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BRIEF COMMUNICATION

Caffeine Effects: Interaction of Drug and Wheelrunning Experience

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MELISKA, C. J., R. E. LANDRUM AND W. H. LOKE. *Caffeine effects: Interaction of drug and wheelrunning experience.* PHARMACOL BIOCHEM BEHAV **23**(4) 633–635, 1985.—Male Sprague-Dawley rats were tested for wheelrunning following repeated injections of caffeine or distilled water after varying amounts of experience with caffeine and wheelrunning. Rats experienced with caffeine in combination with wheelrunning ran significantly more than rats experienced only with caffeine or wheelrunning alone. Results suggest that caffeine's stimulant effects are greater when subjects are experienced with wheelrunning while under the influence of the drug.

Caffeine Wheelrunning Drug experience Behavioral tolerance

AN animal's response to a drug may be influenced by prior experience with it [5]. Sometimes mere exposure to a particular drug—i.e., without behavioral testing—is sufficient to change reactivity to the drug (e.g., [12]). In other cases, changed responsiveness occurs only when the drug is administered in a particular test situation. This latter form of adaptation has been called "behavioral tolerance" and appears to depend on learning or conditioning rather than pharmacodynamic or drug-dispositional changes in the animal [4, 7, 9, 11, 13].

While tolerance typically implies a lessening of drug effect, some behavioral adaptations to drugs involve enhancement of the drug's actions [7]. For example, in a recent study [6], rats experienced with caffeine and wheelrunning ran more wheel revolutions when given the drug than inexperienced rats. However, whether the increment depended upon experience with the drug alone, with wheelrunning alone, or with the combination of drug and wheelrunning could not be determined from the original study. The present experiment was designed to clarify whether rats' changed wheelrunning responsiveness following repeated administrations of caffeine is due to experience with the drug, experience with wheelrunning, or the combination of the two.

METHOD

Subjects

Eighteen experimentally naive, male Sprague-Dawley rats, approximately 80–90 days old at the start, were maintained on ad lib food and water throughout the experiment.

Apparatus

Six standard activity wheels (Wahmann Mfg, Baltimore, MD), 36 cm in diameter × 11 cm wide, were each housed in separate test cubicles. The sliding door at each wheel entrance was closed to prevent animals from leaving the wheel during testing.

Procedure

Rats were randomly assigned to one of three groups of N = 6 each: The (DW)CAF (Distilled Water/Caffeine) group received IP injections of distilled water (DW), 2 ml/kg, on Days 1–8; the injection was switched from DW to caffeine (hydrous Caffeine Alkaloid/MERCK, M.W. = 212.21; 15 mg/kg, IP) on Days 9–16. (This dose was previously shown to be maximally effective in stimulating wheelrunning [6].) The (CAF)DW (Caffeine/Distilled Water) group received caffeine (15 mg/kg, IP) on Days 1–8, then were switched to DW on days 9–16. (DW)CAF and (CAF)DW rats were placed in wheels 20 min after injection, for 60 min tests, on 16 test sessions, each separated by 72 hr to reduce drug carryover effects, over a period of 46 days. A third group of rats, (PRE)CAF, were pretreated with caffeine (15 mg/kg, IP) on eight occasions, separated by 72 hr, in a manner similar to the (CAF)/DW group; however, they were maintained in their home cages rather than being placed in the

wheels following these first eight injections. The wheelrunning tests were begun after the ninth injection, and were continued for a total of 16 test sessions, as in the other two groups.

RESULTS

Wheel revolutions on Days 1, 8, 9 and 16 were analyzed using a two-factor, repeated measures, "mixed" ANOVA. The analysis revealed a significant Group × Day interaction, $F(6,45) = 4.94$, $p<0.001$. Subsequent analyses of simple effects and appropriate two-tailed t-tests showed that caffeine stimulated wheelrunning only marginally on Day 1 relative to DW control, $F(2,60) = 3.28$, $p<0.10$ (see Fig. 1). However, by Day 8 of testing, caffeine enhanced wheelrunning significantly relative to DW, $F(2,60) = 5.43$, $p<0.01$. Furthermore, the (PRE)CAF group, which had been pretreated with caffeine for eight days prior to wheel testing, did not differ significantly ($p>0.05$) from their unpretreated counterparts (CAF) on Day 1 or Day 8.

