Life Sciences Vol. 6. pp. 1887-1893, 1967.

THE BEHAVIOURAL EFFECTS OF SOME DERIVATIVES OF MESCALINE AND N,N-DIMETHYLTRYPTAMINE IN THE RAT

J.R. Smythies, R.J. Bradley and V.S. Johnston

Department of Psychiatry, University of Edinburgh
Morningside Park, Edinburgh, 10, Scotland

F. Leonard[1]

National Institutes of Mental Health
Bethesda, Maryland

(Received 2 May 1967; in final form 13 June 1967)

A comprehensive knowledge of structure-activity relationships in the psychotomimetic compounds should throw some light on their mode of action. To this end, it is important that the measured behavioural correlates of drug action in the experimental animal should reflect the unique psychotropic effect of a drug as well as its relative potency. Little reliable information is available concerning the behavioural effects of hallucinogenic or psychotomimetic agents in animals.

The present study is part of an investigation of the behavioural effects of ring and side-chain substitution in two recognized hallucinogens, mescaline and N,N-Dimethyltryptamine. The compounds studied were 3,4-Dihydroxyphenethylamine (DOPAMINE), 3,4-Dihydroxy-5-methoxyphenethylamine[2], 3,5-Dimethoxy-4-hydroxyphenethylamine[2], 3,4,5-Trimethoxyphenethylamine (MESCALINE), N,N-Dimethyltryptamine, 5-methoxy-N,N-Dimethyltryptamine[2], and 5-methoxy-N-methyltryptamine[2].

Method

Twelve experimentally naive male hooded rats supplied by the National Institute of Medical Research were used in this study. The animals were

---

[1] Deceased October 19, 1966

[2] Synthesized for the Psychopharmacology Research Branch by the Regis Chemical Company, Chicago, Illinois, under Contract No. SA-43-ph-3021

approximately 100 days old at the beginning of the experiment and were allowed food and water ad libitum. Experiments were run in a modified Levine Shuttle-Box; this has been described in detail elsewhere. (1, 2, 3).

The rat was required to cross from one side of the shuttle-box to the other in response to a conditioned stimulus (C.S.) - a buzzer. This conditioned stimulus sounded for five seconds, at the end of which time the unconditioned stimulus (U.C.S.) - electric shock of 1.0 ma - was presented if the animal had failed to cross. A cross to the opposite compartment terminated either the conditioned stimulus or unconditioned stimulus.

All experimental contingencies were controlled by a programming unit placed in an adjacent room. An experimental session of two hours consisted of seven blocks of 20 trials, the blocks being separated by a time interval of 5 minutes. The reaction-time (RT) to each onset of the conditioned stimulus was automatically recorded and printed out correct to 0.1 secs.: i.e. the interval between the onset of the C.S. and the point where the rat crosses to the opposite compartment, thus terminating the C.S. or U.C.S.

Each animal was run seven days per week. After training to a criterion of at least 85% avoidance, injections of either drug or saline were given after 40 trials warm-up: i.e. 2 blocks of 20 trials allowing the animals to become accustomed to the experimental situation. The injected animal was then replaced in the shuttle-box and five minutes later the usual seven blocks of twenty trials began. Drugs or control injections of 0.5 ml isotonic saline were administered intraperitoneally and each drug day was preceded and followed by saline control days.

An animal served as its own control and results for each block of 20 trials are expressed in D-$\bar{S}$ scores (2) i.e. the difference between the drug score and the mean of the pre-drug and post-drug saline scores.

Four animals received each dose level of a given drug according to a random design, and a fortnight was allowed between drug treatments in order to counteract any tolerance effects.

Results and Discussion

Using a technique similar to the one used in this experiment, previous investigations (1, 2, 3) have shown that hallucinogenic compounds have a biphasic effect on reaction time. Large doeses cause an initial inhibition of the conditioned avoidance response (C.A.R.) above control values, which is reflected by an increase in reaction-time. This inhibition is eventually superseded by a decrease in reaction time below control values. During control saline injection sessions the trained rat will make an avoidance response late in the conditioned stimulus. For the first half of the biphasic effect the C.A.R. is inhibited and a response will escape shock rather than avoid it. The resulting increase in reaction time (RT) will give a positive D-$\bar{S}$ score. In the second half of the biphasic effect the animal will cross immediately on the presentation of the conditioned stimulus. Thus there is a decrease in reaction time and a negative D-$\bar{S}$ score. In the main, smaller doses produce only a reduction in reaction time. No non-hallucinogens tested so far demonstrate these properties.

