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Structure-activity Relationship Studies on Mescaline: The Effect of Dimethoxyphenylethylamine and N:N-dimethyl Mescaline on the Conditioned Avoidance Response in the Rat

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With 7 Figures in the Text

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The effect of mescaline on the conditioned avoidance response has been described in a previous communication (SMYTHIES and SYKES 1964). It was found that the response to the drug was characterised mainly by its biphasic nature; thus, an inhibitory phase was followed after about 40 min by an excitatory phase. At low dose levels there was a tendency for the inhibitory phase to be reduced in strength or to vanish altogether, while the excitatory phase remained marked. There was also wide variation in sensitivity to the drug between individuals. This work provides a base-line for structure-activity relationship studies of the chemical relatives of mescaline, so that it should be possible to determine to what extent alterations of the molecular structure of this compound affect the biological activity.

Two compounds have been investigated in this current study, 3:4-dimethoxyphenylethylamine and N:N dimethyl mescaline. Dimethoxyphenylethylamine is of particular interest at present, following several recent reports (FRIEDHOFF and VAN WINKLE 1962; TAKESADA et al. 1963; SEN and MCGEER 1964; KUEHL et al. 1964; BOURDILLON 1965; HORWITT 1965) that this substance is excreted as an abnormal metabolite in the urine of some schizophrenic patients. There have been no previous reports of its activity using a reliable behavioural test.

The second compound, N:N-dimethyl mescaline, was chosen so that the effect of increasing the number of methyl groups could be observed. It was thought that there might be a similarity in action between this substance and the strongly hallucinogenic N-dimethyl derivatives of tryptamine, for example, N:N-dimethyl tryptamine and psilocybin.

Method

Subjects

Twelve experimental naive male hooded rats, supplied by the National Institute of Medical Research, were used in this study. The animals were approximately 22 weeks old at the beginning of the experiment, and were allowed food and water ad libitum.

Apparatus

A modified Levine Shuttle box was used; this has been described in detail elsewhere (SMYTHIES and SYKES 1964). An animal was able to terminate either the conditioned stimulus (CS) or the unconditioned stimulus (US) by crossing from one compartment to the other.

The inter-trial intervals and the duration of the sound and shock were controlled automatically by a programming unit placed in an adjacent room.

Procedure

The procedure has been described fully in an earlier report (SMYTHIES and SYKES 1964) but will be summarised briefly here. The basic response required of an animal in the test situation was a cross from one side of the box to the other in response to a given stimulus. The conditioned stimulus or CS (a buzzer) sounded for five seconds, at the end of which time the unconditioned stimulus or US (electric shock of 1.0 m. a.) was presented if the animal had failed to respond to the CS. Each experimental period of two hours consisted of seven runs of 20 trials each, the runs being separated by a time interval of 5 min. The results were measured as follows: the number of shocks received (escape responses) and hence the number of shocks avoided (avoidance responses), the number of crossings made (an activity measure) and the reaction time, which is the interval between the onset of the CS and its termination by the animal. After training to a criterion of 80—85 % avoidance, intraperitoneal injections of either drug or saline were given after the first 40 trials, i. e. after the first two runs of 20 trials each. The experiment then continued as before.

In the first series, dimethoxyphenylethylamine was administered to 8 animals at three dose levels (25, 50 and 100 mg/kg). These doses were given at fortnightly intervals in a Latin square design. The intervals were introduced to allow any tolerance to disperse, since it has been shown that with mescaline, an injection of the drug every two weeks does not give rise to the development of tolerance.

In the second series, four animals received N:N-dimethyl mescaline. Three dose levels of 25, 50, and 100 mg/kg were used, and were given at intervals of two weeks, again using a Latin square design. As before, the results for each run of 20 trials are expressed in D-$\bar{S}$ scores, or the difference between the drug score and the mean of the pre-drug and post-drug

saline scores. The levels of drugs given were chosen following pilot studies with varying doses.

