STRUCTURE–ACTIVITY RELATIONSHIPS OF MESCALINE

J. R. SMYTHIES and E. A. SYKES

Department of Psychological Medicine, University of Edinburgh, Scotland

IT IS generally agreed that mescaline produces a state of psychosis that has certain similarities to some aspects of the schizophrenic syndrome. It would therefore be of some theoretical interest for biological psychiatry to know on what biochemical system mescaline exerts its effects. One way of studying this is by the structure–activity relationships (SAR) method. We have explored the effect of various analogs of mescaline on animal behaviour. In our early work we used the Winter and Flataker test; latterly we have employed the conditioned-avoidance response (CAR).

Our first task was to determine the effects of mescaline itself on the CAR as the base-line for our subsequent studies. The literature at that date was somewhat confusing. Cook and Weidley (1957) using a pole-jump escape technique had failed to block the CAR in rats with dosages up to 100 mg/kg. Chorover (1960), however, using a shuttle box extinguished the CAR with a dosage of 25 mg/kg.

In our experiments we have used a shuttle box with a buzzer as the conditioned stimulus (CS) and shock as the unconditioned stimulus (UCS). The buzzer-shock interval was 5 sec and the rat had to learn to cross from one compartment of the box to the other within these 5 sec to avoid the shock. Normally this was quickly learned and the rat would cross with a regular buzzer-cross reaction time (RT) of some 4 sec. This leaves scope for detecting both an increase in RT (as produced by CPZ) or a decrease in RT (as produced typically by amphetamine). Each 2-hr experimental period consisted of seven runs of twenty trials each. The trials were randomly spaced and occupied 8 min, and were followed by 5 min time-out. We recorded the number of shocks received and the RT. The injection (of drug or saline) was given between the second and third runs. The first two runs in any experiment were discarded as the animals took some minutes to adapt to the experimental situation (and hence a few shocks were delivered before the CR and RT became stabilized). A series of saline controls was followed by a drug run and then another saline control. The results are expressed in D–S scores, i.e. as the difference between the drug score and the mean of the preceding and following saline scores for each "run" of twenty trials. The statistical significance of the results was assessed by Wilcoxon's non-parametric ranking method for paired replicates.

RESULTS

Mescaline has a biphasic effect on CAR performance. Different animals show widely different degrees of susceptibility to the drug. At 25 mg/kg the drug first inhibits the CAR (increased RT and shocks). This is followed by a *decrease* in RT (Fig. 1). Some animals are more sensitive than others, and Fig. 2 shows the reaction of the most sensitive (n = 4), and Fig. 3 that of the least sensitive (n = 4). At 12·5 mg/kg the inhibitory phase is less marked or absent and the excitatory phase is more marked. At these dosage levels there were no signs of ataxia or "toxic" effects of the drug. This was confirmed by

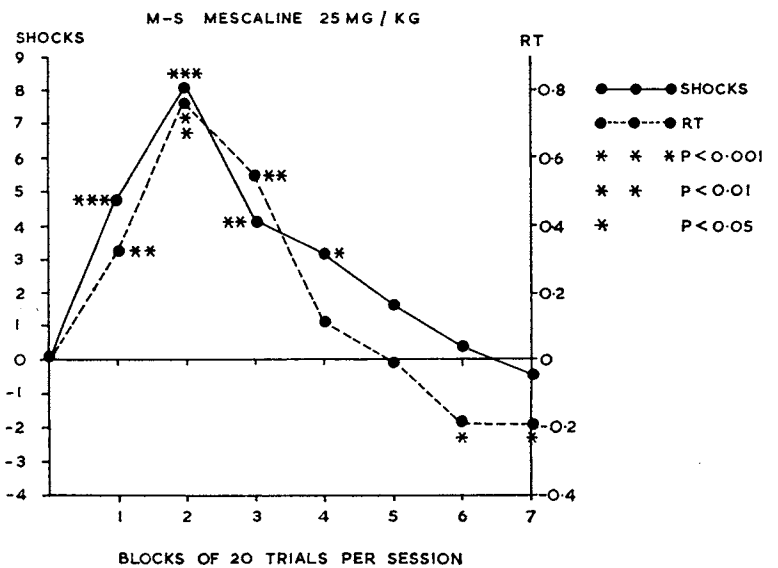


FIG. 1. The effect of mescaline 25 mg/kg on shocks and reaction time (RT: expressed in mm of kymograph paper; 1 mm = 2·5 sec).

