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Effects of Mescaline and Amphetamine on Simultaneous Visual Discrimination in Two Inbred Strains of Mice

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Abstract. The effects of mescaline and amphetamine were investigated in BALB/cJ (BALB) and C57BL/6J (C57) mice using the five-choice Yerkes–Thompson Bryant–Bovet-Nitti apparatus for patterns discrimination. Two sets of experiments were carried out. In the first set, pretrial administration of mescaline (5, 10, and 20 mg/kg) was followed by performance improvements in the C57 mice, while performances of the BALB strain were impaired by the treatment, as compared with those of the saline-injected (4 ml/kg) controls. The pretrial administration of amphetamine (0.1, 0.25, and 0.5 mg/kg) improved performances of both strains. In a second set of experiments, the same effects as in the pretrial experiments were observed in both strains following administration of mescaline (20 mg/kg) and amphetamine (0.5 mg/kg) immediately after each experimental session. No effect was evident when the drugs were injected 2 h after training, suggesting that effects of the pretrial treatments were due to influences of mescaline and amphetamine on the consolidation processes of the two strains of mice tested.

Key words: Mescaline – Amphetamine – Consolidation – Inbred mice

It is well known that mescaline and amphetamine possess similar chemical structures and produce common sympathomimetic effects (Rosenberg et al., 1963).

The effects of these drugs on animal performance and memory processes have been investigated by a number of authors (Doty and Doty, 1966; Cole, 1967; Krivanek and McGaugh, 1969; Evangelista and Izquierdo, 1971; Bridger and Mandel, 1971; Sansone et al., 1974; Castellano, 1974, 1978; Gorelick and Bozewicz, 1975; Gorelick and Bridger, 1977).

Similarities and, in some cases, differences between effects of mescaline and amphetamine have been shown by behavioral (Sparber and Tilson, 1972a; Tilson and Sparber, 1973), neurophysiological (Foote et al., 1969; Aghajanian et al., 1970; Colasanti and Khazan, 1975), and neurochemical (Menon et al., 1967; Carr and Moore, 1969; Leonard and Tonge, 1969; Sparber and Tilson, 1972b) investigations.

In recent years some researches (Bovet-Nitti, 1966, 1969; Castellano, 1977) have been carried out in rats and mice with the Yerkes–Thompson Bryant–Bovet-Nitti apparatus for pattern discrimination, showing the usefulness of this test in psychopharmacogenetic investigations. In this research the five-choice Yerkes–Thompson Bryant–Bovet-Nitti apparatus was employed, adapted for the mouse by Bovet-Nitti (1969).

The aim of this investigation was to show the existence of possible differences between effects of mescaline and amphetamine on the acquisition and consolidation processes of two inbred strains of mice (C57BL/6J and BALB/cJ) which differ in behavior and brain chemicals (Bovet-Nitti, 1969; Bovet et al., 1969; Kempf et al., 1976; Oliverio, 1978).

As to the effects on consolidation processes in particular, we injected the drugs after each experimental session. It is known (McGaugh, 1966) that post-trial administration of a drug may modify the consolidation processes, improving performance corresponding to memory enhancement or impairment due to memory-disrupting effects of the drug.

The results of our research were finally compared with those obtained following administration of the same and other drugs to inbred strains of mice in previous researches (Castellano, 1974, 1978).

Materials and Methods

Male C57BL/6J (C57) and BALB/cJ (BALB) mice, weighing about 25 g at the beginning of the experiments, were used throughout.

The apparatus consisted of a starting box, a discrimination chamber with a grid floor, and a goal box (38 × 20 cm) with five doors on the long side. Only one door could be opened by the animals to

enter the goal box, where they did not receive the electric shock (30 V AC scrambled through a selenium rectifier) administered through the grid floor of the discrimination chamber. The animals had to discriminate between two different patterns; the negative one was painted on each of the four locked doors, the correct one was on the swinging door. The patterns were opposite-oriented, oblique bars. An error was recorded every time a mouse pushed one of the four locked doors carrying the negative pattern with it's nose. Both pretraining and training were carried out from Monday to Friday during 2 consecutive weeks according to previously described schedules (Bovet-Nitti, 1969; Castellano, 1977).

Pretraining

The following program was carried out during 5 consecutive days. On day 1, each group of eight mice was allowed to explore the apparatus and step through the half-open door carrying the positive pattern during a 60-min session. On day 2, the animals were subjected to a 30-min session in the presence of a very slight shock uninterruptedly delivered through the grid floor. On days 3–5, each animal was given five consecutive trials/day during which the shock could be escaped by passing through the randomly situated half-open door.

