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PSYCHOACTIVE COMPOUNDS AND AUDIOGENIC SEIZURE SUSCEPTIBILITY

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Summary

The purpose of these experiments was to gain comparative information about psychoactive compounds on experimental convulsions, a phenomenon that has been used as an index of CNS excitability. LSD, mescaline, d- and l-amphetamine, cocaine and morphine were all effective in blocking audiogenic seizure susceptibility. None of the compounds were effective in blocking the priming of a non-susceptible strain of mice. This latter finding differentiates these compounds from Δ^9-tetrahydrocannabinol which has been previously reported to block priming.

Certain inbred strains of mice, normally not susceptible to audiogenic seizures, can be made susceptible by a priming procedure (1). Recent studies in our laboratory have shown that the psychoactive compound Δ^9-tetrahydrocannabinol (THC) is highly effective in blocking audiogenic seizure susceptibility (AGS) derived from priming a highly inbred strain of mice and is also effective if administered prior to the priming procedure (2). Other studies have shown that amphetamine will reduce AGS (3,4), while lysergic acid diethylamide (LSD) and cocaine will reduce pentylenetetrazol and electrical seizure thresholds (5,6).

In light of these data and the interest of our laboratory in psychoactive compounds and their behavioral effects, we studied the effects of LSD, D-2-bromo-lysergic acid diethylamide (BOL, a non-psychotomimetic derivative of LSD), d- and l-amphetamine, cocaine, morphine and mescaline on AGS. Our aim was to gain comparative information about these compounds on a behavior that has been used as an index of central nervous system excitability and to gain data that may prove useful in later studies of neurochemical correlation to drug action on behavior.

Materials and Methods

Subjects. Normally non-audiogenic seizure susceptible C57BL/6 mice, a seizure-susceptible mutant, C57BL/6-S (7) of this strain, and the seizure susceptible strain of mice DBA/2, were used in these studies. The animals were bred in our colony in the A.J. Carlson animal facilities of the University of Chicago. They were maintained under our standard laboratory condition of 12 hour light cycle (7 a.m. - 7 p.m.), a temperature of 74±2° F. and *ad libitum* access to Purina Mouse Breeder Chow and tap water. Approximately equal numbers of male and female mice were used. The ages of the mice are specified in the Results section.

Drugs. The drugs used in these experiments were LSD, BOL, d- and l-amphetamine, cocaine, morphine and mescaline. LSD and morphine were obtained from National Institutes of Mental Health. Both d- and l-amphetamine were received from Smith, Kline and French Laboratories, Philadelphia, Pa. Cocaine (cocaine hydrochloride) was obtained from Merck, Sharp and Dohme, West Point, Pa., BOL (BOL-148) from Sandoz Pharmaceuticals, Hanover, N.J. and mescaline from Regis Chemical Co., Chicago, Ill.

The dose and time regimens for these drugs are given in figures of the Results section. The doses are expressed as amount of free base. All drugs were mixed in saline and saline was used for control injections. All injections were intraperitoneal in a volume of 0.2 ml/10 g mouse.

Behavioral Procedures. Audiogenic seizure susceptibility was determined by placing the animals one at a time into a chromatography jar (12" deep x 12" I.D.) within a large styrofoam insulated box (16" x 17½" x 19½"). The box has a small plastic window through which to observe the mice. A 3" door bell (Lugen #13 by Edwards) generating 105±2 db of noise at the level of the mouse was mounted over the jar within the box. Approximately 10 seconds after placing the mouse into the chamber the bell was rung for 40 seconds or until the animal started to extend its hind legs after clonus. The incidence of wild running, clonic, tonic seizures and death were recorded.

C57BL/6 mice were made susceptible to audiogenic seizures through a priming

procedure (1). The animals when 19 or 20 days of age were exposed one at a time to the bell (priming) for one minute, returned to their home cage and retested for AGS, as detailed above, when 28 days of age.