the Rushton–Steinberg test for ataxia which showed no ataxia at 25 mg/kg. At 50 mg/kg, however, signs of paralysis of the hind legs appeared, so it seems that 25 mg/kg should normally be the maximum dose.

One first analog was trimethoxyphenylalanine (Fig. 4) which we supposed might cross the blood-brain barrier more easily than mescaline. However, it proved almost completely inactive even in a dosage of 100 mg/kg. This may be correlated with the report (Blaschko, 1965) that this substance is not a substrate for decarboxylase.

We then investigated two compounds: 3–4,dimethoxyphenylethylamine (d.m.p.e.) and N,N-dimethylmescaline (Fig. 4). The former was chosen because of its current interest as a possible abnormal metabolite in schizophrenia. Figures 5–7 show its effect on the CAR at 25, 50 and 100 mg/kg.

At each dose level there were two notable features about its effects: (i) it inhibited the CAR with little sign of the later excitatory action of mescaline, and (ii) the degree of inhibition has a bimodal distribution. This is not due to compounding the results from two populations of rats, one of which reacts earlier than the other, as Fig. 8 indicates that this "double hump" is present in the individual records from every rat. This suggests that the action of the drug itself may be followed by that of some metabolite. It is an effect that we

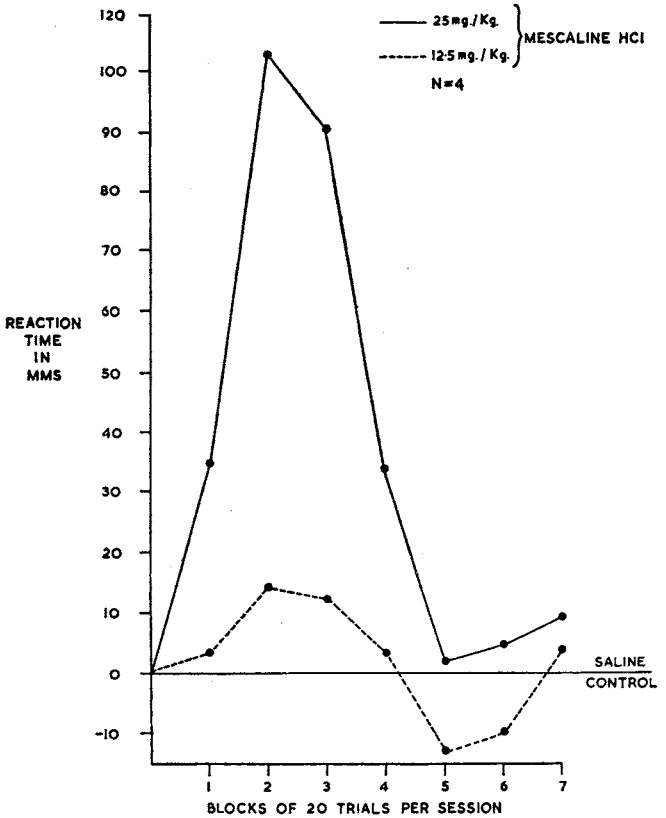


FIG. 2. The effect of two doses of mescaline on RT: Class I animals (n = 4).

have seen reported for no other drug. However, one of us (*in* Berger *et al.*, 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. 9. The test was a modification for mice of the Winter and Flataker test, and the same bimodal curve is noticeable. The difference in time course may be accounted for by the different metabolic rates of rats and mice. This suggests that the active fraction in toxic schizophrenic serum, shown by the Worcester group to be a small molecule, may

