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The Role of Locomotion in Conditioning Methylphenidate-Induced Locomotor Activity

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SCHREIBER, H. L., W. G. WOOD AND R. H. CARLSON. *The role of locomotion in conditioning methylphenidate-induced locomotor activity.* PHARMAC. BIOCHEM. BEHAV. 4(4) 393–395, 1976. – This experiment determined whether overt performance of the entire response (actual running) was necessary for the conditioning of methylphenidate-induced locomotor activity (wheel-running) in guinea pigs. Four guinea pigs were given daily injections of 2.5 mg/kg methylphenidate and were allowed to run in activity wheels; 4 other guinea pigs were given methylphenidate and were placed in locked activity wheels; a third group of 4 guinea pigs were administered saline and allowed to locomote; a fourth group of 4 guinea pigs received saline injections and were placed in locked activity wheels. After 12 days of injection, all animals were given saline injections on the 9 subsequent days and allowed to run freely in the wheels. The 2 groups which had received methylphenidate showed more locomotor activity than the saline injected animals but were not distinguishable from each other on the basis of prior opportunity to engage in locomotor activity. These results were interpreted to indicate that (a) increased methylphenidate-induced locomotor activity may be conditioned with repeated administration of the drug, and (b) actual running is not essential for the conditioning of drug-induced wheel-running.

Methylphenidate Locomotor activity Chronic drug administration Tolerance

IT has been well-established that increased or decreased levels of locomotor activity may be conditioned by the repeated administration of many psychoactive drugs [3, 7, 8, 9, 12]. In this paradigm, the combined stimuli of the act of injection serve as the conditioned stimulus (CS); the internal drug stimuli which impel activity serve as the unconditioned stimulus (US); and, locomotor activity serves both as the conditioned and unconditioned response (CR, UR). A number of prior experiments have shown that overt performance of the complete response is not essential for conditioning to occur [3]. Therefore, full-fledged running should not be necessary for conditioning increased levels of drug-induced wheel-running. The present study tested this hypothesis using the mild psychomotor stimulant methylphenidate (Ritalin).

METHOD

Animals

Eighteen male Hartley strain guinea pigs with a mean weight of 369.1 (S.D. = 50.7) were individually housed in (6 mm) wire mesh cages (24 cm × 30 cm × 15 cm) in a colony room with controlled temperature and a 12 hr light/dark cycle (lighted from 10 a.m. to 10 p.m.). Guinea pigs were given free access to water and mash, which consisted of pelletized Purina rabbit chow, powdered Vitamin C and water; this diet was supplemented by biweekly rations of fresh lettuce or carrots.

Apparatus

Activity was measured in half-revolutions in Wahmann activity wheels, modified by hardboard panels to prevent egress from the revolving portion of the wheels.

Procedure

The experiment was divided into 3 periods: a 14 day adaptation period, a 12 day training period, and a 9 day withdrawal period.

Adaptation. During the adaptation period, the animal were randomly divided among 3 shifts. On each shift, each animal was given a subcutaneous injection of saline (.10 cc) just prior to placement in the activity wheels. The daily testing sessions were of 2 hr duration for each shift.

Training Following the adaptation period, the animals were matched in groups of 4 according to their total wheel-running activity during the last 4 days of the adaptation period. Members of each matched group were

then randomly assigned to 1 of 4 treatment conditions for the remainder of the experiment. Two guinea pigs which had received the lowest total locomotor activity scores were excluded from the remainder of the study. Thus, the following 4 groups were formed: (a) one group of 4 guinea pigs received methylphenidate injections (2.5 mg/kg, 1 cc/kg, SC between scapulae) and were placed in freely rotating activity wheels for the daily testing sessions (Ritalin/training); (b) another group of 4 guinea pigs received methylphenidate injections (2.5 mg/kg, 1 cc/kg, SC between scapulae) and were placed in non-rotating activity wheels for the daily testing sessions (Ritalin/non-training); (c) the third group of 4 guinea pigs received comparable amounts of saline (SC between scapulae) and were placed in freely-rotating activity wheels, (saline/training) and; (d) the fourth group of 4 guinea pigs received comparable subcutaneous injectinos of saline between the scapulae and were placed in non-rotating activity wheels (saline/nontraining). The non-rotating activity wheels were immobilized with removable wire hooks, such that, when the wheels were locked, the greatest possible movement was a slight back-and-forth rocking (± 2 cm).

The animals were divided into 4 shifts for daily testing, each shift containing 4 guinea pigs. The shifts were tested at approximately the same hr from day to day. The daily testing session for each shift was 2 hr and 15 min long. Each animal was tested in the same, individually-assigned, activity wheel throughout the training and withdrawal periods. Wheel assignments were arranged from shift to shift such that each activity wheel was used to test 1 animal from each of the 4 treatment groups on any given day of training or withdrawal.

Withdrawal. All procedures established for the training period were continued during the withdrawal period, except that all animals received saline injections and all animals activity wheels were unlocked and allowed to rotate freely.