Statistical Analysis. Chi Square analysis were performed by comparing the incidence for a particular parameter in the drugged animals with the incidence for that parameter in the control. Though significant differences are expressed as $p \leq .05$, many comparisons exceed this level of statistical significance.

Results

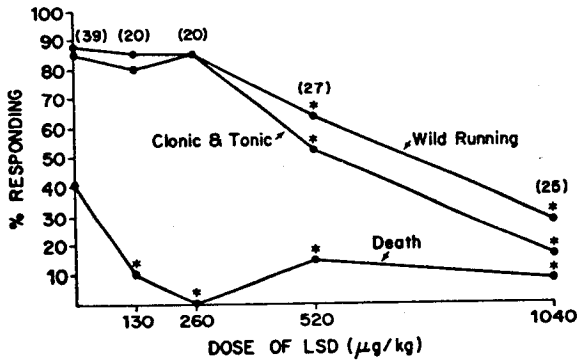

FIG. 1

Dose response effect of LSD on AGS. Animals (25 day old C57BL/6-S mice) were tested 10 min after injection. Numbers in parenthesis indicate number tested. *$p \leq .05$ when compared to control value for that parameter.

Doses of 1040 and 520 μg/kg of LSD given 10 minutes before testing were effective in reducing all indices of AGS while doses of 130 and 260 μg/kg LSD reduced the number of animals dying from audiogenic seizures (Figure 1). BOL at a dose of 1040 μg/kg and tested 10 minutes after injections was ineffective in reducing any index of AGS. The time course study of LSD on AGS shows that 1040 μg/kg LSD was effective in reducing all seizure indices 2½, 5 and 10 minutes after drug treatment and continued to be effective in reducing the incidence of death 20 minutes after treatment (Figure 2). Tolerance to 520 μg/kg LSD given once per day for seven days was found to develop in that the seventh injection

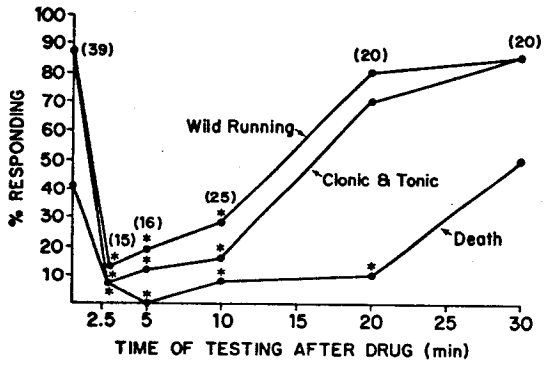

FIG. 2

Time response effect of LSD on AGS. Dose of LSD was 1040 µg/kg. Numbers in parenthesis represent number of animals (25 day old, C57BL/6-S mice) tested. *p<.05 when compared to control value for that parameter.

was less effective in blocking AGS than was a single dose of LSD given after six days of saline injection (Figure 3).

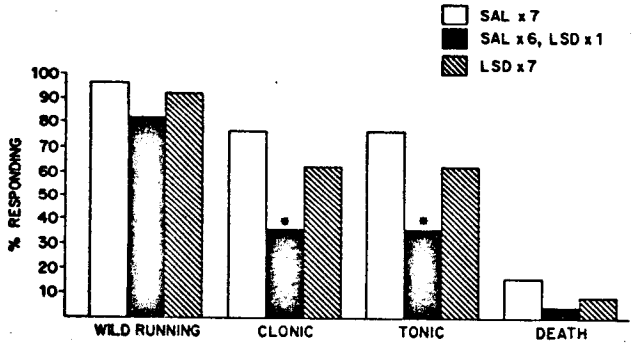

FIG. 3

Effect of multiple injections of LSD on AGS. Dose of LSD was 520 µg/kg. Animals (25 day old C57BL/6-S mice) were tested 10 min after injection. *p<.05 when compared to the control value for that parameter.

Mescaline at doses of 30 and 60 mg/kg but not 15 mg/kg was effective in blocking audiogenic seizures. The time course response of this drug at 30 mg/kg show that the drug at this dose is more effective at 30 minutes than at 15 and

90 minutes (Figure 4).

