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BRIEF COMMUNICATION

Effects of Methaqualone on Learning: A Failure to Observe Tolerance[1]

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FRANKENBERGER, W. R. AND H. ZENICK. *Effects of methaqualone on learning: a failure to observe tolerance.* PHARMAC. BIOCHEM. BEHAV. 3(3) 529–531, 1975. – The study was designed to assess the effects of Methaqualone (MTQ) on learning, as well as the effects of 15 days of pretask drug exposure on performance. Forty CFE rats were randomly divided into four groups: Group I received daily IP injections of MTQ for 15 days prior to and throughout the duration of the task; Group II served as a control for Group I, receiving injections of the carrier vehicle; Group III received MTQ at the start and throughout the duration of the task; Group IV served as the control for Group III. The task consisted of two pretraining days of swimming down a straight, all-white alleyway, followed by 5 trials/day for 4 days on a black-white discrimination task in a water T maze, with the white side being reinforced for all animals. Analyses revealed that MTQ animals made significantly more errors than controls. Pretask drug exposure did not significantly alter Group I performance versus Group III. Furthermore, continued injections for half of the animals in Group I and II for eight days following the last learning day did not improve Group I performance when retested on the same task. Thus MTQ adversely affected learning with prolonged drug exposure failing to reverse such debilitation.

Methaqualone Discrimination learning

INTRODUCED to the American medical market in 1965 as a nonbarbiturate hypnotic with a low incidence of physical dependence, Methaqualone (MTQ) became a fad drug of abuse by 1972–73 [8]. Although MTQ has been the object of a variety of investigations, there is no research on the effect of the drug on learning and memory. In fact, the only related study involved a MTQ derivative and its ability to disrupt a previously acquired conditioned avoidance response at hypnotic dosages [6]. It is possible that the development of behavioral and/or physical tolerance to a drug may compensate for the debilitating effects the drug may have on learning [2,5]. MTQ deserves additional investigation in view of the possible tolerance that develops to the drug [4,5].

The present study was designed to assess the effects of MTQ on the acquisition of a black-white discrimination task. In addition, the effect of pretask drug exposure was examined.

METHOD

Animals

Forty CFE female rats, 105 days of age were used. Animals were housed individually and maintained on a 12 hr deprivation schedule with water ad lib.

Apparatus

A water-escape, T maze was constructed of galvanized iron and painted with a flat black enamel paint. The stem was 76 cm long and 15.5 cm wide; the alleyways were 30.9 cm long and 14.2 cm wide. A white panel that fit along one side of the stem and an arm of the maze was also constructed. This panel was interchangeable with both sides of the maze. The water in the maze was 20.32 cm deep and was maintained at 29°C.

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Drugs

Pilot studies, examining a range of MTQ dosages (5–50 mg/kg) revealed that dosages between 20–30 mg/kg successfully disrupted discrimination learning. Higher dosages incapacitated the animal to the extent that task performance was not possible. The dosage employed in this study was 25–30 mg/kg of MTQ (free base) dissolved in dimethyl sulfoxide (DMSO) and brought to a concentration of 50 mg/ml for IP injection. Larger animals required the larger dosage (4 animals, weighing between 225–250 g) with loss of the righting reflex being the criterion for effective dosage. Control injections consisted of equivalent volumes of DMSO based upon the animal's weight.

Groups and Conditions

Animals were randomly divided into four groups with ten animals/group. The groups were further divided into squads for running on the learning task. Squad 1 consisted of 20 animals, 5 animals randomly selected from each group and Squad 2, the remaining 20 animals. The treatment protocol was as follows: Group I (GI) received daily injections of MTQ for 15 days prior to the start of the learning task and then throughout its duration; Group II (GII) served as a control, receiving injections of DMSO on the same temporal schedule as GI; Group III (GIII) received MTQ at the start of the learning task and throughout the course of the test phase; Group IV (GIV) served as a control receiving DMSO on the same schedule as GIII.

Procedure

All animals lost the righting reflex within 5 min following injection. All animals had recovered when testing began, 1 hr later. Animals received 5 trials/day for 2 days in a straight, all-white, water runway with an escape ramp placed at the end. The learning task began on the third day in the T maze, with all animals being reinforced for white. Animals received 5 trials/day for 4 days with the correct side being counterbalanced across the 20 trials. Errors were recorded for each animal, with an error being defined as any turn inconsistent with escape. Thus if the animal entered the wrong arm (entry past forelegs) or turned and headed back up the stem, an error was scored.

Animals in GI and GII, Squad 2, were continued on the injection schedule and retested 8 days later, with each animal receiving 5 trials on the same task. This manipulation was done to assess the degree of retention as well as any improvement or worsening in performance resulting from continued drug exposure. The data conformed to a 2 (squads) X 2 (drug-no drug) X 2 (pretask exposure or none) X 4 (days) repeated measures analysis of variance.