Statistical Analysis

All locomotor activity scores for 3 day blocks were averaged to form a mean score per animal in order to reduce day-to-day variation; these 3 day means were subjected to a Poisson transformation ($\sqrt{X} + .5$) in order to meet the homogeneity of variance requirements of analysis of variance designs. The training period activity scores of the Ritalin/training and the saline/training groups were analyzed using a split-plot factorial (2 × 4) analysis of variance (A = drug group. B = day of training). The activity scores of the Ritalin/training, Ritalin/non-training, saline/training and saline/non-training groups for the first day of withdrawal were analyzed using a completely-randomized factorial (2 × 2) analysis of variance (A = drug group; B = opportunity to locomote). The activity scores of the 4 groups for the entire withdrawal period were analyzed using a split-plot factorial (2 × 2 × 3) analysis of variance (A = drug group; B = opportunity to locomote; C = day of withdrawal). Subsequent comparisons between means and tests of simple main effects were performed according to Kirk [5, pp. 283–291]; significance was designated at $p \leq 0.05$.

RESULTS

Training

As expected, the guinea pigs in the Ritalin/training group showed significantly more wheel-running than the saline/training group during the total training period $F(1,6) = 21.502$, $p = 0.004$). Subsequent comparisons between means for the guinea pigs showed that, whereas the Ritalin/training group was not significantly more active than saline/training group on the first 3 day block, they were significantly more active than the saline/training group by the last 3 day block. The Ritalin/training group showed a significant increase in their level of wheel-running from the first 3 day block to the fourth 3 day block; the saline/training group showed a nonsignificant decline in locomotor activity from the first 3 day block to the fourth 3 day block. Thus, a Drug × Day of Training interaction was suggested $F(3,18) = 1.842$, $p = 0.1748$), as illustrated in Fig. 1.

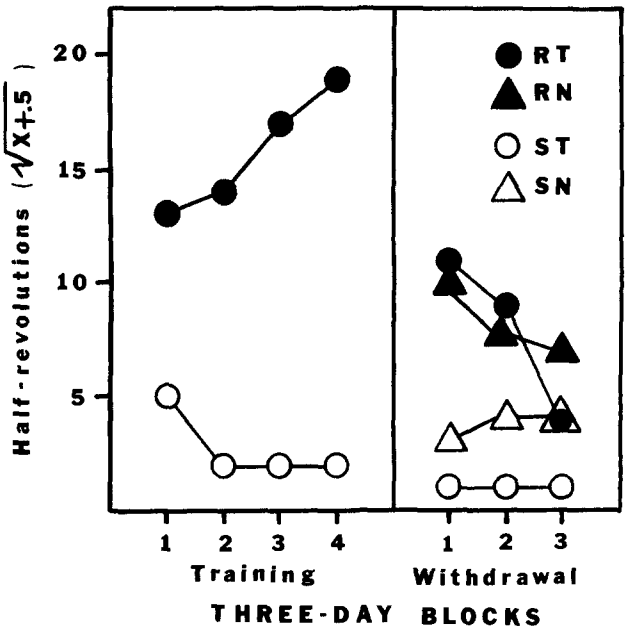

FIG. 1. Mean number of half-revolutions per 3 day block for Ritalin/training group (RT), Ritalin/nontraining group (RN), saline/training group (ST) and saline/nontraining group (SN) during Training and Withdrawal periods.

Withdrawal

During withdrawal, no animals received methylphenidate, but the guinea pigs which had received methylphenidate injections showed significantly more wheel-running activity than the guinea pigs which had received saline injections $F(1,12) = 14.383$, $p = 0.0028$). However, the opportunity to run during the training period had relatively little effect on the level of locomotor activity upon drug withdrawal: the activity levels of guinea pigs with training were not significantly different from the activity levels of the guinea pigs with nontraining $F(1,12) = 0.018$, $p = 0.8900$). The guinea pigs which had received methylphenidate showed a significant Drug Group × Day of Withdrawal interaction $F(2,24) = 8.448$, $p = 0.0013$) such that both the Ritalin/training and Ritalin/nontraining groups showed a continuous decline in wheel-running over the three 3 day blocks of the withdrawal period, as illustrated in Fig. 1. By the third 3 day block, no significant difference was found among the 4 treatment groups.

DISCUSSION

During the training period, the guinea pigs in the Ritalin/training group showed increasingly higher levels of locomotor activity as would be expected if conditioning were taking place. During the withdrawal period, the guinea pigs in the Ritalin/training group showed decreasing levels of locomotor activity as would be expected if extinction were taking place. Thus, the wheel-running activity patterns of the Ritalin/training guinea pigs seemed to fit the model for the conditioning of locomotor activity. The lack of observable tolerance development in *d*-amphetamine-induced motor activity has been explained by the conditioning of increased levels of locomotor activity [7, 8, 12]. Whereas early studies [6, 11, 13] have noted the absence of tolerance in methylphenidate-induced locomotor activity, more recent reports [1, 10, 14] have noted behavioral tolerance development with the drug. Therefore, the present results suggested the same potential explanation for the conflicting reports of methylphenidate tolerance that was asserted for the absence of tolerance in *d*-amphetamine-induced motor activity.

