BRIEF COMMUNICATION

Memory Retention: Effect of Prolonged Cholinergic Stimulation in Mice[1]

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FLOOD, J. F., G. E. SMITH AND A. CHERKIN. *Memory retention: Effect of prolonged cholinergic stimulation in mice.* PHARMACOL BIOCHEM BEHAV 20(1) 161–163, 1984.—The fundamental hypothesis that drugs may affect memory processing by prolonging transmitter action was tested by extending the time of drug action, using repeated administrations of the cholinergic agonist, arecoline hydrobromide (ARE). The ARE was injected intracerebroventricularly into mice immediately after training (T-maze footshock avoidance) and at 90-min intervals thereafter, for a total of 1, 2, or 3 injections. The results indicate that 1 injection had no effect whereas 3 successive injections significantly improved memory retention test performance. The results confirm the hypothesis being tested; six control groups ruled out other plausible interpretations of the results.

Arecoline   Avoidance conditioning   Cholinergic   Memory   Mice   Retention

FOR two decades, researchers have attempted to alter memory processing by administering drugs which affect neurotransmitter systems. Numerous reports have demonstrated that increasing the activity of the cholinergic system by drug administration improves memory retention in animals [1–3, 8–14, 16, 17] and man [1, 4–6, 15, 18, 19]. A basic assumption of this research is that an increased level or duration of neurotransmitter activity alters memory processing. We tested and confirmed the hypothesis that increasing the duration of cholinergic activity will improve memory processing, by giving 1, 2, or 3 successive low-dose injections of a cholinergic agonist, arecoline hydrobromide (ARE, Sigma Chemical Co.), at 90-min intervals starting 3 min after T-maze active avoidance training.

METHOD

The subjects, male albino CD-1 mice, 60–70 days of age (Charles River Breeding Laboratories), were acclimated to the laboratory for 1 week before training. The mice were prepared, 24 to 48 hr prior to training, for intraventricular administration of ARE or saline solution. Intraventricular injections were used so that the results would reflect changes induced in the central nervous system. Details of the procedure have been published [8] and involved anesthetizing the mouse with methoxyflurane (Metofane), placing the mouse

into a stereotaxic instrument, deflecting the scalp, then drilling a single hole through the skull (−0.5 mm relative to bregma, 0.5 mm right of the central suture). The hole was covered with a light application of bone wax. The mice were housed singly following surgery and for the remainder of the experiment.

The mice were partially trained to avoid footshock (0.30 mA) in a T-maze constructed of black plastic. The maze consisted of an alley with a start box and guillotine door at one end and two opposed goal boxes at the other end of the alley. A shock grid floor ran throughout the maze [7]. A mouse was placed into the start box on the first training trial, the guillotine door was raised and simultaneously a buzzer sounded, followed 5 sec later by continuous scrambled footshock. The goal box which the mouse first entered was designated "incorrect" and the footshock continued until the mouse entered the opposite goal box. On all subsequent training trials, the latter goal box was "correct" for a given mouse. On the next three training trials, the mouse was placed in the start box, the buzzer was sounded as the guillotine door was raised and a 5-sec non-shock interval was allowed for the mouse to reach its correct goal box and thereby avoid footshock. If the mouse did not reach the correct goal box in 5 sec, it received footshock until it did so. After the fourth training trial, the mouse was anesthetized with ether and placed into the stereotaxic instrument. The

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Effects of Pentobarbital and d-Amphetamine on Oral Phencyclidine Self-Administration in Rhesus Monkeys

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CARROLL, M. E. *Effects of pentobarbital and d-amphetamine on oral phencyclidine self-administration in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV 20(1) 137–143, 1984.—Three rhesus monkeys self-administered phencyclidine (0.25 mg/ml) during daily 3-hr sessions. Water was also available under a concurrent fixed-ratio (FR) 16 schedule. In Experiment 1, saline or three doses of pentobarbital (2.5, 5 or 10 mg/kg) were injected 10 min before phencyclidine (and water) self-administration sessions. The 2.5 mg/kg pentobarbital dose increased phencyclidine-maintained responding, the 5 mg/kg dose produced mixed effects among the three monkeys, and the 10 mg/kg dose consistently decreased phencyclidine-maintained responding. Subsequently, a saccharin solution (0.03% wt/vol) replaced phencyclidine, and the pentobarbital pretreatment procedure was repeated. Pentobarbital produced dose-related decreases in saccharin-maintained responding. In Experiment 2, saline or three doses of d-amphetamine (0.05, 0.1 or 0.2 mg/kg) were injected 10 min before the phencyclidine self-administration sessions. The 0.05 mg/kg dose produced increases in phencyclidine-maintained responding, while the two higher doses produced dose dependent decreases in responding. When a saccharin solution (0.03%, wt/vol) replaced phencyclidine during the daily sessions, d-amphetamine produced only dose-related decreases in saccharin-maintained responding. These results indicate that pentobarbital and d-amphetamine have a biphasic effect on phencyclidine-maintained behavior; low doses increased responding and high doses decreased responding.

