ACTION OF A CHRONIC ADMINISTRATION OF MESCALINE IN DYNAMIC BEHAVIOURAL SITUATIONS

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Abstract

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1. The modifications of the rat behaviour caused by a chronic administration of mescaline were studied in two schedules of operant conditioning.
2. In the "periodic conditioning" test, the schedule of reinforcement was changed from a fixed ratio to a fixed interval schedule. Mescaline (4 mg/kg/day and 10 mg/kg/day) caused no modification of the ability of the rat to adapt its behaviour to the new experimental situation.
3. In the "reversal test" the contingency for food delivery was switched from one lever, where responses were previously reinforced to the other lever where responses had no programmed consequences.
4. A chronic administration of mescaline (4 mg/kg/day) caused a total incapacity of the rat to switch to the lever which became reinforced in the reversal trial.
5. A chronic administration of 9 mg/kg/day of mescaline had an excitatory effect and the number of reinforced responses in the II and III reversals exceeded the unreinforced responses in a measure greater than in the controls.

Keywords: fixed interval, fixed ratio, learning, memory, mescaline, reversal trials.

Abbreviations: D-lysergic acid diethylamide (LSD)

Introduction

The acute administration of mescaline, LSD and related drugs causes several behavioural modifications that can be used as a behavioural model for the action of psychotomimetics (Herz 1960; Jacobs et al. 1977; Commissaris et al. 1981; Mokler and Rech 1984) but in general they are inadequate in offering evidence of an action of these drugs on learning and mnemonic processes. Important in this context is the observation of Stoff et al. (1974) that an

acute administration of LSD caused in the rat a facilitation of learning on shuttlebox escape/avoidance. In the rat, Weissman (1967) reported no modification of retrograde amnesia after acute administration of LSD, mescaline and psylocybin.

Considering that Blacker et al. (1968) suggested utilizing chronic human users of LSD (the "Acidheads") to improve our knowledge on the action of psychotomimetics on the human "mind", we examined if a chronic administration of mescaline causes behavioural modifications in the rat which may offer evidence of an action of mescaline on memory and learning processes.

Methods

Animals. Thirty male albino rats (Wistar derived strain) were used. The animals, weighing 200-250 g at the beginning of the experiments, were kept in groups of five in cages (temperature around 20°C) with food (purina chops) and water ad libitum. All the rats were trained to a fixed ratio schedule (one reinforcement every ten responses). The reinforcer was pellets of food (45 mg).

Fifteen rats were trained in a Grason and Stadler Skinner box with one lever. The other 15 rats were trained in a similar box with two levers. Each session lasted 15 minutes. The experiments were performed daily in the morning. Rats were kept without food for 10-12 hours before the trial. After two months training the response rate was virtually constant in successive sessions.

Drug administration. Mescaline sulfate was dissolved in water at two concentrations: 50 mg/liter and 100 mg/liter. The animals of the control group drank water and the two experimental groups drank the solutions of mescaline.

The doses of mescaline given to the animals were calculated from the total quantity of the solution drunk in the period of the experiment, taking into account the number of rats and their average weight. The fluid intake was between 30-35 ml/day/rat and no difference was observed between controls and experimental groups.

Experimental procedure. Two tests of operant conditioning were used. In one test the schedule of reinforcement was changed for the first time to a fixed interval schedule: only the first response given after 5 minutes was reinforced. The fixed interval trial lasted 100 minutes. We will refer to this test, previously utilized to characterize antidepressants (Fundarò et al. 1983a), as the "periodic conditioning" test. The fifteen rats trained in the single lever box were divided in three groups of 5 animals: one group (control) drank water, the other two groups drank the solution of 50 or 100 mg/liter of mescaline sulfate. Drug administration began 30 days before the variation from the fixed ratio to the fixed interval schedule of reinforcement. The average dose calculated was 4 mg/kg/day in the group drinking the solution of 50 mg/liter and 10 mg/kg/day in the group drinking 100 mg/liter of mescaline.