Training

The animals were given ten consecutive trials/day during 5 consecutive days. A correct response was scored when the mouse entered the swinging door without pushing one of the remaining four doors with it's nose. Immediately after each escape, the mice were returned to the starting box for the next trial.

Two sets of experiments were carried out. In the first, mescaline (5, 10, or 20 mg/kg) and amphetamine (0.1, 0.25, or 0.5 mg/kg) were injected 15 min before testing. In a second set, mescaline (20 mg/kg) and amphetamine (0.5 mg/kg) were injected immediately, or 2 h, after each training session.

In both sets of experiments and for each strain, each dose was administered to a different group of eight animals and the performances of the drugged mice were compared to saline-injected (0.9% NaCl, 4 ml/kg) controls.

Mescaline (HCl) and *d*-amphetamine (sulfate) were dissolved in saline and injected i.p.

The results of both the pre- and the post-trial experiments were statistically evaluated by trend analysis (Edwards, 1960). Additional analyses were carried out when necessary to obtain individual between-treatment comparisons (Lison, 1961).

Results

Pretrial Treatments (Figs. 1 and 2)

Saline Groups. In agreement with previous results (Bovet-Nitti, 1969; Castellano, 1977) the BALB mice performed better than the C57 strain in the patterns discrimination test. The trend analysis showed, in particular, significant differences between treatments ($df = 1/14$, $F = 186.6$, $P < 0.001$), between sessions ($df = 4/56$, $F = 167.3$, $P < 0.001$), and also a significant treatments × sessions interaction ($df = 4/56$, $F = 29.1$, $P < 0.001$).

Saline groups were the same for both mescaline and amphetamine treatments.

Mescaline. Mescaline administrations were followed by performance impairments in the BALB strain, and by performance improvements in the C57 strain.

The trend analysis showed, in particular for the BALB mice, significant differences between treatments ($df = 3/28$, $F = 85.0$, $P < 0.001$), between sessions ($df = 4/112$, $F = 765.5$, $P < 0.001$), and also a significant treatments × sessions interaction ($df = 12/112$, $F = 14.4$, $P < 0.001$).

In the C57 strain, the trend analysis showed significant differences between treatments ($df = 3/28$, $F = 275.1$, $P < 0.001$), between sessions ($df = 4/112$, $F = 260.2$, $P < 0.001$), and also a significant treatments × sessions interaction ($df = 12/112$, $F = 10.1$, $P < 0.001$).

In additional analyses of individual between-treatments comparisons the significance of F values was tested on the basis of 1/28 *df*.

The lowest dose of mescaline (5 mg/kg) did not modify significantly the performances of BALB mice compared with the saline-injected controls ($F = 3.3$, $P > 0.05$). Significant performance impairments (compared with controls) were observed in this strain following administration of both 10 mg/kg ($F = 5.3$, P

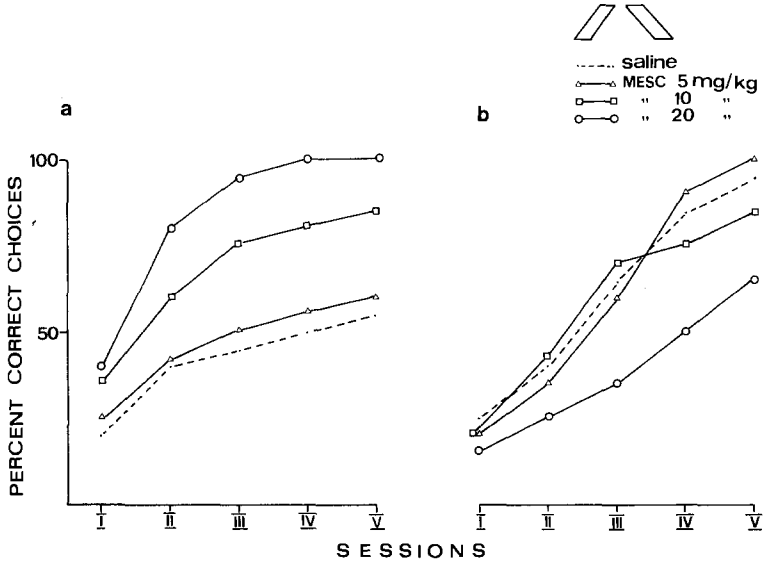

Fig. 1
a Mean % correct choices of C57BL/6J mice injected with mescaline (MESC. 5, 10, 20 mg/kg) or saline 15 min before each experimental session.
b Mean % correct choices of BALB mice injected with mescaline (MESC. 5, 10, 20 mg/kg) or saline 15 min before each experimental session. Groups of 8 animals. Pattern: opposite-oriented oblique bars.

