d-AMPHETAMINE-CHLORPROMAZINE
ANTAGONISM IN A FOOD REINFORCED OPERANT¹

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Dose effect curves for *d*-amphetamine and chlorpromazine were obtained with rats on a milk reinforced FR 10 schedule. A dose of *d*-amphetamine (2.5 mg/kg, i.p.) which completely suppressed all responding for 60 min was administered simultaneously (concomitant with the pretreatment times) with various doses of chlorpromazine. The *d*-amphetamine-induced cessation of responding was removed by several of the doses of chlorpromazine with maximal antagonism occurring at a dose of 1.5 mg/kg i.p. This dose of chlorpromazine, when administered independently, produced no observable side effects and showed no effect on the FR 10 schedule. One animal appeared to develop tolerance to the repeated dosages of *d*-amphetamine.

Some amphetamines have been shown to have a variety of central nervous system actions, which under certain circumstances, can be antagonized by other centrally active agents. Lasagna and McCann (1957) have demonstrated the antagonism of the aggregate toxicity effect of *dl*-amphetamine with chlorpromazine and other central depressants. Teitelbaum and Derks (1959) have presented evidence of an antagonistic effect of chlorpromazine against *dl*-amphetamine in forced drinking behavior maintained by electric shock avoidance. Further, *dl*-amphetamine is known to depress certain food reinforced operants (Dews and Morse, 1961), and it has been used to antagonize chlorpromazine effects on conditioned avoidance responses in rats (Jenney and Healy, 1959). This report describes a procedure in which other behavioral effects of amphetamine can be antagonized.

PROCEDURE

Four male Wistar rats from the animal colony of the Walter Reed Army Institute of Research, kept at 80 to 90% of their established *ad libitum* feeding weight, were used.

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They were six to eight months of age and weighed 275 to 350 g at the beginning of the experiment. They had free access to multi-vitamin supplemented water, except during the experimental session. After initial training, the rats were exposed daily to a FR 10 schedule of reinforcement. Each daily session lasted until the subject had received 125 reinforcements. The apparatus was a small animal chamber with a single response lever and liquid feeder for reinforcement. Lever responses were reinforced with 3-sec access to 0.1 cc sweetened multi-vitamin supplemented condensed milk.

After behavior had stabilized under the FR 10 schedule, at an average rate of approximately 100 responses per min, the dose effect relation of reduction in responding with *d*-amphetamine (Dexedrine Sulphate, Smith Kline and French) and chlorpromazine (Chlorpromazine Hydrochloride, Smith Kline and French) was established for each subject. Doses of chlorpromazine were then used to challenge some of the behavior disrupting effects of *d*-amphetamine. That is, in the antagonism sessions both drugs were administered successively in accordance with their respective pretreatment times. All injections were made intraperitoneally in volumes of 0.1 ml/100 g of body weight from an appropriate solution in 0.9% NaCl. All solutions were prepared daily. At least 72 hr elapsed between injections of either drug, and sessions without injections were continued during the interval. A minimal effective dose (MED) of *d*-amphetamine was de-

Fig. 1. Dose effect curves in responses per minute for *d*-amphetamine (upper) and chlorpromazine (lower). Each point represents the mean of three sessions.

Fig. 2. Dose effect curve in responses per minute for the antagonism sessions. The abscissa represents the dose of chlorpromazine used to antagonize the MED effect of *d*-amphetamine. Each point represents the mean of at least three sessions. It can be seen that in all instances maximum antagonism occurred at 1.5 mg/kg.

terminated. The MED was defined as the smallest dose ± 0.5 mg/kg, which produced complete cessation of responding (zero responses per min) for a minimum of 1 hr. Subsequently each rat was treated with its

Fig. 3. Sample cumulative recordings of antagonism sessions compared with saline control sessions (C) and the MED effect of *d*-amphetamine (0.0). The numbers represent the doses (mg/kg) of chlorpromazine used to antagonize the MED effect.

Fig. 4. Cumulative recordings of the performance of rat WRA-3 showing evidence of tolerance to successive administrations of *d*-amphetamine. The upper record shows the MED effect, the lower records show the successive loss of this effect.

MED of *d*-amphetamine and possible antagonism with various doses of chlorpromazine was studied. Antagonism was defined as the reinstatement of lever pressing behavior during the 1 hr interval under the MED dosage of *d*-amphetamine.

Since tolerance to certain behavioral effects of amphetamine can occur (Schuster and Zimmerman, 1961), the subjects were tested regularly with *d*-amphetamine alone as an assessment for the development of tolerance.

RESULTS AND DISCUSSION

Dose effect curves for several doses and pretreatment times of *d*-amphetamine indicated a minimal effective dose of 2.5 mg/kg with a 20 min pretreatment (Fig. 1). Complete cessation of responding occurred for 90 to 120 min (therefore, it was decided to use a session length of 1 hr in the antagonism sessions). In most cases, chlorpromazine showed characteristic dose range effects from 2.0 to

3.0 mg/kg with a 25 min pretreatment. The dose response functions for chlorpromazine are also shown in Fig. 1. Dose effects of chlorpromazine above 3.0 mg/kg were complicated by observable side effects.

In the antagonism sessions, chlorpromazine had a distinct dose effect in its antagonism of the MED of *d*-amphetamine. There appeared to be one dose (1.5 mg/kg) which maximally antagonized the MED of *d*-amphetamine (Fig. 2 and 3). Also dose levels of chlorpromazine which had no measurable behavioral effects on FR 10, had clear antagonistic effects. In other words, the antagonistic effect was more sensitive to chlorpromazine than was the maintained behavior under study. Indeed, maximum antagonism occurred at doses below those which showed activity in standard dose range observations.

Evidence of tolerance occurred in only one rat (WRA-3, see Fig. 4). In the other animals the behavior under *d*-amphetamine remained stable for the duration of the study.

The results of this experiment, then, demonstrate the existence and measurement of *d*-amphetamine-chlorpromazine antagonism in a food reinforced operant. This antagonism has many psychopharmacological implications, some of which are now under investigation.

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