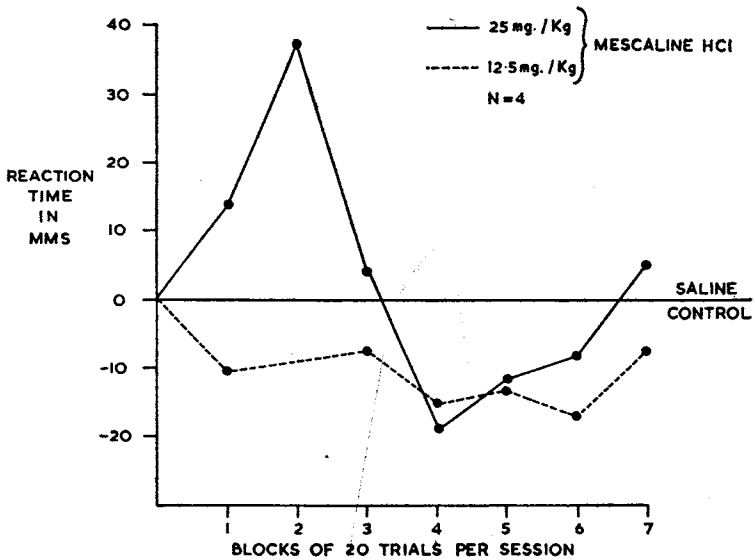


FIG. 3. The effect of two doses of mescaline on RT: Class II animals ($n = 4$).

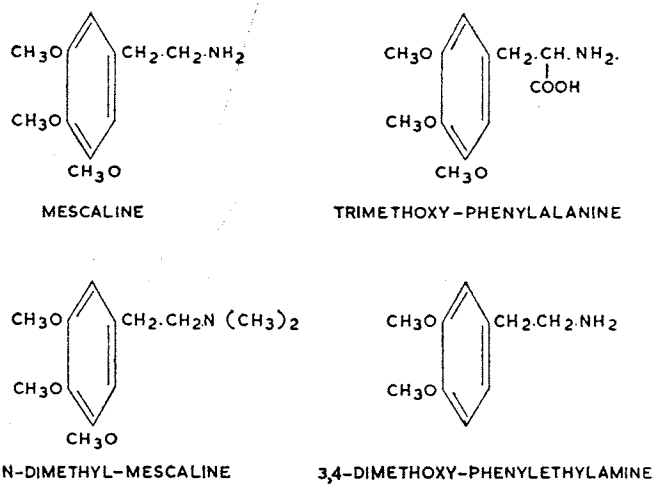


FIG. 4. Structural formulae of mescaline and some of its analogs.

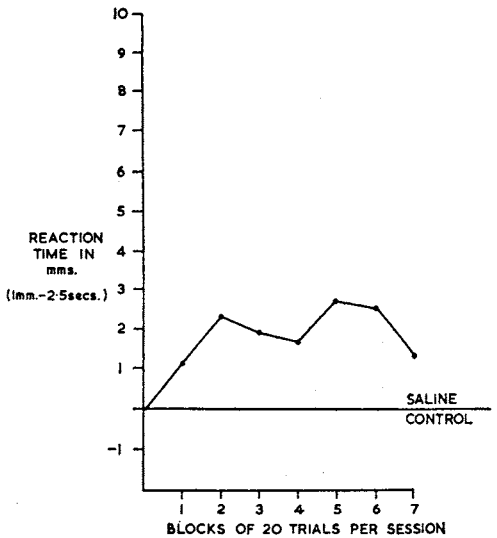


FIG. 5. The effect of dimethoxyphenylethylamine (d.m.p.e.) on RT: 25 mg/kg ($n = 8$).