In the second test, 15 rats trained in the double lever box were used. During the preliminary training only the responses on the lever to the left of the food tray were reinforced. The responses and the reinforcers were registered with a double pen recorder. In this experimental situation most of the responses were made on the lever connected to the food magazine and only exceptionally rats gave a few responses on the lever to the right of the food tray where responses were not reinforced. At the stabilization of this behaviour the levers were interchanged and the responses on the lever to the right of the food tray were reinforced while the responses on the left lever where no longer reinforced. The rats were trained in this new situation till (after 14 days) they gave practically no response on the left lever and concentrated all the responses on the right lever. At this point a new reversal was performed: the food magazine was disconnected from the right lever and connected to the left lever. At stabilization (after 13 days) of the rat behaviour in this experimental situation a new reversal was performed: only the responses on the right lever were reinforced. Finally after 14 days the fourth reversal was performed, connecting the food magazine to the left lever. All the experimental sessions lasted 15 minutes. We will refer to this test as the "reversal" test.

Rats were divided in three groups of five animals: one group (controls) drank water, the other two groups drank the solutions of 50 or 100 mg/liter of mescaline sulfate. Drug administration began 10 days before the first reversal and was continued during the whole duration of the experiment (41 days). The average dose calculated was 4 mg/kg/day in the group drinking the solution of 50 mg/liter of mescaline and 9 mg/kg/day in the group drinking 100 mg/liter of mescaline.

Statistical analysis. In the "periodic conditioning" test, the number of responses/reinforcement was evaluated in the first 20 minutes and in the last 20 minutes of the experiment. Means and standard errors of the means (S.E.) were calculated and the Student's t test was used to evaluate the significance of the differences between the means.

In the "reversal" test the total number of responses (reinforced plus non reinforced responses) made by the rat in the four successive reversal trials was evaluated. The Student's t test for the difference between means was used to estimate the significance of the differences between controls and treated animals. The differences between cumulative reinforced and non reinforced responses were also evaluated every two minutes in the reversal trials. Means and standard errors were calculated.

Results

"Periodic conditioning" test. The number of responses/reinforcement given in the first 20 minutes of the trial in which the schedule of reinforcement changed from the fixed ratio to the fixed interval were 184±20 (S.E.) in the controls. After the chronic administration of 4 mg/kg/day and 9 mg/kg/day they were respectively 181±26 (S.E.) and 167±21 (S.E.).The differences between these means are not significant. The number of responses/reinforcement given in the last 20 minutes of "periodic conditioning" trials were

33±13 (S.E.), 36±9 (S.E.) and 30±2 (S.E.) respectively in the controls, in the rats treated with 4 mg/kg/day and with 9 mg/kg/day of mescaline.

The per cent differences $(\frac{N20' - N100'}{N20'})$ x 100 between the number of responses/reinforcement given in the first 20 minutes (N20') and in the last 20 minutes (N100') of experiment are 82% in the controls (N20' = 184±20 S.E.; N100' = 33±13 S.E.); after 4 mg/kg/day they are 80% (N20' = 181±26 S.E.; N100' = 36±9 S.E.) and after 9 mg/kg/day the reduction is 82% (N20' = 167±20 S.E., N100' = 30±2 S.E.). The significance of the reduction of the number of responses from the beginning to the end of the trial is always highly significant (less than 0.1% of probability of a casual result).

"Reversal" test. The mean ±S.E. of the total number of responses given by the three experimental groups in the four reversals are reported in Table 1. The Student's t test for the differences between controls and mescaline treated rats are also reported. It results that in the rats treated with 4 mg/kg/day of mescaline there is a significant reduction of the total number of responses in the I, III and IV reversals. On the contrary, in the group treated with 9 mg/kg/day there is a significant increase of the total number of responses in the II and III reversals.

Table 1

Total responses given by rats in the four reversal trials

Treatments		I reversal	II reversal	III reversal	IV reversal
Controls	$\bar{X}$±S.E.	408.8±40.4	195.8±36.3	584.0±112.9	720.0±142.0
	n	5	5	5	5
Mescaline 4 mg/kg/day	$\bar{X}$±S.E.	132.0±39.5	103.3±64.4	165.6±63.5	72.6±42.0
	n	5	5	5	5
	P	1-0.1%	30-20%	5-2%	2-1%
Mescaline 9 mg/kg/day	$\bar{X}$±S.E.	283.3±67.1	794.0±94.6	942.0±94.1	722.3±162.7
	n	5	5	5	5
	P	10-20%	< 0.1%	~ 5%	> 80%

Means ±standard errors are reported. The Student's t test was used to estimate the probability (P) of a casual result.

The means ±S.E. of the differences between the reinforced and the unreinforced responses, evaluated every two minutes in the four successive reversal trials, are reported in Fig. 1. Negative values indicate that the rat continued to respond mostly on the lever that before the reversal was connected to the food magazine and positive values indicate that the rat switched and responded on the lever now connected to the food magazine.