Fig. 1,A compares the action of 5-methoxy-dopamine at two different dose levels, 50 and 25 mg/kg. This compound produces merely an inhibition of the CAR. Fig. 1,B illustrates the less severe but similar inhibition induced by dopamine. It has been reported that 5-hydroxy-dopamine causes a greater inhibition of rope-climbing behaviour in the rat than does dopamine itself (4). The increase in activity is also manifested in our data when a methoxy-group is substituted in the 5-position.

Fig. 1,C demonstrates the decline in activity of mescaline when the 4-methoxy-group is removed and replaced by OH. The inactivity of the resulting compound at 50 mg/kg can be compared with 25 mg/kg mescaline which produces the specific hallucinogenic biphasic profile on this test. Similarly Fig. 1,D illustrates a comparable reduction in mescaline activity following substitution of the 5-methoxy group by OH.

Since it is unlikely that these hydroxylated compounds can cross the

blood-brain barrier, they might be active if injected intrathecally. Furthermore, it is probable that the inhibitory effect of the dihydroxylated compounds may be due to some peripheral action.

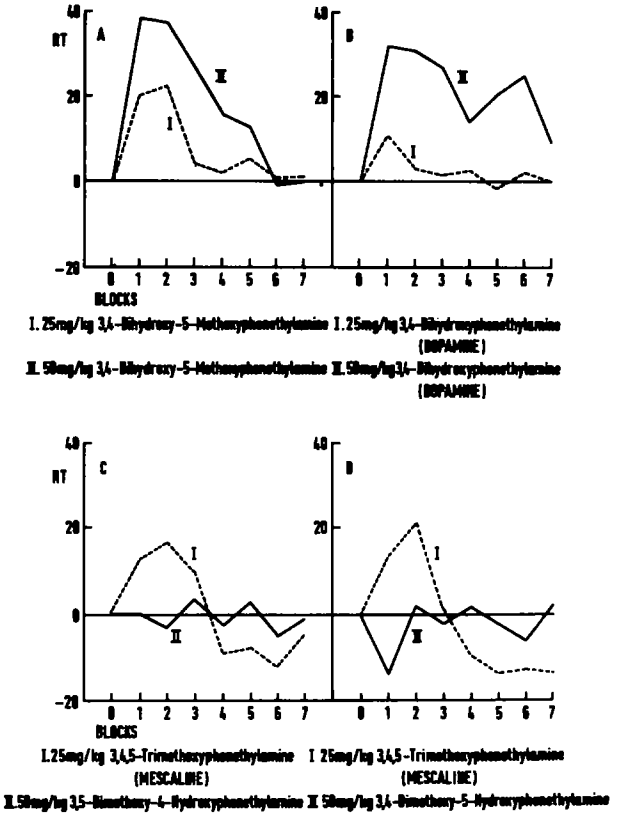

FIG. 1

Comparison of effects of mescaline and three analogues. Abscissa: Blocks of runs of 20 trials each. The interval between runs represents 13 min. in each case (run 8 min., 5 min. time out). Ordinate: Mean change in reaction time in seconds (D-S). Each point represents 80 readings (20 trials x 4 animals) averaged.

In Fig. 2, the behavioural effects of two close analogues of N,N-Dimethyltryptamine are presented. Fig. 2,A and C show the action of 5 and 10 mg/kg 5-Methoxy-N-methyltryptamine respectively, each compared with a similar dose of N,N-Dimethyltryptamine. In a similar fashion Fig. 2,B and D compare the

effects of 5-methoxy-N,N-dimethyltryptamine and N,N-Dimethyltryptamine. These results show clearly the biphasic profile produced by N,N-Dimethyltryptamine. Also evident is the more rapid onset and increased effect of this drug over mescaline in both halves of the biphasic response, but with a shorter lasting inhibitory action. In man DMT produces a more intense, shorter acting effect than mescaline with a more rapid onset (5) so the results obtained in the rat seem to be comparable.