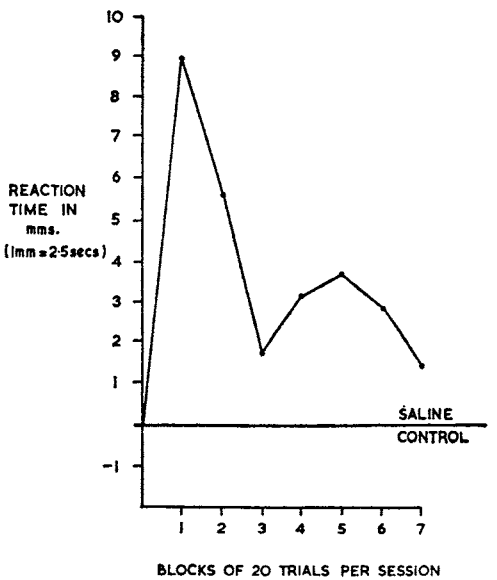


FIG. 6. The effect of dimethoxyphenylethylamine (d.m.p.e.) on RT: 50 mg/kg ($n = 8$).

possibly be d.m.p.e. (tied loosely to the globulin). At any rate, this working hypothesis suggests experiments to confirm or refute it. D.m.p.e. on this test was about one-half as active as mescaline in inhibiting the CAR, a result obtained in previous work (Smythies and Levy, 1960). A dose of 12·5 mg/kg had no observable effect, neither excitatory nor inhibitory.

We investigated N,N-dimethylmescaline to explore the idea that increasing methylation increases behaviour-disrupting potency, and keeping the strongly hallucinogenic effects of N,N-dimethyl derivatives of tryptamine and 4- and 5-

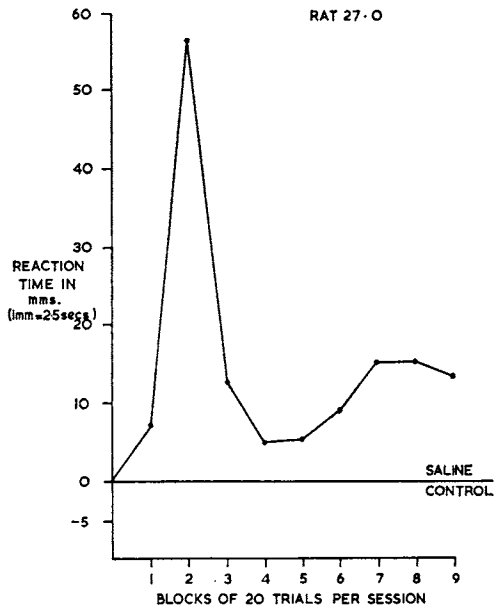


FIG. 7. The effect of dimethoxyphenylethylamine (d.m.p.e.) on RT: 100 mg/kg ($n = 1$).

hydroxytryptamine in mind. Figs. 10–12 show the result at 25, 50 and 100 mg/kg. These results indicate that this compound has a strong "excitatory" (amphetamine-like) effect on rat behaviour, decreasing the RT, but it has none of mescaline's inhibitory effect on the CAR even at 100 mg/kg.

Our next experiments were directed towards estimating the degree of cross-tolerance between mescaline and these two compounds as measured by this test. Our procedure here was to give drug *X* alone to a group of animals. Two weeks later 25 mg/kg mescaline was given every day for 7 days, followed by a second dose of *X*. In this period marked tolerance develops to mescaline (Figs. 13, 14). The primary inhibition in the CAR is abolished or greatly attenuated (depending on the initial sensibility of the rat), whereas the second "excitatory phase" becomes more prominent or unmarked. This differential effect of tolerance on the two actions of mescaline is itself of interest.