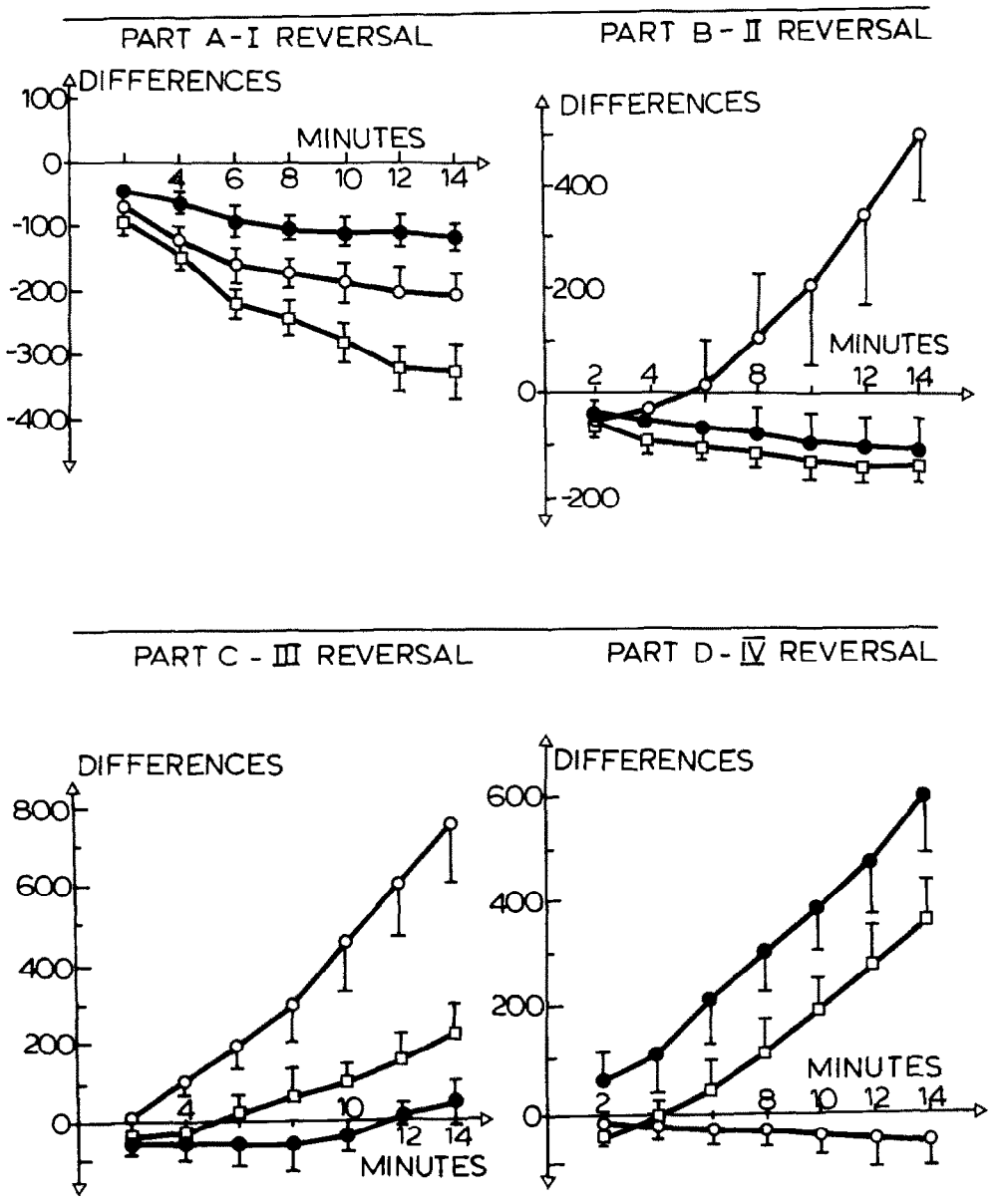

Fig. 1. Action of a chronic administration of mescaline in four successive reversals. (On the abscissa, the time in minutes from the beginning of the reversal trial is given. On the ordinate, the differences between the reinforced and the unreinforced responses are reported. Each point is the average of values obtained from rats in the same experimental conditions. The standard error of the means are reported. —●—●—●— mescaline 4mg/kg/day —○—○—○— mescaline 9mg/kg/day —□—□—□— controls).