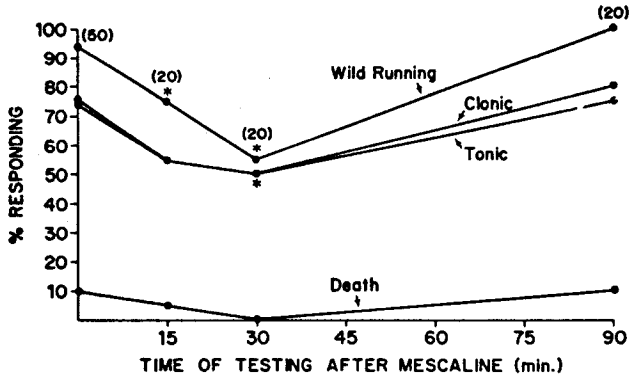

FIG. 4

Time response effects of mescaline. Dose of mescaline was 30 mg/kg. Numbers in parenthesis indicate number of animals (28 day old C57BL/6-S mice). *p≤.05 when compared to the control value for that parameter.

d- and l-Amphetamine given 15 minutes before testing were equally effective in decreasing the clonic and tonic aspects of AGS. However, d-amphetamine appears somewhat more effective in reducing wild running than l-amphetamine (Figures 5, 6), since 10 mg/kg d-amphetamine significantly decreases wild running whereas l-amphetamine at this dose did not.

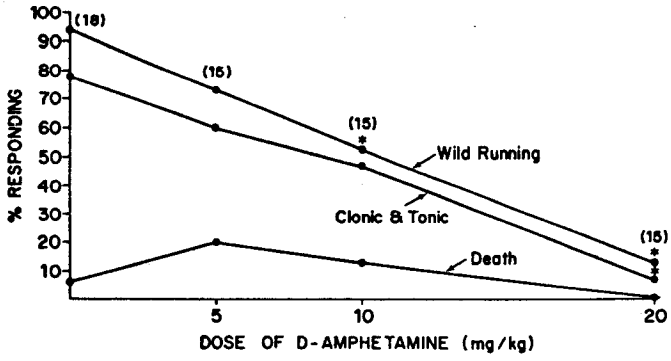

FIG. 5

Dose response effects of d-amphetamine on AGS. Animals (25 day old C57BL/6-S mice) were tested 15 min after drug. Numbers in parenthesis indicate number tested. *p≤.05 when compared to control value for that parameter.

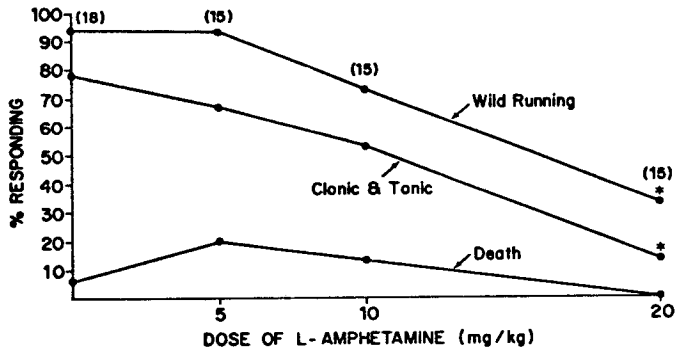

FIG. 6

Dose response effects of l-amphetamine on AGS. Animals (25 day old C57BL/6-S mice) were tested 15 min after drug. Numbers in parenthesis indicate number tested. *p≤.05 when compared to the control value for that parameter.

Cocaine at doses of 12.5, 25.0 and 50.0 mg/kg given 30 minutes before testing was effective in decreasing the AGS of these mice (Figure 7).

