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Short communication

Low-dose oral caffeine induces a specific form of behavioral sensitization in rats

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Abstract:
The present study assessed the effects of a low dose of orally administered caffeine on sensitization of open-field behavior in rats. Rats had free access to untreated water every day or water containing 0.2 mg/ml of caffeine every other day of the 14-day experiment. On alternate days discrete movements (horizontal and vertical) and ambulatory distance were measured in open-field activity monitors. Although caffeine intake significantly decreased across test sessions in caffeine-treated rats, the number of discrete horizontal movements significantly increased. These findings suggest that low doses of orally administered caffeine induce a specific form of behavioral sensitization in rats.

Key words:
caffeine, open-field, rat, sensitization

Introduction

The psychomotor stimulant caffeine is one of the most widely consumed drugs in the world. While the acute behavioral and physiological effects of caffeine have been well characterized [3], comparably little is known about the effects of repeated caffeine exposure. A well-documented result of repeated exposure to other psychomotor stimulants, such as amphetamine and cocaine, is the development of behavioral sensitization [16, 19]. Behavioral sensitization refers to a progressive augmentation of the locomotor-activating effects of drugs following repeated, intermittent exposure, and is considered a useful animal model of addiction because it is thought to reflect an increase in the incentive motivational properties of drugs that contributes to drug craving and relapse [15, 21]. Although caffeine produces locomotor sensitization [10, 11], very few studies have investigated sensitization to caffeine when administered at doses relevant to human caffeine intake [8] or following oral administration [10, 12]. Also, these studies measured a relatively small range of behaviors: specifically, locomotion or wheel running. Given that caffeine shares several features with other highly addictive psychostimulants, further research on the behavioral effects of repeated caffeine exposure is warranted. Thus, the present study was conducted to determine whether a low dose of orally administered caffeine would produce sensitization across three different types of open-field behavior in rats.

Materials and Methods

Animals

Sixteen male albino rats of the Sprague-Dawley strain (Zivic-Miller), with an average weight of 600 g, were the subjects for this experiment. Rats were individu-

ally housed with free access to food (Prolab Laboratory animal diet) and water. The colony room, maintained at a temperature of 22°C, was on a 12:12 h light-dark cycle with lights on at 6 a.m. All procedures were in compliance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research [1], and approved by the Bloomsburg University Institutional Animal Care and Use Committee.

Apparatus and Procedure

A Tru Scan Photo Beam Tracking System (Coulbourn Instruments, Whitehall, PA, USA) measured the activity of the rats between 8 a.m. and 11 a.m. for a 15-min period. This system consisted of a Rat Arena (E63-20) with inside dimensions of 40.64 × 40.64 × 40.64 cm, a sensor ring (E63-22), and an Interface Linc (E63- O1HS). Data acquisition and analysis were controlled by Tru Scan (2.02) System Software. Body weight (g) and water intake (ml) were measured daily for 14 days. Rats that were randomly assigned to the caffeine group (n = 8) had free access to tap water containing 0.2 mg/ml of caffeine (200 mg "alertness aid" caffeine tablets; Eckerd Drug Company, Clearwater, FL, USA) every other day beginning on Day 1 (odd days) for the 14-day experiment, and free access to tap water on even days. Rats in the control group (n = 8) had free access to tap water every day. Rats were tested for activity under dim lighting conditions on Days 2, 6, 10, and 14. Data were analyzed using a 2 × 4 (treatment × day) mixed ANOVA for each of the dependent variables. The variables measured were number of discrete horizontal and vertical movements (movements were defined as successive photo beam coordinate changes in floor plane sensor and vertical plane sensor, respectively, with no rest, where rest is defined as recording the same coordinates for at least two successive sample intervals) and distance traveled in cm (the sum total of all vectored coordinate changes in the floor plane).

Results and Discussion

The mean (± SEM) daily caffeine intakes before each test session were 10.2 (1.0), 11.5 (1.6), 9.8 (1.4), and 8.6 (0.8) mg/kg, respectively, $F(3, 21) = 3.36$, $p = 0.038$. Rats gained an average of 40 and 30 g across the 14-day experiment in the caffeine and control groups, respectively. Regarding caffeine-treated rats, the average volume of water consumed per 24 h was 30.6 and 27.5 ml on the days prior to Test Sessions 1 and 4, respectively. Rats given access to tap water with caffeine had more vertical movements [a mean (± SEM) of 40.7 (3.3) compared to 28.4 (2.6)] and ambulated more [a mean (± SEM) distance of 981.2 (36.1) cm compared to 817.0 (26.9) cm] than rats given only tap water, $F(1, 14) = 4.52$, $p = 0.05$ and $F(1, 14) = 7.00$, $p = 0.02$, respectively (see Fig. 1a and 1b). There were no group by session interactions for either vertical movements or distance traveled, $F(3, 42) = 0.17$ and $F(3, 42) = 0.38$, respectively. However, there was a significant group by session interaction for the number of horizontal movements, $F(3, 42) = 2.86$, $p = 0.048$. Thus, caffeine-treated rats increased the number of discrete movements over the four test sessions, while rats given only tap water had equivalent number of movements over the test sessions (see Fig. 1c).

