pharmacologists to try these things in man. I don't know how to interpret your DOPA experiment since we do know that DOPA when given to animals produces a reduction in motor activity which in itself would antagonize the tremor.

DR. GESSNER: In our mice the doses of DOPA we gave were not sedative. With respect to your other remarks, I am with you 100 percent. To determine by what mechanism these compounds cause hallucinations in man their study in man will be necessary. The question remains as to who will undertake this work. For instance, we have synthesized a number of bufotenine esters. Knowledge of their structure-activity relationships in man would be extremely informative. Yet they are just sitting in our safe; we can't do this work ourselves.

Incidentally, while I am on the subject, after Dr. Holmstedt showed that 5-methoxy-N,N-dimethyltryptamine was a major component of the hallucinogenic *epéna* snuff, there have been various statements in the literature that it is hallucinogenic in man. I wonder if anybody knows whether it has actually been given as the pure compound to man and whether under those conditions it proves hallucinogenic. If so, it would be interesting to put it on the record.

DR. SHULGIN: We have it in clinical trial now. It is much more active than dimethyltryptamine. It is much less active than LSD and it is only active parenterally, as is the case with DMT. This is about all I can say.

DR. SNYDER: How does it compare with psilocin?

DR. SHULGIN: It is more active than psilocin, but I can't say how much more with any confidence.

DR. GESSNER: This is all in accord with our data.

DR. SHULGIN: We used 5 to 10 mg of 5-methoxy-N,N-dimethyltryptamine; perhaps even a lower dose can be used.

DR. HOLMSTEDT: I have not tested the pure compound, but I have tested in the field the *epéna* the South American Indians use, and that takes effect very quickly, within 30 seconds if you inhale it. I took back with me the same material and analyzed it. It contained 11 percent alkaloids, out of which about 10 percent were 5-methoxy-N,N-dimethyltryptamine.

DR. GESSNER: May I ask another question of those who are knowledgeable? Dr. Richard Alpert has told me that people who use dimethyltryptamine repeatedly over a short period of time do show tremor. Has anybody else seen this?

DR. HOLMSTEDT: This is not something you see when the Indians take this. The somatic symptoms are: staggering gait, characteristic facial expression, and profuse sweating. Not tremor. I have not seen that.

DR. DIAMOND: I have seen tremor with 100 μg of LSD in an experienced user, someone who has taken over 1500 doses. It has to be amplified to be seen. It was very rapid, very fine, and it came at about the same time as pupillary dilatation and an increase in pulse rate.

DR. DOMINO: I would like to raise the question whether 5-methoxy-N,N-dimethyltryptamine acts like [illegible] two different types of receptors: the receptors D and M, as described by Gaddum, in the intestine. In his experiment, both morphine and dibenzylene blocked the actions of 5-HT. Your data would suggest that both receptors are involved because morphine, as well as dibenzylene, were antagonistic to tremorogenic effect of 5-methoxy-N,N-dimethyltryptamine.

DR. GESSNER: You refer to the D and M receptors in the guinea pig ileum. One cannot extend those concepts to other tissues. It does not work.

DR. DOMINO: Can one extend this concept to rat stomach fundus?

DR. GESSNER: No, one cannot. The rat stomach fundus is different, it has no M receptors.

DR. DOMINO: You mean morphine does not block the action of 5-HT on the gut?

DR. GESSNER: I do not know, but the M receptors in the guinea pig ileum are blocked by atropine. Atropine, however, is without effect on the ability of 5-HT and other tryptamines to contract the rat stomach fundus.

DR. KOPIN: I would like to ask you about the interpretations of the results of the experiments you reported. Can you tell me if you could distinguish between an animal that is struggling and an animal with tremor, and can you distinguish the various types of tremor? Clinically there are certainly many types of tremors that one sees in patients, and conceivably tremors could be of different types in animals as well.

In interpretation of drug effects, especially with something like brom-LSD (BOL) and LSD, where the structures are very closely related, one need not

assume that they interact at the same receptor. They might react with a transport system.