RESULTS AND DISCUSSION

There were no differences in weight gains between MTQ treated and control subjects. Kohli *et al.* [4] have made similar observations.

The analysis of variance was calculated assigning drugs, exposure, and squads as between group sources and days as a within group source. Because there were no significant differences attributable to squads or to any interactions involving squads, the residual mean square was used as an error estimate for between subjects components; likewise, the corresponding residual was used for within subjects comparisons. The analysis of variance revealed three significant factors; namely, drug, day, and drug X day interaction. Neither pretask drug exposure nor squad variables nor any other interactions were significant.

Animals receiving MTQ (GI, GIII) made significantly more errors than the controls GII, GIV, $F(1) = 27.67$, $p<0.001$. The significant days' effect, $F(3) = 5.39$, $p<0.05$, reflected improvement for all groups across days of testing; however, the drug X day interaction, $F(3) = 3.43$, $p<0.05$, indicated a significantly better rate of learning by the controls. Group mean errors across days are plotted in Fig. 1. Scores were collapsed across squads, since this variable was not significant. It can be seen in Fig. 1 that the drug X day interaction can in part be attributed to increased errors by the drug groups on Days 2 and 3.

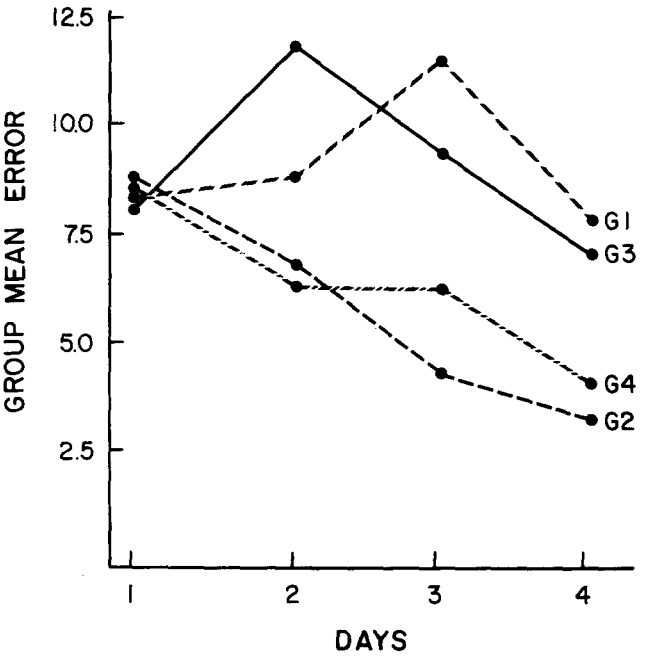

FIG. 1. Day by day group mean errors. Graph symbols: GI = MTQ pretask drug exposure; GII = pretask exposure control; GIII = MTQ task-only exposure; GIV = task-only exposure control.

A matched *t*-test comparing last day acquisition errors vs retest errors for animals in GI and GII, Squad 2, revealed no significant differences in transfer for the two groups, indicating that further MTQ exposure did not worsen performance. However, an independent *t*-test comparing retest errors between the two groups, indicated that GII still performed better than their drug counterparts ($t = 3.55$, $df = 8$, $p<0.01$). Thus continued MTQ exposure did not reverse any previous debilitation.

Tolerance to MTQ has been noted in animals on such measures as spontaneous motor activity and rectal temperature [4]. Such tolerance was not observed on the task employed in this study. Pretask drug exposure did not reverse the adverse influence of MTQ on either test or retest performance.

Kohli *et al.* [4] reported that only partial tolerance occurred when rats were exposed for seven days to 392.6 mg/kg/day via a semifluid diet. Tolerance did occur within the same animals at lower doses of 138.3 and 284.4

mg/kg/day administered for seven days respectively. It is difficult to equate the potency of a dosage added to a diet with the method employed in the present study; namely injecting the drug IP into 12 hr, food-deprived animals. In either case, both studies may indicate that a high dosage of MTQ decreases the probability that tolerance will develop.

Another possible factor is the time between injections. Singh [7] has found that maximum tolerance to pentobarbital occurs 17–22 hr following injections with a decline beyond that length of time. It is possible that MTQ injections must be closer than a 24 hr interval for tolerance to develop. However, data on MTQ turnover in the brain does not support this contention since MTQ is still present in the brain 24 hr after injection [1].

Although tolerance was not reflected on this task, it has been seen on other behavioral parameters. Thus the conclusions regarding this aspect of MTQ use remain inconclusive. What is conclusive, however, is that MTQ exposure did adversely affect discrimination learning. This finding is of special importance in light of the current widespread abuse of the drug.

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