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Bupropion hydrochloride produces conditioned hyperactivity in rats

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Abstract

Bupropion is marketed as an antidepressant, Wellbutrin® and smoking cessation aid, Zyban®. Although the therapeutic neurological mechanisms of bupropion have not been fully elucidated, bupropion shares some behavioral similarities with classic psychomotor stimulants. The present study sought to further investigate these psychomotor stimulant effects of bupropion by assessing whether repeated administration of bupropion in a distinct environment produced conditioned hyperactivity. Paired rats received 10 daily IP injections of bupropion (2.5–30 mg/kg) before placement in locomotor chambers for 30 min. Bupropion (10–30 mg/kg) produced acute locomotor hyperactivity compared to Unpaired controls. After repeated administration, there was no progressive increase or decrease in bupropion-induced activity. In a subsequent drug-free session conditioned hyperactivity was observed at 5–30 mg/kg doses. In a follow-up experiment, we examined whether responsiveness to novelty predicted the subsequent unconditioned and conditioned locomotor effect of bupropion. Reactivity to inescapable novelty, novel environment approach, and novel-object interaction were measured before locomotor conditioning with 30 mg/kg bupropion. We replicated the previous experiment, but scores on the novelty screens did not predict locomotor response to bupropion. This study extends the literature by demonstrating that environmental cues repeatedly paired with the stimulant effects of bupropion come to evoke elevated activity in the absence of drug (i.e., conditioned hyperactivity). This finding is consistent with the literature suggesting that bupropion shares many behavioral similarities with other psychomotor stimulants which also produce conditioned hyperactivity. However, a predictive relation between reactivity to forced novelty and the subsequent locomotor effect of bupropion may not be one of these similarities.

Keywords: Activity; Individual differences; Locomotor; Nicotine; Pavlovian conditioning; Psychomotor stimulant; Sensitization; Smoking cessation; Wellbutrin®; Zyban®

Bupropion hydrochloride is the purported active ingredient in the antidepressant Wellbutrin® and the smoking cessation aid Zyban®. Moreover, bupropion is also being considered as a potential treatment for attention deficit hyperactivity disorder [1,2]. Given bupropion's widespread use for several fiscally and personally expensive health problems, there is much interest in its mechanisms of action. At the neurobiological level, bupropion blocks dopamine and norepinephrine re-uptake by inhibiting the transporter for these neurotransmitters [3,4]. Further, it acts as a nicotinic acetylcholine receptor (nAChR) antagonist [5–8]. At the behavioral level, bupropion has many stimulant-like qualities. For example, acute administration of bupropion increases activity in rodents [9–12]. This locomotor stimulant effect is maintained and sometimes enhanced with repeated administration [10,13]. Finally, the acute locomotor stimulant effects of bupropion are enhanced if rats are repeatedly pre-exposed to nicotine [12].

Although the unconditioned locomotor stimulant effects of bupropion have been somewhat described, no one has examined whether repeated treatment with bupropion might support conditioned locomotor activity. That is, when distinct environmental cues (e.g., locomotor apparatus) are repeatedly paired with the stimulant effects of certain drugs (e.g., amphetamine, methamphetamine, nicotine, etc.) that environment comes to evoke increases in activity even in the absence of drug [14–17]. This increase in activity above control levels reflects a conditioned response (CR) evoked by a Pavlovian-conditioned association between the environmental conditioned stimulus (CS) and the locomotor stimulant effects of the drug unconditioned stimulus (US). The evidence for sustained stimulant effects of bupropion across repeated administrations [10], along with its

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ability to increase dopamine in the nucleus accumbens [10], maintain self-administration behavior [18,19], and condition a place preference [11] suggests that bupropion, like other stimulant drugs, will function as a US in a conditioned locomotor task with rats. Accordingly, a primary goal of the present research was to test this prediction using a wide range of bupropion doses (2.5 to 30 mg/kg) as the US.