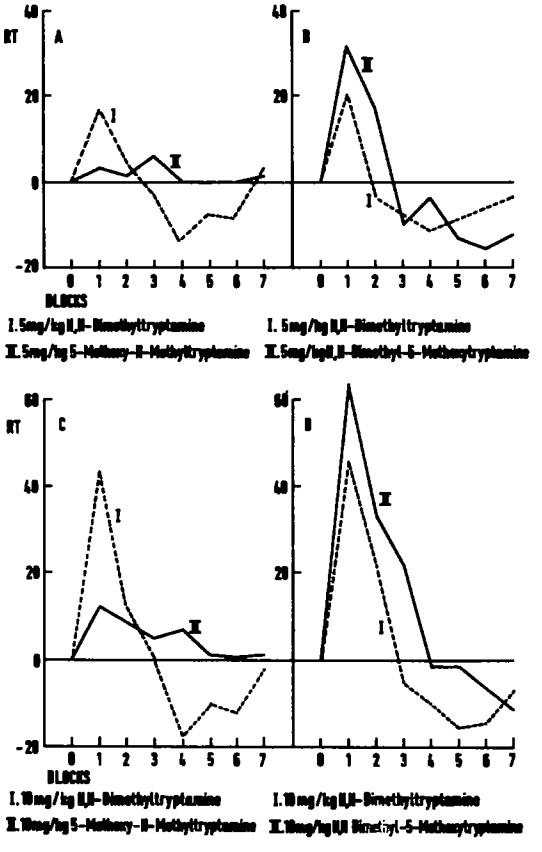

FIG. 2

Comparison of effects of N,N-Dimethyltryptamine and two analogues.

Fig. 2,B and D suggest that 5-methoxy-N,N-dimethyltryptamine could be a more potent hallucinogen than DMT, as the biphasic effect produced is greater than that caused by the same dose level of DMT.

Benington, Morin and Clark have examined some of the pharmacological and behavioural properties of this drug and predict that it will be an hallucinogen in man (6). This prediction is supported by the fact that certain Indian tribes in South America take an hallucinogenic snuff (Epena), which has been found to contain 5-Methoxy DMT as a major component together with small quantities of DMT and Bufotenine (7).

Fig. 2,A and C show that the closely related substance 5-methoxy-N-methyltryptamine is relatively inactive, producing only a slight inhibitory effect at 10 mg/kg.

Summary

The behavioural effects of some analogues of mescaline and N,N-Dimethyltryptamine have been studied in the rat. Both these compounds produce a characteristic biphasic effect on reaction-time as measured on shuttle-box avoidance. The nature of these drug profiles in the rat parallels the quantitative differences in the course of action of the two drugs in man.

Several mescaline-like compounds with ring-hydroxy groups were tested and none of these produced biphasic responses.

The tryptamine analogue 5-methoxy-N-methyltryptamine was found to be almost inactive whereas 5-methoxy-N,N-Dimethyltryptamine produced a biphasic response greater than that of DMT.

It is predicted that 5-methoxy-N,N-Dimethyltryptamine is a potent hallucinogen in man and the close analogue 5-methoxy-N-methyltryptamine will be inactive.

Acknowledgements

We are most grateful to Professor G.M. Carstairs for his continued support of this work. This work was supported by a grant from the Medical Research

Council and by Grant No. MH 11969-01, from the National Institute for Mental Health.

References

1. J.R. Smythies and E.A. Sykes, Psychopharmacologia 6, 163 (1964).

2. J.R. Smythies and E.A. Sykes, Psychopharmacologia 8, 324 (1965)

3. J.R. Smythies, E.A. Sykes and C.P. Lord, Psychopharmacologia 9, 434 (1966).

4. J.R. Smythies and C.K. Levy, J. Ment. Sci. 106, 531 (1960).

5. S. Szara, S. in Garattini and V. Ghetti (eds.), Psychotropic Drugs, p. 460, Elsevier, Amsterdam (1957).

6. F. Benington, R.D. Morin and L.C. Clark Jr., Alabama J. Med. Sci. 2, 397 (1965).

7. B. Holmstedt, Amines and Schizophrenia, Atlantic City, N.J., Pergamon Press, 1967.