As expected, switching from CAF to DW on Day 9 produced a significant decrease in wheelrunning in the (CAF)DW group, $t(45) = 3.94$, $p<0.001$. However, rats switched from DW to CAF on Day 9 did not show evidence of caffeine stimulation; in fact, the (DW)CAF mean on Day 9 and the (CAF)DW mean on Day 1—the first days of testing with caffeine in each group—were virtually identical (47.7 ± 5.7 vs. 45.0 ± 8.2, respectively). (DW)CAF also ran somewhat less with caffeine on Day 9 than they had with DW on Day 8, $t(45) = 1.18$, $p>0.05$, and were also somewhat below the group receiving DW, $t(60) = 1.25$, $p>0.05$. The (PRE)CAF group, which continued to receive caffeine on Days 9–16, remained above both (DW)CAF ($p<0.01$) and (CAF)DW ($p<0.05$) on Day 9.

With repeated caffeine injections combined with wheelrunning, (DW)CAF increased significantly between Day 9 and Day 16, $t(45) = 3.62$, $p<0.001$, but remained not significantly different from (CAF)DW, $t(60) = 0.80$, $p>0.05$, and marginally below (PRE)CAF, $t(60) = 1.90$, $p<0.10$.

DISCUSSION

Our results confirm the earlier report [6] suggesting an interaction between caffeine experience and wheelrunning experience. Rats which were experienced with wheelrunning while drugged with caffeine reacted differently to the drug than those which were not experienced with the combination. Caffeine's stimulant action increased as animals' experience with both the drug *and* wheelrunning increased. Pretreatment with caffeine, without wheelrunning, (e.g., the (PRE)CAF group), did not enhance the stimulation effect; nor did prior wheelrunning with DW (e.g., the (DW)CAF group). Only the combination of wheelrunning-plus-caffeine produced increased stimulation.

It is noteworthy that while the increase above control (+91.5 wheelrevs/hour) with caffeine on Day 8 was statistically greater in *absolute* terms than the increase on Day 1 (+25.8 wheelrevs/hour), the *proportional* increase of about 2.3-fold was the same on both days. Nevertheless, rate-dependency considerations [10] would predict relatively greater stimulation at the lower baseline (Day 1) than at the higher baseline (Day 8), which we did not find.

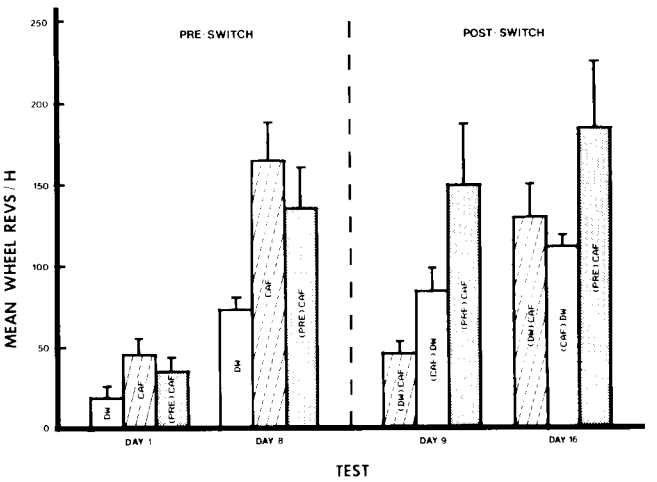

FIG. 1. Effects of caffeine (15 mg/kg, IP) and distilled water (DW) on wheelrunning in rats with varying amounts of wheelrunning experience. Injections were switched on Day 9: (DW)CAF = distilled water on Days 1–8, caffeine on Days 9–16; (CAF)DW = caffeine on Days 1–8, DW on Days 9–16; (PRE)CAF = caffeine for 8 days without wheelrunning, followed by caffeine plus wheelrunning on Days 1–16. (Vertical bars represent ±1 S.E.M.)

Taken together, these findings support the notion that some behavioral adaptations to drugs arise via other than drug-dispositional or pharmacodynamic adaptations. Overton [8] suggests that such adaptations occur because drugs possess stimulus properties of their own, which become part of the context in which a behavior is learned, and which may lead to "dissociation" of learning when drug-stimulus characteristics are changed (e.g., when a previously-drugged animal is tested in a non-drugged condition).

Implications for future studies are also apparent. The effect a particular drug produces may depend on how experienced the subject is with the drug and the behavioral task in question. A drug which fails to stimulate, or even depresses responding in naive subjects, may have the opposite effect in experienced subjects (as has been reported with nicotine [1, 2, 3] and ketamine [7]). Researchers will need to control for this experience factor in studies involving repeated measures on the same subjects—a common model in behavioral pharmacology. Also, this drug-experience/task-experience interaction needs to be tested with agents other than caffeine, and with behaviors other than wheelrunning, to determine how general the effect is. Some drugs and some behaviors may be more susceptible to experience effects than others. For example, a drug/task-experience interaction was found previously [6] with caffeine in the wheel, but not in the open field.

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