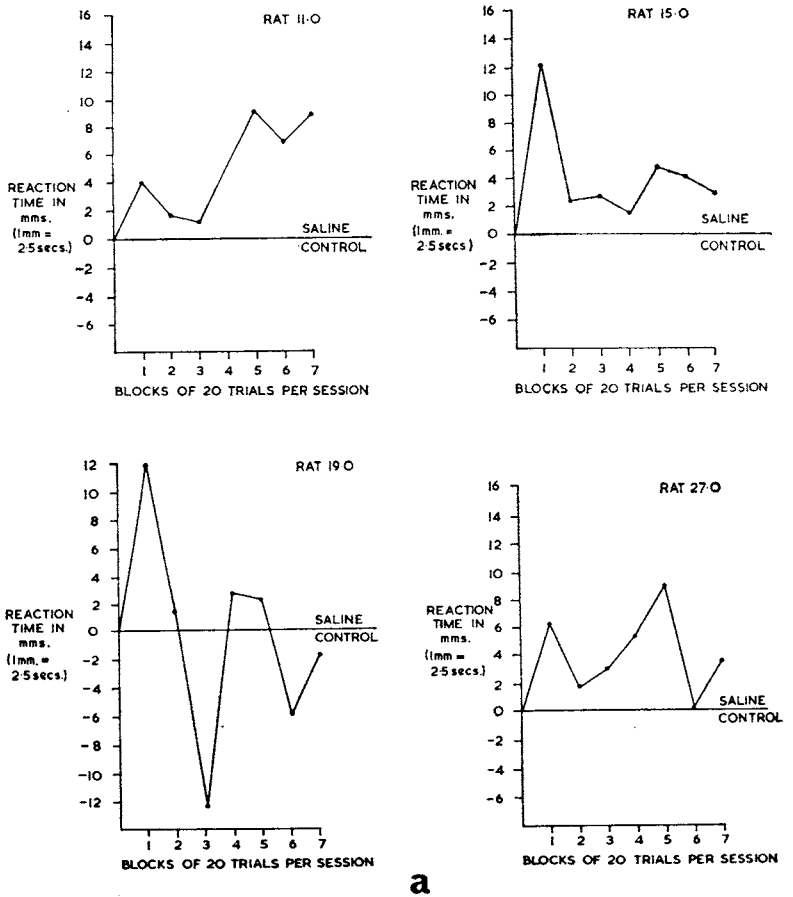
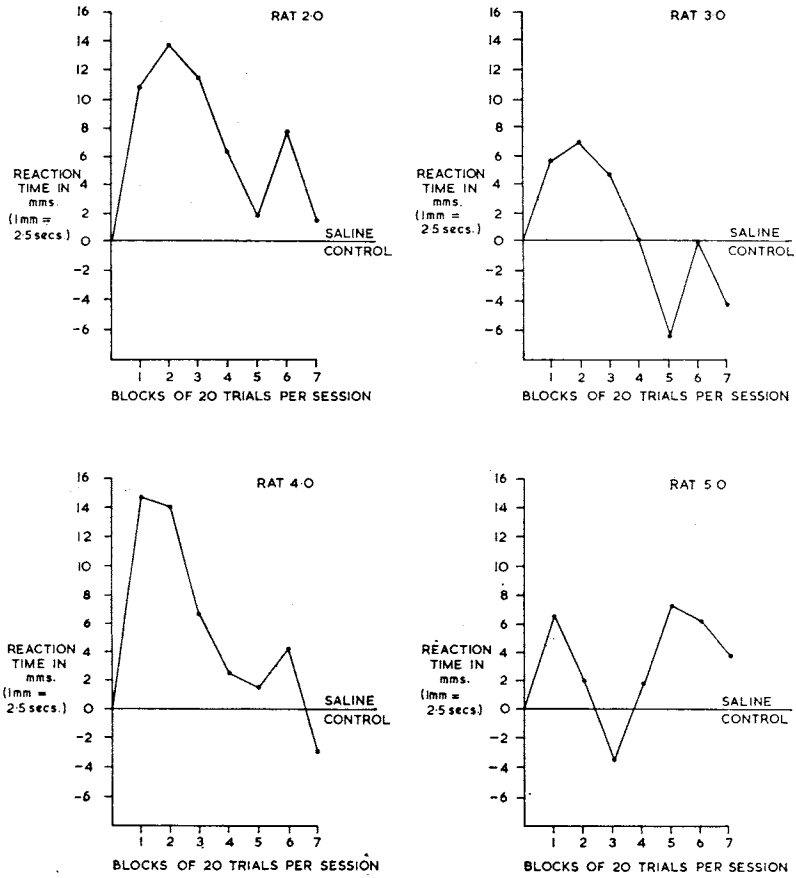


FIG. 8 (a, b). Individual reaction times to d.m.p.e. for eight rats.