d-Amphetamine   Drug interaction   Oral drug self-administration   Pentobarbital   Phencyclidine
Rhesus monkeys   Saccharin

THERE has been considerable interest in the dissociative anesthetic, phencyclidine, due to its broad spectrum of central nervous system activity [19] and its widespread illicit use [6]. Phencyclidine is often abused in combination with other psychoactive drugs [40] as a result of its misrepresentation as another substance [34] or due to intentional polydrug abuse [20].

There have been a number of investigations of the effects of parenterally administered phencyclidine in combination with other psychoactive drugs. Generally, phencyclidine has been found to potentiate the action of barbiturates. Phencyclidine increased sleep time produced by hexobarbital and ethanol [46] and the lethality of pentobarbital [15] in mice. In rhesus monkeys [15,52] and patas monkeys [47] pentobarbital increased disruptive effects of phencyclidine on schedule-controlled behavior. However, phencyclidine did not increase pentobarbital's depressant effects in squirrel monkeys [14]. Phencyclidine has also been reported to increase disruptive effects of Δ^9-tetrahydro-cannibinol on conditioned avoidance behavior, rotarod performance, photocell activity and schedule-maintained performance in rats [43]. Phencyclidine increased amphetamine stereotypy in rats [3]; however, the two drugs produced infraadditive effects on schedule-controlled responding in rats [42].

The purpose of the present investigation was to study the effects of parenterally-administered pentobarbital and d-amphetamine on oral phencyclidine self-administration. With the exception of studies concerning specific blocking agents (e.g., [22–25, 27, 51]), there have been few reports of drug interactions in the self-administration context. While previous studies have shown that phencyclidine enhances or inhibits the disruptive effects of pentobarbital and d-amphetamine on schedule-controlled behavior, it was the goal of the present study to determine whether these drugs would increase or decrease phencyclidine self-administration. The effects of pentobarbital and d-amphetamine pretreatment on saccharin self-administration were also studied to compare effects due to drug interactions to the direct effects of pentobarbital and d-amphetamine on schedule-controlled behavior.

METHOD

Animals

Three adult male rhesus monkeys (M-A, M-M1 and M-R) were used in these experiments. Monkey M-A received previous exposure to phencyclidine and saccharin in a phencyclidine tolerance study [9], M-R had previous experience with

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is unlikely because this group performed significantly better than did any of the 5 other groups which also received 3 injections. Three spaced low-dose injections of ARE were required to improve retention test performance since this group (ARE+ARE+ARE) performed significantly better than did either the ARE+SAL+SAL group ($p<0.01$, Dunnett's T-test) or the ARE+ARE+SAL group ($p<0.05$, Dunnett's T-test). The total cumulative dose of ARE (150 ng) did not account for the high retention test scores in the ARE+ARE+ARE group because the SAL+SAL+3ARE group, which also received 150 ng of ARE but in a single injection, did not remember as well as did the group receiving the same dose spread over three successive injections (Table 1).

One may question what evidence exists that the partial training the mice received resulted in a memory trace which the drug treatments could modify. The left-right discrimination is remembered well by all groups. This is evidenced by the fact that only 10% of the saline-injected mice and 5% of the ARE+ARE+ARE mice, made a discrimination error on the first trial of the retention test. The mice remembered where to escape from footshock but unlike the ARE+ARE+ARE treated mice, control mice do not remember enough of the training to make an avoidance response on trials 1–3 of the retention tests.

The results of this experiment support a fundamental hypothesis of cholinergic drug studies in experimental and clinical research that prolonging cholinergic receptor activity promotes better memory processing. It will be the goal of future research to determine if these results are generalizable to other cholinergic agonists or to other transmitter systems whose increased activity is associated with improved retention.

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