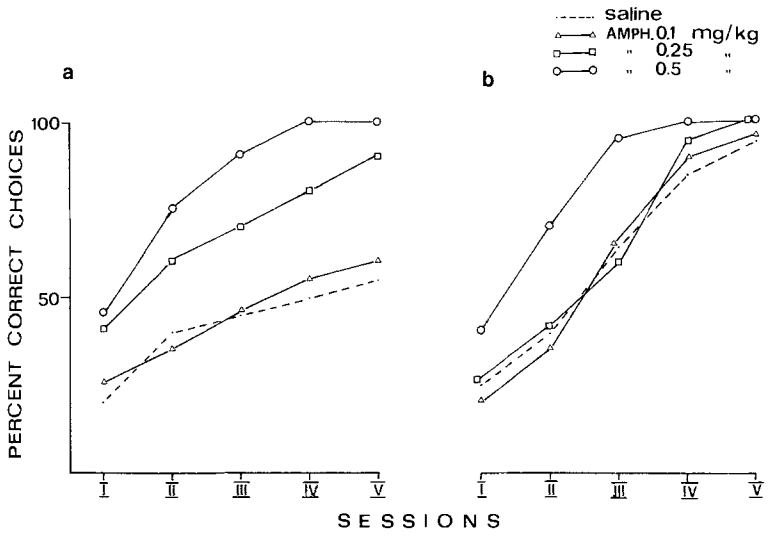

Fig. 2
a Mean % correct choices of C57 mice injected with amphetamine (0.1, 0.25, 0.5 mg/kg) or saline 15 min before each experimental session.
b Mean % correct choices of BALB mice injected with amphetamine (0.1, 0.25, 0.15 mg/kg or saline 15 min before each experimental session. Groups of 8 animals

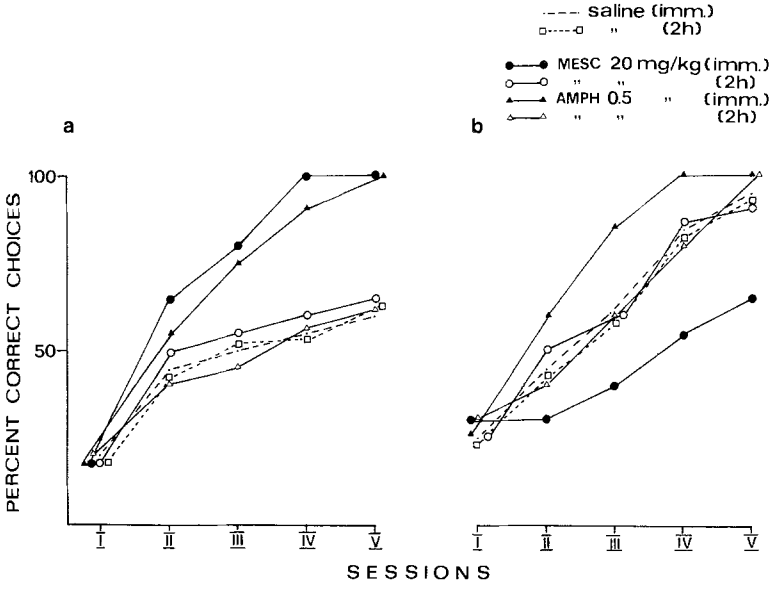

Fig. 3
a Mean % correct choices of C57 mice injected with mescaline (20 mg/kg), amphetamine (0.5 mg/kg), or saline immediately (imm.) or 2 h after each experimental session.
b Mean % correct choices of BALB mice injected with mescaline (20 mg/kg), amphetamine (0.5 mg/kg), or saline immediately (imm.) or 2 h after each experimental session Groups of 8 animals

< 0.05) and 20 mg/kg of mescaline ($F = 192.0$, $P < 0.001$).

Compared with the saline-injected controls, the lowest dose of mescaline (5 mg/kg) did not significantly modify the performances of C57 mice, ($F = 3.7$, $P > 0.05$); significant performance improvements were observed in this strain following administration of 10 and 20 mg/kg of the hallucinogen ($F = 236.4$ and 575.5 respectively, $P < 0.001$).