RAT 2·0
RAT 3·0
RAT 4·0
RAT 5·0
REACTION TIME IN mms. (1mm = 2·5 secs.)
SALINE CONTROL
BLOCKS OF 20 TRIALS PER SESSION
16
14
12
10
8
6
4
2
0
-2
-4
-6
1 2 3 4 5 6 7

b

FIG. 8 (cont.)

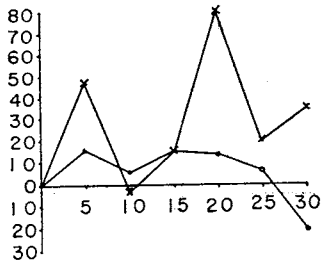


FIG. 9. Mean change in climbing time per set of twenty mice, expressed as schizophrenic score minus control score. ×–×–×: using plasma protein fractions shown to be most active by Bergen; ○–○–○: using fractions chosen at random (from *Archives of Neurology*, **2**, 146–50, 1960).

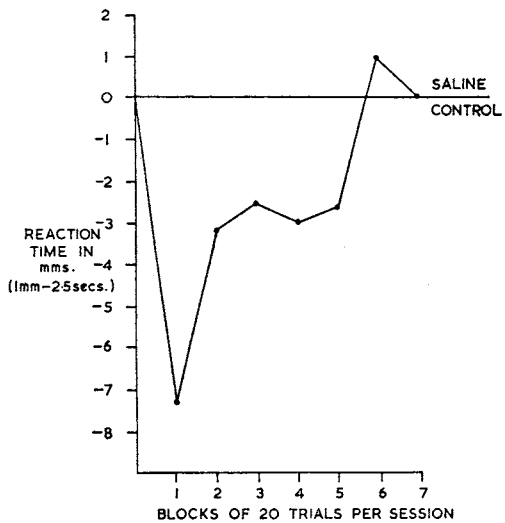


FIG. 10. The effect of N,N-dimethylmescaline (DMM) on RT: 25 mg/kg (n = 4).

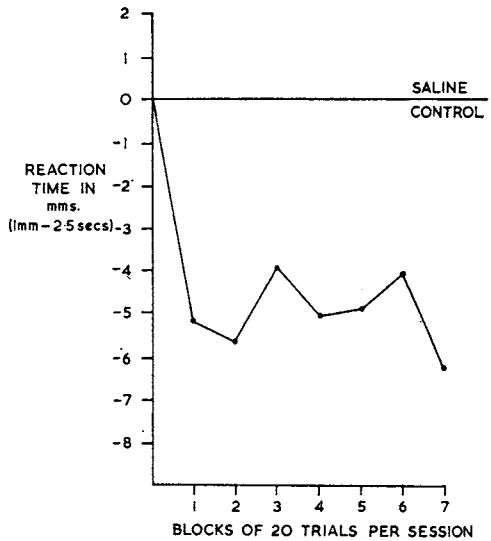


FIG. 11. The effect of N,N-dimethylmescaline (DMM) on RT: 50 mg/kg (n = 4).

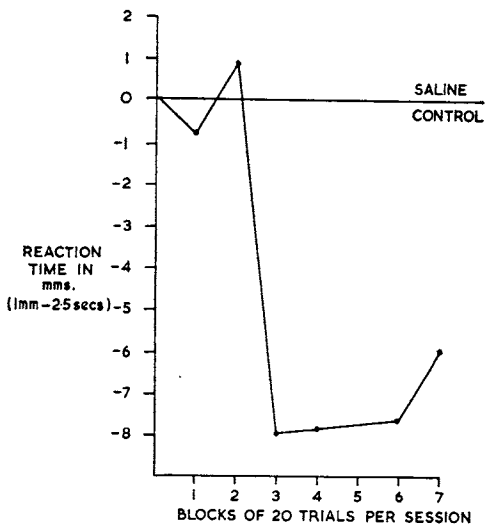


FIG. 12. The effect of N,N-dimethylmescaline (DMM) on RT: 100 mg/kg (n = 4).