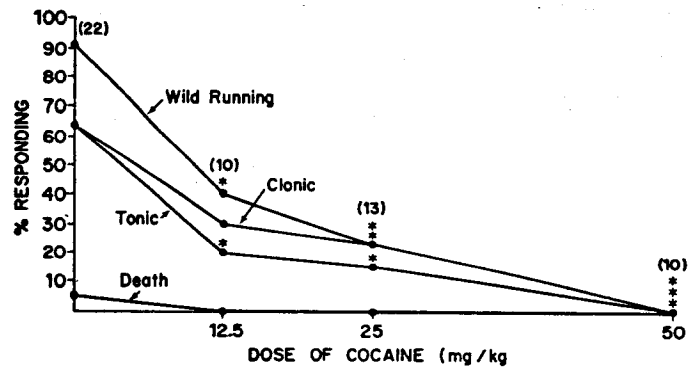

FIG. 7

Dose response effect of cocaine on AGS. Animals (28 day old C57BL/6-S mice) were tested 30 min after injection. Numbers in parenthesis indicate number tested. *p≤.05 when compared to the control value for that parameter.

Morphine in doses of 0.625, 1.25, 2.5 and 5.0 mg/kg was effective in blocking AGS in DBA/2 mice 20 minutes after injection (Figure 8). (DBA/2 mice were used in these experiments because the C57BL/6-S mice used in all previous experiments became unavailable.)

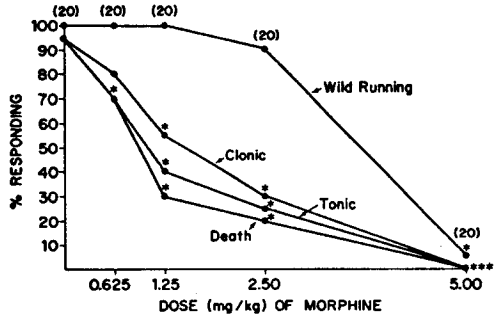

FIG. 8

Dose response effects of morphine on AGS. Animals (21 day old DBA/2 mice) were tested 20 min after injection. Numbers in parenthesis indicate number tested. *p<.05 when compared to the control value for that parameter.

None of the compounds tested were effective in blocking AGS derived from priming. The drug, the dose, and the time of priming after administration of the drug was as follows: LSD, 1040 µg/kg, 10 min; d-amphetamine, 10 mg/kg, 15 min; mescaline, 30 mg/kg, 30 min; cocaine, 50 mg/kg, 30 min; and morphine, 5 mg/kg, 20 min. These doses and times were chosen because they had been found effective in blocking AGS in normally susceptible mice as reported above.

Discussion

One of the purposes of these experiments was to gain comparative information about the effects of LSD, BOL, mescaline, d- and l-amphetamine, cocaine, and morphine on audiogenic seizure susceptibility. The fact that all the compounds with the exception of BOL (at the one dose and time studied) produced dose dependent inhibition of seizure susceptibility suggests that these compounds may have some common mode of action. Whether their effects are mediated through their effects on neurochemical, neurophysiological, or some other yet unspecified system remains to be determined.

It seems paradoxical that LSD which appears (through gross behavioral observation) to stimulate the animal, and d-amphetamine which increases the motor activity of the animal should block a major motor component (wild running) of

the seizure sequence as well as the other indices of the seizure. These data emphasize the necessity of classifying the actions of compounds in terms of individual behaviors rather than trying to make generalized statements about the drugs.

The protection afforded at 10 mg/kg by d-amphetamine, but not l-amphetamine against the wild running component of the seizure syndrome is interesting since Taylor and Snyder (8) found that d-amphetamine was 10 times more potent than l-amphetamine in enhancing motor activity. Svenssen (9), however, only found small differences in the motor activity of his mice after 10 mg/kg of d- and l-amphetamine.

The lack of effects of these compounds on the priming of C57BL/6 mice is not surprising, since general anesthetics, anticonvulsant drugs, food deprivation, electroconvulsive shock, and compounds which raise and lower brain amine concentrations have all been ineffective (10, 11). These findings, however, accent the relative unique quality of THC in being effective in reducing susceptibility from priming (2). The data suggest that mechanisms exist with respect to priming which differentiate THC from the psychoactive compounds tested in this study.

Acknowledgment

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