Amphetamine. Amphetamine administrations were followed by performance improvements in both the BALB and C57 strains.

The trend analysis showed, in particular for the BALB mice, significant differences between treatments ($df = 3/28$, $F = 113.2$, $P < 0.001$), between sessions ($df = 4/112$, $F = 922.8$, $P < 0.001$), and also a significant treatments × sessions interaction ($df = 12/112$, $F = 13.2$, $P < 0.001$).

In the C57 strain, trend analysis showed significant differences between treatments ($df = 3/28$, $F = 437.1$, $P < 0.001$), between sessions ($df = 4/112$, $F = 243.0$, $P < 0.001$), and also a significant treatments × sessions interaction ($df = 12/112$, $F = 5.7$, $P < 0.001$).

In additional analyses of individual between-treatments comparisons the significance of F values was tested on the basis of 1/28 *df*.

Only the highest dose of amphetamine (0.5 mg/kg) significantly improved performances of BALB mice, compared with saline-injected controls ($F = 240.6$, $P < 0.001$). Both 0.1 and 0.25 mg/kg did not significantly modify, compared with controls, the performances of this strain ($F = 0$ and 2.6 respectively, $P > 0.05$).

The lowest dose of amphetamine (0.1 mg/kg) did not modify significantly performances of C57 mice, compared with those of the saline-injected controls ($F = 2.3$, $P > 0.05$). Significant performance improvements, compared with controls, were observed in this strain following administration of 0.25 and 0.5 mg/kg of this drug ($F = 394.3$ and 933.3 respectively, $P < 0.001$).

Post-trial Treatments

Mescaline Mescaline (20 mg/kg) administrations immediately after each training session were followed by performance impairment in the BALB strain and by performance improvement in the C57 strain.

The trend analysis showed, in particular for the BALB mice, significant differences between treatments ($df = 1/14$, $F = 127.7$, $P < 0.001$), between sessions ($df = 4/56$, $F = 178.3$, $P < 0.001$), and a significant treatments × sessions interaction ($df = 4/56$, $F = 19.7$, $P < 0.001$).

In the C57 strain, trend analysis showed significant differences between treatments ($df = 1/14$, $F = 156.5$, $P < 0.001$), between sessions ($df = 4/56$, $F = 319.9$, $P < 0.001$), and a significant treatments × sessions interaction ($df = 4/56$, $F = 38.0$, $P < 0.001$).

The performances of both BALB and C57 mice injected with the hallucinogen 2 h after each session were not significantly different from those of the saline-injected controls.

The trend analysis showed, in particular for the BALB strain, not significant differences between treatments ($df = 1/14$, $F = 0.1$, $P > 0.05$), significant differences between sessions ($df = 4/56$, $F = 274.4$, $P < 0.001$), and a not significant treatments × sessions interaction ($df = 4/56$, $F = 1.2$, $P > 0.05$).

In the C57 mice, trend analysis showed no significant differences between treatments ($df = 1/14$, $F = 0.8$, $P > 0.05$), significant differences between sessions ($df = 4/56$, $F = 57.7$, $P < 0.001$), and a not significant treatments × 7 sessions interaction ($df = 4/56$, $F = 0.6$, $P > 0.05$).

Amphetamine. Significant performance improvements were evident both in the BALB and C57 strains following administration of amphetamine (0.5 mg/kg) immediately after each training session, compared with saline-injected controls.

The trend analysis showed, in particular, for the BALB mice, significant differences between treatments ($df = 1/14$, $F = 105.8$, $P < 0.001$), between sessions ($df = 4/56$, $F = 402.3$ $P < 0.001$), and a significant treatments × sessions interaction [$df = 4/56$, $F = 8.9$, $P < 0.001$).

In the C57 strain, trend analysis showed significant differences between treatments ($df = 1/14$, $F = 112.2$, $P < 0.001$), between sessions ($df = 4/56$, $F = 242.7$, $P < 0.001$), and a significant treatments × sessions interaction ($df = 4/56$, $F = 27.7$, $P < 0.001$).

The performance of both BALB and C57 mice injected with amphetamine 2 h after each session were not significantly different from the saline-injected controls.

The trend analysis showed, in particular for the BALB strain, no significant differences between treatments ($df = 1/14$, $F = 0.1$, $P > 0.05$), significant differences between sessions ($df = 4/56$, $F = 413.7$, $P < 0.001$), and a significant treatments × sessions interaction ($df = 4/56$, $F = 3.3$, $P < 0.01$).