Analysis of Results. Since the reaction times of an animal during a saline run vary to some extent from day to day, and since there is also variation between individuals, non-parametric statistics were used.

Any difference between S_1 and S_2 was also evaluated by Wilcoxon's method for paired replicates for three different series of eight animals (i. e. pre- and postmescaline, DMPE and DMM) selected at random from the series. In no case did the test reveal any significant difference between S_1 and S_2. In these cases the drug effect was significant when evaluated against each saline individually as well as against the mean of the salines. Reaction times were measured in tenths of a second by means of a print-out counter.

The D—$\bar{S}$ scores for each animal were obtained were obtained as follows:

If x = each individual drug reaction time

y = each individual pre-drug saline reaction time

z = each individual post-drug saline reaction time

Then

$$D-\bar{S} = \Sigma_{20}^{0} \times - \sum_{20}^{0} \frac{y+z}{2}$$

Therefore, each point on the graphs $= \dfrac{\Sigma_{N}^{0}(E-\bar{S})}{N}$

where N = number of animals used in that experiment.

The significance of each graph was tested by means of Wilcoxon's Non-Parametric Paired Replicates test.

Results

The effect of dimethoxyphenylethylamine on the CAR at 25, 50, and 100 mg/kg is shown in Figs. 1, 2, and 3. At each dose level there are two notable features:

(a) the CAR is depressed, or even totally inhibited, with little sign of the later excitatory action of mescaline, and

(b) the degree of inhibition has in some animals a bimodal distribution. This latter effect is not due to compounding the results from two populations of rats, one of which reacts earlier than the other; this "double hump" is present in the individual record from every rat in this series, but only in a proportion in another population to be reported on in a subsequent paper. The peaks of inhibition occur at approximately 25 and 65 min, although there is some individual variation. Dimethoxyphenylethylamine on this test was about one half as active as mescaline in inhibiting the CAR, a result which supports the findings of Smythies and Levy (1960).

Behavioural observations showed that, under the influence of this substance, the rat tended to crouch at the end of the box; there was little

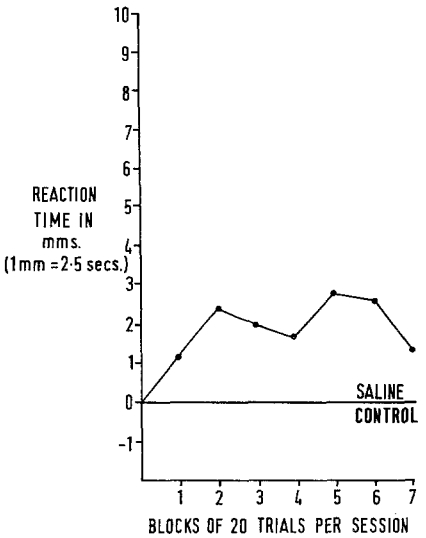

Fig. 1

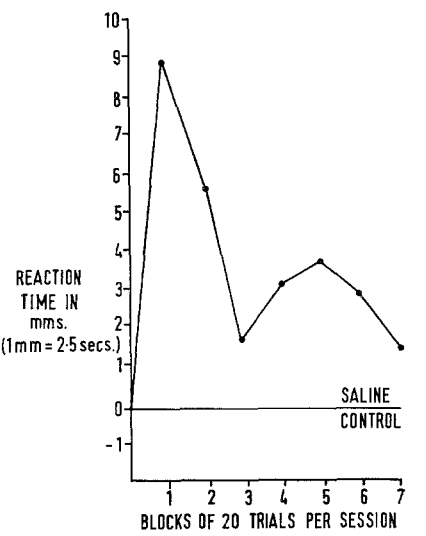

Fig. 2

Fig. 1. The effect of 25 mg/kg of dimethoxyphenylethylamine upon the reaction time for 8 rats expressed as (D—$\bar{S}$) scores ($p < 0.001$ for total curves)

Fig. 2. The effect of 50 mg/kg of dimethoxyphenylethylamine upon the reaction time for 8 rats expressed as (D—$\bar{S}$) scores ($p < 0.001$)