Figure 15 gives the results for cross-tolerance between mescaline and d.m.p.e. The total RT increase is not changed to a statistically significant extent. The bimodal distribution is still present but each peak is delayed in time by 1 block (i.e. about 13 min). Thus, there appears to be no clear cross-tolerance between mescaline and d.m.p.e., but some subtle effect is possibly

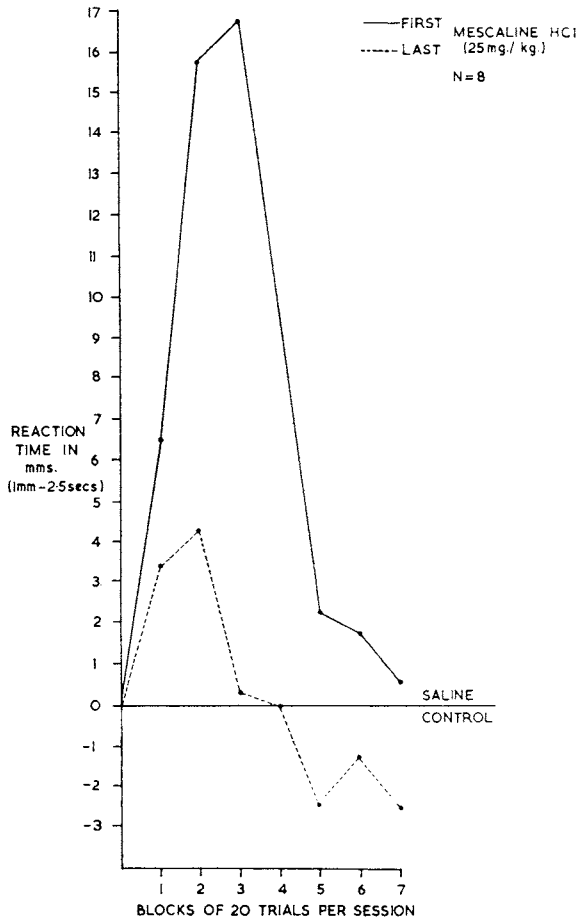


FIG. 13. The development of mescaline tolerance (25 mg/kg) showing effect on RT of first and last of eight successive doses (DMPE groups) (n = 8).

suggested by this shift in the peak time. Figure 16 gives the results for cross-tolerance between mescaline and N,N-dimethylmescaline (DMM). This gives a figure of some 40% cross-tolerance. Studies on the reverse tolerance between these compounds and mescaline are proceeding.

From previous work (Peretz *et al.*, 1955; Smythies and Levy, 1960) one

can say that α-methyl substitution doubles activity. The 4-methoxy group is necessary for activity as substitution by an hydroxyl abolishes activity, whereas a larger benzyloxy group here increases activity.

Our current programme is (i) to determine to what extent the biphasic mode of action of mescaline in this test is specific—e.g. is it shared by other similar