DR. GESSNER: We thought of that.

DR. KOPIN: There is a whole series of variables in drug distribution and metabolism and interference with access that should be considered when you are dealing with the action of one drug on another. I am sure you have thought of them, but these have not yet entered the discussion. I thought that this might be an appropriate time to bring them up.

DR. GESSNER: I think the first point to make clear is that the interpretations which are given are obviously given with the thought of trying to piece the thing together somehow. They are not more than informed guesses or working hypotheses. The first and simplest hypothesis, in terms of the interaction of drugs, is that they interact at the same receptor. However, with BOL, this appears to be a low probability hypothesis because we know that both 5-methoxy-N,N-dimethyltryptamine and BOL can act on a 5-HT receptor by inhibiting it. So the possibility that pretreatment with BOL somehow blocks the access of LSD to whatever receptor it acts on appears to be a more reasonable hypothesis. To test it we administered LSD first and BOL afterwards. BOL reversed the effects of LSD. It does not appear therefore that this interaction is due to BOL blocking the passage of LSD to its site of action. I don't have an explanation.

DR. WEST: Dr. Holmstedt, can you explain the metabolism of our compound?

DR. HOLMSTEDT: Yes, but I would like to discuss this last question first. I don't think, Dr. Kopin, there are too many clinical kinds of tremor. I would appreciate the opinion of the clinicians present here, but as I have read, tremor is very constant among various animal species. Actually one should not speak of tremor because Dr. Gessner is not recording tremor, and he said so. I hope he does not write "tremor" in his paper. One can isolate tremor frequencies. In most cases and in most animals, tremor has a frequency between approximately 15 to 30 cycles per second; one could insert a filter in the recording machine and largely remove the spontaneous movements of the animals, *i.e.,* the excitation which isn't due to tremor. It has been said that tremor is the oldest primitive kind of movement. You find it in jellyfish and throughout the animal species, but there is one notable exception, and this is the tremor in Parkinson's disease, which can go below five cycles per second, unluckily for the experiments of pharmacologists.

DR. GESSNER: Well, I wanted to get to the term "tremor." I will say that there are certainly different types of tremors. For instance, carbachol causes a tremor which is blocked by atropine and is inhibited by norepinephrine. I believe Dr. Holmstedt tried blocking the "tremor" from 5-methoxy-

N,N-dimethyltryptamine with atropine and it didn't work. But you can block it.

DR. HOLMSTEDT: You can block it with chlorpromazine.

Since I probably shall not have time to go into this during my own presentation, perhaps you would now like to hear what happens to this compound in the metabolism of the rat.

We gave 5-methoxy-N,N-dimethyltryptamine to rats in doses of five, ten, and 70 mg/kg, which are huge doses. Now, several things happened here. It becomes converted to 5-methoxyindoleacetic acid. There is a portion of it which goes to bufotenine by O-demethylation. This bufotenine is then metabolized, either to 5-hydroxyindoleacetic acid or to the corresponding alcohol. A certain amount of the compound, between six and twelve percent, is excreted unchanged. There is a slight amount of bufotenine, but the interesting thing is that when you step up the dose, much more is converted to the 5-methoxyindoleacetic acid than to these other compounds, relatively speaking. No 5-methoxy-6-hydroxy compound is formed.

A VOICE: This is in reference to tremor that one can see. One kind of tremor is the shivering that one sees with the onset of hyperthermia, and particularly since it is correlated with the rising phase of temperature. I wonder whether it is that kind of shivering that is seen here. Of course, there are other kinds of tremors in man. I don't know about animals. You have the epinephrine-type tremor of outstretched extremities. It is very different from the kind of thing you see in Parkinson's disease, of course, and the kind of tremors one sees with muscle fatigue, for example, or those initiated at the cord level. So there are many different modes of producing tremor from central mechanisms.

DR. GESSNER: It is still a way of measuring the effect of these drugs, and if it is due to hyperthermia and that is correlated with the hallucinogenic properties of these agents in man, we are still on similar ground.