Our results show for the first time that repeated administration of low doses of orally administered caffeine induces a specific form of behavioral sensitization. Thus, the number of discrete open-field horizontal movements significantly increased over the course of four test sessions in caffeine-treated rats. This increase was not due to increased caffeine intake – indeed, caffeine intake significantly decreased across test sessions. On the other hand, vertical movements and ambulatory distance both decreased over test sessions in both caffeine-treated and control animals, likely reflecting a habituation to the test environment. Although the functional significance of the increase in caffeine-induced movements is not known, these data extend previous findings showing that repeated exposure to higher doses of experimenter-administered (10.0–15.0 mg/kg, *ip*) or orally administered (40–60 mg/kg/day) caffeine induces sensitization of locomotor activity [4, 8, 11, 17] or wheel running [10], respectively, by showing that low doses of orally administered caffeine that are relevant to human caffeine use [20] also induce a form of behavioral plasticity. Interestingly, chronic caffeine in similar doses was reported to impair the anticonvulsant activity of certain antiepileptic drugs, and in some cases, there was an apparent sensitization-like effect to this action of caffeine [5]. Finally, it is noteworthy that the doses of caffeine ingested by rats in the present study translate to amounts consumed by light human users (~1 cup of coffee/day; [14, 18]).

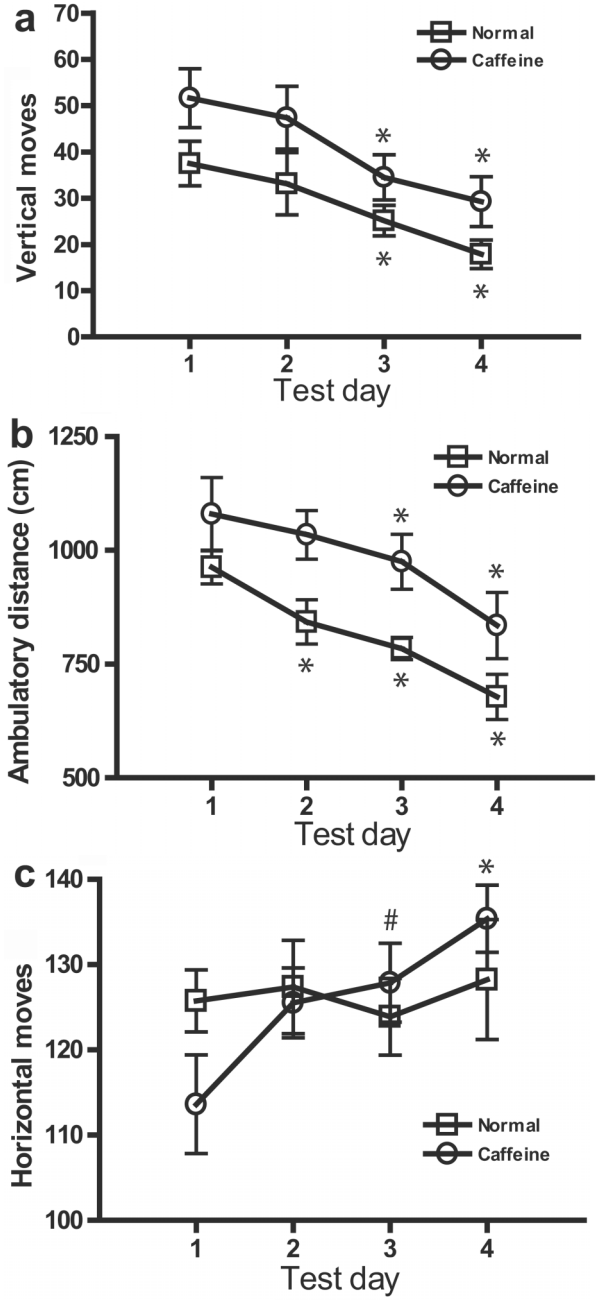

Fig. 1. Effects of oral caffeine on (**a**) number of vertical moves, (**b**) ambulatory distance, and (**c**) number of horizontal moves during four 15-min test sessions. Rats had free access to untreated water every day or water containing 0.2 mg/ml of caffeine every other day beginning on day 1 of the 14-day experiment. Test days correspond to days 2, 6, 10, and 14. Points represent the mean (± SEM). # $p < 0.05$ and * $p < 0.01$ compared to day 1 in same treatment group (Tukey HSD)

Although the neurobehavioral effects of caffeine are distinct from those of other psychomotor stimulants, such as amphetamine and cocaine, caffeine shares several important properties with these addictive drugs. For example, caffeine is reinforcing both to humans [6, 7] and to animals [2, 13], and a caffeine-withdrawal syndrome is well documented [9]. In addition, some caffeine users engage in a compulsive use pattern that in the most extreme cases leads to a syndrome termed "caffeinism" [3], a condition characterized by a number of behavioral and physiological symptoms mimicking a primary anxiety disorder. Given the widespread use of caffeine and the present results showing that low doses of caffeine can induce behavioral sensitization, more research on the behavioral effects of repeated caffeine exposure is warranted.

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