In the drug research literature with humans, there is often interest in individual differences and identifying constructs that predict individual vulnerability/sensitivity to the drug of interest. Although similar research is not as common in preclinical animal models, there is a growing literature on identifying predictive individual differences in rodent's reactivity to abused drugs. A major catalyst for this interest was research by Piazza and colleagues [20] showing that rats that were more active when confined to a novel environment were also more active when challenged with amphetamine and were more likely to self-administer amphetamine. Of particular interest in the present report is the finding that novelty-induced activity also predicts the unconditioned activity of such locomotor stimulants as caffeine, cocaine, ethanol, methamphetamine, and morphine [15,21–23]. Novelty-induced activity also predicts locomotor conditioning effects of amphetamine, methamphetamine, and morphine [15,24,25]. Given the evidence for the dose-dependent nature of the unconditioned and conditioned locomotor effects of bupropion in the present report, another goal of the present research was to assess whether reactivity to inescapable novelty predicted rats subsequent reactivity to a widely used dose of bupropion (30 mg/kg) in a manner similar to amphetamine and methamphetamine.

To be comprehensive in our assessment of individual differences we included 2 additional measures of reactivity to novelty-interaction with a novel object and approach to a novel environment. In contrast to the "forced" exposure of the inescapable novel environment, these alternative measures provide an index of reactivity to novelty in a choice or unforced manner. That is, the rat may or may not interact with the object or enter into the novel environment from the familiar environment at any moment in time. This distinction between forced versus unforced (choice) exposure to novelty appears to be justified in the literature. Forced exposure to novelty involves corticosterone and differential sensitivity to stress [see [26,27]], whereas unforced exposure relates to a non-stress process (e.g., novelty seeking/reward; see [28,29]). Notably, exposure to forced novelty predicts later reactivity to the locomotor effects of stimulant drugs [15,20–23]; this predictive relation does not exist with reactivity to unforced exposure to novelty (e.g., [15,30]).

1. Materials and methods

1.1. Animals

Naïve male Sprague–Dawley rats ($n=83$) from Harlan (Indianapolis IN, USA) were housed individually in plastic tubs lined with wood shavings. Food and water were continuously available in the home cage. The colony room was on a 12-hour light/dark cycle; all experiments were conducted during the light cycle. Each rat was handled about 2-min daily for 3 days before the start of an experiment. The experimental procedures were approved by the University of Nebraska Institutional Animal Care and Use Committee and were conducted in accordance with the "Principles of Laboratory Animal Care" (NIH publication No.85–23, revised 1985).

1.2. Drugs

Bupropion hydrochloride (Sigma, St. Louis MO, USA) was dissolved in 0.9% saline. Consistent with most published research bupropion injections were intraperitoneal (IP) at a volume of 1 ml/kg. The doses, reported as salt, were chosen based on past studies that have found discriminative properties as well as locomotor effects at similar doses [10–12,31–33].

1.3. Apparatus

Activity was measured in one of 8 circular chambers (30.5 cm diameter) made of white PVC pipe. Two infrared emitter/detector units were positioned 4 cm above the wire mesh floor such that each chamber was divided into four equal sections. Activity was defined as the number of infrared beam breaks automatically recorded by a computer. The chambers were located in a room separate from the colony. Located in the same room were two similar three-compartment chambers used for the novelty approach experiments. Each end compartment was $31\times24\times45.5$ cm ($l\times w\times h$). One end compartment had black walls and rod floors with newspaper lining the litter tray. The other end compartment had white walls and mesh flooring with wood chips lining the litter tray. The end compartments were separated by a center compartment ($15\times24\times45.5$ cm) with gray walls and an aluminum floor. The novel object was a plastic scouring pad (diameter=9 cm) attached to a paint roller (length=7.5 cm). An 80-dB continuous white noise masked external sounds and a fluorescent ceiling light provided general illumination.

1.4. Experiment 1: bupropion locomotor conditioning

1.4.1. Conditioning

Rats (311±7 g) were randomly assigned to one of the following doses of bupropion paired with the chamber: 2.5, 5, 10, 20, or 30 mg/kg (Paired, $n=10$ per dose). Each rat in the Paired condition received an IP injection of its assigned dose of bupropion immediately before placement in the locomotor chamber for 30 min. Rats in the Unpaired ($n=13$) condition were injected IP with saline immediately before placement. Further, the Unpaired rats were randomly assigned to receive 2.5, 5, 10, 20, or 30 mg/kg bupropion IP in the home cage ($n=2$ or 3 per dose) approximately 5 h after chamber exposure. These rats were pooled to form the Unpaired group for analyses and graphic display. Rats in the Paired conditions received a saline injection in the home cage. This procedure was repeated daily for 10 days.