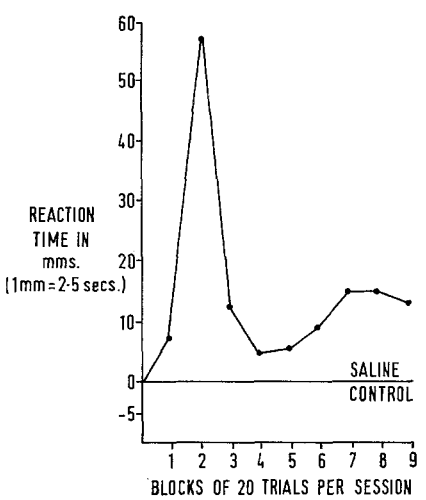

Fig. 3

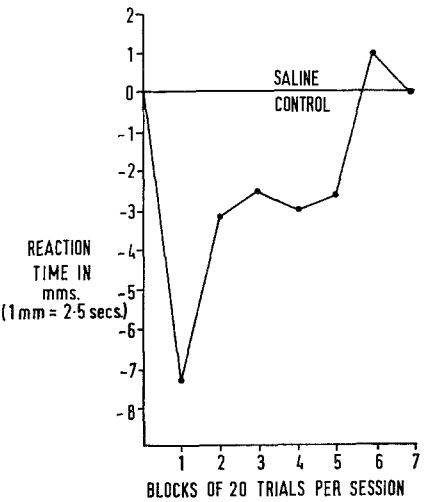

Fig. 4

Fig. 3. The effect of 100 mg/kg of dimethoxyphenylethylamine upon the reaction time for 1 rat expressed as (D—$\bar{S}$) scores ($p < 0.01$)

Fig. 4. The effect of 25 mg/kg of N:N-dimethyl mescaline upon the reaction time for 4 rats expressed as (D—$\bar{S}$) scores ($p < 0.01$)

extra movement, but no signs of either paralysis or ataxia. The onset of the CS produced an increase in the rate of breathing, but the CAR was usually retarded or absent. The escape response to the US was not affected.

In the case of N:N dimethyl mescaline, Figs. 4, 5, and 6 show that the effect it has on the CAR is quite different to that of both either mescaline or dimethoxyphenylethylamine. There was marked excitation

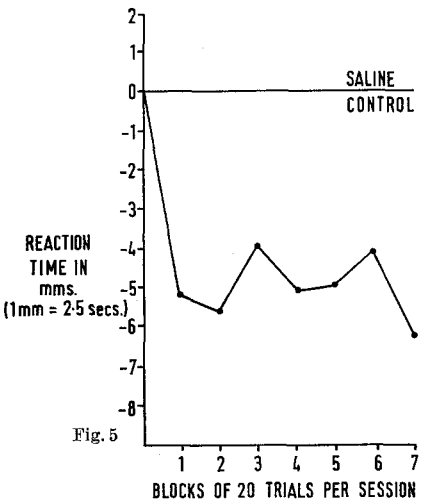

Fig. 5

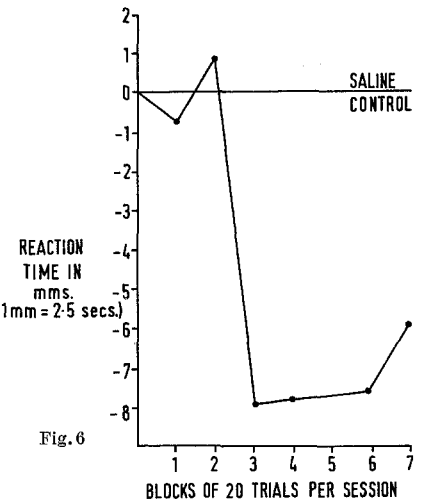

Fig. 6

Fig. 5. The effect of 50 mg/kg of N:N-dimethyl mescaline upon the reaction time for 4 rats expressed as (D—$\bar{S}$) scores ($p < 0.001$)

Fig. 6. The effect of 100 mg/kg of N:N-dimethyl mescaline upon the reaction time for 4 rats expressed as (D—$\bar{S}$) scores ($p < 0.001$)

(similar to that produced by amphetamine) and any inhibition of the CAR was negligible, the chief feature being that the onset of the excitation was delayed as the dose increased. The activity level, as measured by the number of inter-trial crosses, and the amount of exploratory behaviour, as observed visually, rose sharply.