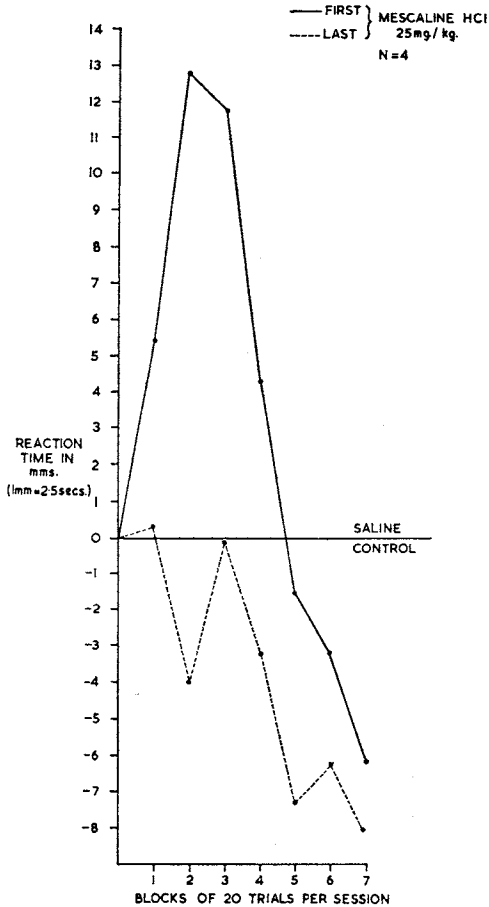


FIG. 14. The development of mescaline tolerance (25 mg/kg) showing effect on RT of first and last of eight successive doses (DMM group) (n = 4).

hallucinogens such as LSD, psilocybin and trimethoxyamphetamine, or is it shared by any non-hallucinogenic compounds?—(ii) to attempt to increase the potency of action of mescaline-like compounds by increasing their liquid solubility (e.g. 3,4,5-trifluophenylethylamine), (iii) by widening our biological testing methods to include ethological and other techniques.

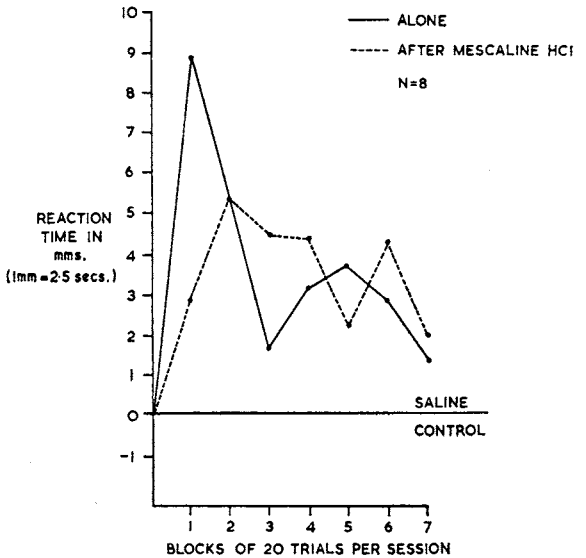


FIG. 15. Cross-tolerance study between mescaline and d.m.p.e. The effect of d.m.p.e. (50 mg/kg) on RT: (i) alone, (ii) after development of the degree of mescaline tolerance shown in Fig. 13.

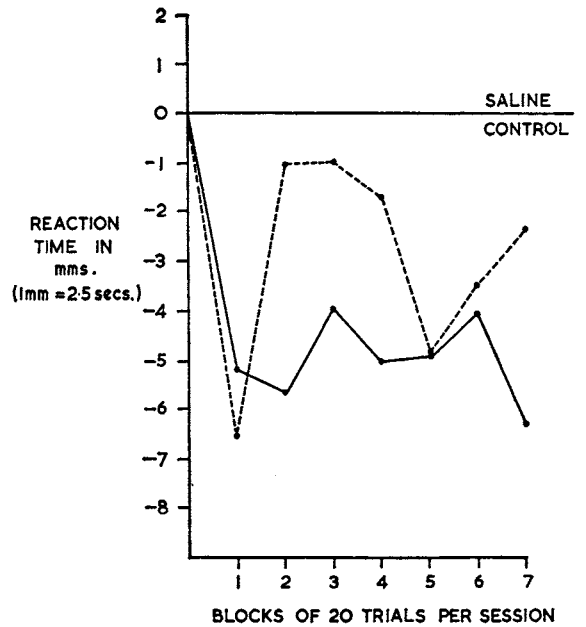


FIG. 16. Cross-tolerance study between mescaline and DMM. The effect of DMM (50 mg/kg) on RT: (i) alone, (ii) after development of the degree of mescaline tolerance shown in Fig. 14.

ACKNOWLEDGMENT

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