It is evident (Fig. 1 part A) that in the first reversal the number of responses on the lever reinforced before the reversal prevails. In the second reversal (Fig. 1 part B) the controls and the group treated with 4 mg/kg/day of mescaline persisted in responding on the lever which was disconnected from the food magazine in the reversal trial. On the contrary in the group treated with 9 mg/kg/day of mescaline the reinforced responses increase linearly with time from the beginning of the experiment. In the third reversal (Fig. 1 part C) the reinforced responses increase in the group of controls and in the rats treated with 9 mg/kg/day: the prevalence of the reinforced responses is more evident in the mescaline group. In the group of rats treated with the lower dose of mescaline the difference between reinforced and unreinforced responses is around 0 (Fig. 1 part C). In the last reversal (Fig. 1 part D) the prevalence of the reinforced responses is evident in the control group and at the higher dose of mescaline (9 mg/kg/day). The difference between these two groups is, in the reversal, much reduced. In the group of rats treated with 4 mg/kg/day of mescaline, the unreinforced responses still tend to prevail.

Discussion

A modification of the number of responses/reinforcement in the first 20 minutes of the "periodic conditioning" trial may be taken as an indication that mescaline caused a variation in the state of excitability. Our results indicate that there is no difference between controls and treated rats, suggesting that in this test mescaline has no excitatory effect. Bridger and Mandel (1971) and Bridger et al. (1973) observed on acquisition of shuttlebox avoidance/escape an excitatory effect after acute and chronic mescaline administration. These contradictory results may be explained taking into account that the rats received a long training and when the "periodic conditioning" test was performed they responded at such a high rate that an eventual further increase may have become undetectable.

The reduction of the number of responses/reinforcement, when the schedule of reinforcement changes from FR to FI, may be taken as an evaluation of the ability of the animal to adapt its behaviour to a new experimental situation. This is the definition given by Kreeze (1971) for "learning". Our results indicate that the chronic administration of mescaline causes a reduction of the number of responses from the beginning to the end of the trial, which is practically the same as that observed in the control group. This suggests that in the range of tested doses, a chronic administration of mescaline causes no damage to the ability of the rat to adapt to the new experimental situation ("learning").

In the "reversal" test, the control group in the first two reversals persisted in responding on the lever which was no longer connected to the food magazine. The reduction of the total number of responses in the second reversal also suggest a partial extinction of the conditioned reflex. From the third reversal an increase of the reinforced responses was observed in the control group, as if the negative experience accumulated in the first two reversals, influences the rat to respond on the other lever. The chronic administration of 4 mg/kg/day of mescaline caused a total incapacity of the

rat to pass from one lever to the other and in the last reversal a reduction of the total number of responses was also observed, suggesting a partial extinction of the conditioned reflex. Considering that in the "periodic conditioning" test no damage to the learning capacity of the rat was evident, the results in the reversal test may indicate that mescaline causes, at a low dose, a damage to the capacity of the animals to make use of the negative experiences of the preceeding reversals.

The rats treated with the higher dose (9 mg/kg/day) of mescaline displayed completely unexpected behaviour. From the second reversal an increase of the reinforced responses was observed which is, at least in the second and third reversals, higher than that of the controls. This observation might suggest a facilitation of learning analogous to that reported by Stoff et al. (1974) with LSD on shuttlebox escape/avoidance. Bridger and Mandel (1971) and Bridger et al. (1973) demonstrated that mescaline administration has an excitatory effect. This is in agreement with the increase of total responses we observed at 9 mg/kg/day of mescaline, but this excitatory effect is insufficient to explain the increase of reinforced responses in the reversal test. Actually, the increase in the number of responses is not equally distributed on the two levers but most of the responses are given on the lever connected to the food magazine. A simple excitatory effect, for example of amphetamine, certainly does not improve the rat behaviour in this test (Fundarò et al. 1983b). To interprete this apparent facilitation of learning caused by a rather high dose of mescaline is now impossible particularly considering firstly that a lower dose (4 mg/kg/day) of mescaline has a completely opposite effect and secondly that the data obtained in the "periodic conditioning" test offered no evidence that the administration of a similar dose (10 mg/kg/day) of mescaline causes learning facilitations.

Conclusion

Mescaline caused no damage to the ability of the rat to adapt to a new experimental situation ("learning"). A damage to the capacity of the rat to make use of the negative experiments of the preceeding trials ("memory") is evident only at low doses. The "memory" improvement observed at high doses may be, in part, correlated to the excitatory effect of mescaline.

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