In C57 mice, trend analysis showed, no significant differences between treatments ($df = 1/14$, $F = 0.6$, $P > 0.05$), significant differences between sessions ($df = 4/56$, $F = 114.6$, $P < 0.001$) and no significant treatments × sessions interaction [$df = 4/56$, $F = 0.8$, $P > 0.05$).

Discussion

As far as the control mice are considered, our results show that the BALB strain reach higher performance levels, compared with the C57 strain, in the patterns discrimination test. This is in agreement with previous results obtained under the same experimental conditions (Bovet-Nitti, 1969).

From the first set of experiments it is clear that both mescaline and amphetamine pretrial administrations improve the performance of the C57 strain. In the BALB mice, performance improvements followed the higher amphetamine administration only, while mescaline exerted, in this strain, an inhibiting effect. These results agree with results of investigations carried out with different animal species (rats, hamsters) trained in a variety of experimental conditions (Bignami et al., 1965; Cole, 1967; Bridger and Mandel, 1971; Bridger et al., 1972; Sansone et al., 1974; Gorelick and Bozewicz, 1975).

It must be stressed that, as to amphetamine, our experiments show that C57 mice are more sensitive than BALB mice to the improving effects of this drug on performance. This result is in agreement with results of previous researches carried out in rats (Rech, 1966) and mice (Meier et al., 1963). Meier et al. have shown in particular an 'exaggerated response' in the 'high arousal' C57 strain, and a much lower response in the 'low arousal' BALB strain with administration of the stimulant.

In the second set of experiments, when the drugs were injected immediately after each experimental session, the same effects were observed as in the pretrial experiments. No contrary effect was evident when the drugs were injected 2 h after each training session. It seems possible, then, to ascribe the effects of pretrial

administrations of mescaline and amphetamine to influences exerted by these drugs on the memory processes of the two strains tested.

The role of task, dose, and experimental conditions on effects of mescaline on memory has been demonstrated by some investigations (Kahn et al., 1974). It must be emphasized, in particular, that no effect on memory, following post-trial administrations of this hallucinogen, has been shown in thirsty rats trained to barpress for water or in rats trained in a passive avoidance task (Weissman, 1967; Siegel and Jarvik, 1971). Memory process improvements, following post-trial mescaline administrations have been shown in rats tested in a passive avoidance situation by Kahn et al. (1974).

As to amphetamine, memory-facilitating effects following the post-trial administration of this drug have been observed by a number of investigators (Doty and Doty, 1966; Krivanek and McGaugh, 1969; Evangelista and Izquierdo, 1971; Castellano, 1974).

It must be stressed that previous experiments (Castellano, 1978) have shown, in agreement with the present results, memory improvements in C57 mice swimming toward the dark in a light-dark discrimination test (Y water maze) following mescaline administration. The present results show, moreover, memory improvement following amphetamine and memory impairment following mescaline administrations in the Balb strain. Opposite effects, such as those observed in the BALB mice, have recently been (Castellano (1974, 1978) demonstrated following administrations of these drugs in DBA mice tested in the Y water maze.

It seems interesting, at this point, to underline differences in brain chemicals between the strains tested in the present and in previous presearch. Neurochemical investigations have demonstrated the existence of higher norepinephrine levels in the pons medulla hippocampus and cortex of the C57, compared to the BALB strain; higher levels of serotonin in pons medulla midbrain and forebrain of the BALB mice have also been demonstrated, compared to C57 mice (Kempf et al., 1976; Oliverio, 1978). Recently, the more active cholineacetyltransferase activity, leading to greater acetylcholine availability, in the hippocampus of the BALB strain, compared to the C57 strain, has been related to the greater capacity for long-term memory evident in the former strain (Jaffard et al., 1977. Finally, it must be pointed out that levels of mediators in the brain areas of the DBA strain are intermediate between those of C57 and BALB mice, and, in some areas (e.g. noradrenaline levels in pons medulla and hypothalamus) they are very similar to the BALB strain (Kempf et al., 1976; Oliverio et al., 1979).

In conclusion, the results of our research clearly stress the importance of genetic makeup in modulating effects of mescaline and amphetamine on behavior in the mouse. Wider pharmacogenetic and neurochemical investigations will clarify the role played by the levels and turnover of brain mediators in the reactivity of different strains of mice drugs tested here and in previous researches.

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