Discussion

The effect of dimethoxyphenylethylamine (or mescaline without the 5-methoxy group) is interesting. This effect is selective, since the CAR is affected, while the UCR (or escape response) is not. The two apparent peaks of action, the first occurring at approximately 25 and the second at about 65 min, suggest that it is possible that the drug itself is directly responsible for the first peak, whereas some metabolite is responsible for the second peak. In view of the current interest in dimethoxyphenylethylamine in many laboratories, its metabolism could be determined, and its metabolites could then be investigated for their behavioural effect to test this hypothesis.

Although this apparent bimodal effect of dimethoxyphenylethylamine is one that we have seen reported for no other drug, SMYTHIES (1960), working at the Worcester Foundation on the effect of plasma protein fractions from schizophrenic patients on a mouse behaviour test, noted a very similar effect, as shown in Fig. 7. The test was a modification for mice of the Winter and Flataker test, and a similar bimodal curve is noticeable. The difference in time course may be accounted for by the different metabolic rates of rats and mice. These results suggest that the active fraction in toxic schizophrenic serum, shown by the Worcester group to be a small molecule, may possibly be dimethoxyphenylethylamine tied loosely to globulin. At any rate, this working hypothesis suggests experiments to confirm or refute it.

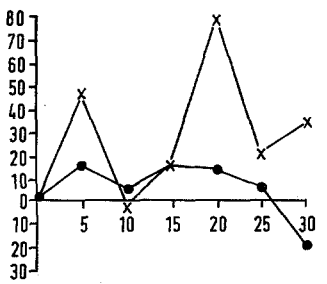

Fig. 7. Mean change in climbing time per set of 20 mice expressed as score using plasma fractions from schizophrenic patients minus score using plasma fraction from normal controls. Ordinate: mean increase in climbing time in seconds; Abscissa: time after injection in minutes. × plasma from schizophrenic whose plasma was most toxic to rats (BERGEN et al. 1960) using the WINTER and FLATAKER test. • random selection of schizophrenic plasmas

N:N dimethyl mescaline was investigated to explore the idea that increasing methylation accentuates behaviour-disrupting potency, particulary in view of the strongly hallucinogenic effects of N:N dimethyl derivatives of tryptamine and 4- and 5-hydroxytryptamine. The effect of this compound was not a merely quantitative increase in mescaline-like activity, but rather a qualitatively different result, in that the excitatory effect was augmented, whereas the inhibitory effect (on the CAR) did not appear.

In order to be able to give a wider interpretation to these results, it is necessary to determine (a) whether all hallucinogens induce a biphasic reaction under these experimental conditions, and (b) whether drugs that do not — for example the two analogues reported on here — are hallucinogenic in humans. One would predict that N:N dimethyl mescaline would have a weak amphetamine-like effect, and that dimethoxyphenylethylamine is not hallucinogenic.

Summary

Structure-activity relationship studies on two mescaline analogues have been conducted, using rats trained on a CAR buzzer-shock schedule. 3:4-dimethoxyphenylethylamine has been shown to depress the CAR with an apparent bimodal distribution of peak activities, in contrast to the biphasic inhibitory and excitatory effect of mescaline. The effect of this dimethoxy compound is similar to that previously reported for a

protein fraction from schizophrenic plasma; this is of particular interest as six groups have recently reported the isolation of this compound from schizophrenic urine.

The effect of N:N-dimethylation of mescaline is to abolish its inhibitory action on the CAR and to augment its excitant action. The significance of these findings is discussed.

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