The guinea pigs in the Ritalin/nontraining group showed essentially the same pattern of locomotor activity upon methylphenidate withdrawal that the guinea pigs in the Ritalin/training group showed. Although the guinea pigs in the Ritalin/nontraining group were prevented from wheel-running by the locked activity wheels, they were able to engage the wheels in a slight back-and-forth rocking. This rocking, once associated with the act of injection, may have been sufficient to have spurred the increased wheel-running seen during the withdrawal period.

An alternative explanation for the similarity between the Ritalin/training and the Ritalin/nontraining groups during the withdrawal period was that methylphenidate-induced anorexia, rather than conditioning was responsible for the changes in activity level. Although food consumption was not measured in the present experiment, this explanation was rejected for 2 reasons. First, guinea pigs who received the same dosage of methylphenidate (2.5 mg/kg, 1 cc/kg, SC) in a subsequent experiment showed no decrease in food or water consumption over 12 days of drug administration (Schreiber, Wood and Carlson, unpublished manuscript). Second, food was continuously available in the animals' home cages long after methylphenidate's reported duration of effect had ended [4]. A second alternative explanation for the present results was considered unlikely, but could not be immediately rejected. Some physiological change resulting from the chronic administration of methylphenidate may have produced the parallel activity pattern of the 2 Ritalin groups during withdrawal. In another study [15], 1 group of rats received 25 consecutive daily injections of methylphenidate (2.5 mg/kg, 1 cc/kg, SC) while a second group of rats received 24 consecutive injections of saline and 1 injection of methylphenidate on Day 25. There was no significant difference between the groups' activity scores when both groups were given a saline injection and tested in a Y-maze on Day 26. Nonetheless, since guinea pigs, not rats, were subjects in the present experiment, this alternative explanation (methylphenidate dependence) could not be rejected out of hand.

REFERENCES

1. Fregly, M. J. and B. A. Black. Effect of methylphenidate on spontaneous activity, food intake and cold tolerance of propylthiouracil-treated rats. *Can. J. Physiol. Pharmac.* **42:** 415–429, 1964.
2. Hilgard, E. R. and D. G. Marquis. *Conditioning and Learning*, revised by G. A. Kimble. New York: Appleton-Century-Crofts, 1961, pp. 224–225.
3. Irwin, S. and P. Armstrong. Conditioned locomotor response with drug as the unconditioned stimulus: Individual differences. In: *Neuropsychopharmacology*, edited by E. Rothlin. Amsterdam: Elsevier, 1961, pp. 151–157.
4. Karczmar, A. G. Anorexigenic action of methylphenidate and pipradrol. *Proc. Soc. exp. Biol. Med.* **102:** 163–167, 1959.
5. Kirk, R. E. *Experimental Design: Procedures for the Behavioral Sciences.* Belmont: Brooks/Cole Publishing Co., 1968.
6. Meier, R., F. Gross and J. Tripod. Ritalin, eine neuartige synthetische verbidung mit spezifischer zentralerrengender wirkungskomponente. *Klin. Wschr.* **32:** 445–450, 1954.
7. Pickens, R. and W. Crowder. Effects of CS-US interval on conditioning of drug response, with assessment of speed of conditioning. *Psychopharmacologia* **11:** 88–94, 1967.
8. Pickens, R. and J. Dogherty. Conditioning of the activity effects of drugs. In: *Stimulus Properties of Drugs*, edited by T. Thompson and C. Schuster. New York: Appleton-Century-Crofts, 1971, pp. 39–50.
9. Ross, S. and S. Schnitzer. Further support for a placebo effect in the rat. *Psychol. Rep.* **13:** 461–462, 1963.
10. Schreiber, H. L., W. G. Wood and R. H. Carlson. Tolerance in methylphenidate-induced locomotion in prairie dogs (Cynomys Ludovicianus). *Psychopharmacologia* (accepted for publication as a Brief Report, October 6, 1975) in press.
11. Sommer, S. and R. Hotovy. Zur differenzierung der zentralerrengenden wirkung von 2-athylamino-3-phenylnorcamphan. *Arzneimittelforsch.* **11:** 967–972, 1961.
12. Tilson, H. A. and R. H. Rech. Conditioned drug effects and absence of tolerance to *d*-amphetamine induced motor activity. *Pharmac. Biochem. Behav.* **1:** 149–153, 1973.
13. Utena, H. and S. Takano. Reduction of spontaneous activity of mice induced by drugs. *Folia psychiat. neurol. jap.* **6:** 38–47, 1960.
14. Wood, W. G., H. L. Schreiber, R. Villescas and R. H. Carlson. Pharmacological and behavioral tolerance to methylphenidate-induced activity in rats. *Neuroscience Abstracts* Vol. 1. Bethesda: Society for Neuroscience, 1975, p. 380.