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Research report

Basal activity level in mice predicts the initial and sensitized locomotor response to nicotine only in high responders

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HIGHLIGHTS

- It is important to identify factors that may contribute to nicotine responding.
- *High* basal activity correlated with both the acute and sensitized response to nicotine in mice.
- Only mice with *low* basal activity demonstrated a significant CPP.
- Basal locomotor activity may be of use to predict nicotine responding.

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ABSTRACT

Not all humans become addicted to drugs of abuse following casual use. Thus, it is important to identify factors that may contribute to subsequent drug responding. Previous studies have identified characteristics such as novelty-seeking, impulsivity, and anxiety as factors involved in the progression to drug dependence. The current experiment investigated basal locomotor activity in C57Bl/6N mice as a potential predictor of subsequent nicotine responses. We examined the ability of differences in basal locomotor activity to predict the acute and sensitized response to nicotine, as well as nicotine conditioned reinforcement. A median split was used to distinguish between low and high responders with regard to basal locomotor activity in mice. We then measured the acute response to nicotine (0.5 mg/kg IP) in these mice, followed by measures of conditioned place preference (CPP; 0.5 mg/kg IP) and locomotor sensitization (0.5 mg/kg IP), to determine whether basal locomotion is predictive of subsequent responding to nicotine. High, but not low, basal activity was found to be a predictor of both the acute and sensitized response to nicotine. Interestingly, only mice classified as having low basal activity demonstrated a significant CPP, suggesting that pre-exposure to nicotine differentially affects conditioned reinforcement on the basis of initial activity level. Basal locomotor activity may be an efficient measure of subsequent locomotor responding to nicotine, but only in animals classified as having high basal activity. However, animals with low basal locomotor activity may be more susceptible to the reinforcing properties of nicotine.

1. Introduction

In humans, not all drug users progress from drug-taking to addiction, with only a small percentage reaching the clinical criterion for a diagnosis of drug dependence [1]. Thus it is critical to determine the factors that lead some individuals to compulsive drug-taking behaviors. In recent years much preclinical research has been devoted to identifying risk factors to predict subsequent drug responding, many of which have been based on measures of locomotor activity. Alterations in locomotor activity in response to drugs of abuse in animals, such as the development of behavioral sensitization, have long been suggested to model the neurobiological adaptations that induce drug craving following drug use in humans [2–4], especially changes in mesocorticolimbic dopamine circuits that underlie both sensitization and the reinforcing properties of drugs of abuse and drug-associated cues [5,6].

Previous studies have examined differences in a variety of measurements based on the initial locomotor responsiveness to psychostimulants such as cocaine. For example, Allen et al. [7] demonstrated that only rats classified as low responders (LCRs) based on their acute locomotor response to cocaine developed locomotor sensitization in response to repeated injections, while high responders (HCRs) failed to sensitize to the locomotor activating effects of cocaine. Furthermore, LCRs and HCRs have been shown to differ in both intravenous cocaine CPP [7] and cocaine self-administration [8], with only LCRs exhibiting CPP, and LCRs demonstrating increased responding under a progressive ratio

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schedule of reinforcement. Thus, LCRs demonstrated an increased sensitivity to the stimulant effects of cocaine, consistent with an increase in sensitivity to cocaine as measured using CPP and self-administration.

Another locomotor activity-based model used to identify susceptibility to subsequent increased drug responding is that of novelty-induced locomotion. An enhanced exploration in novel environments has been suggested to predict vulnerability to drugs of abuse. For example, rats classified as high responders based on their performance in a novel environment demonstrated an increased acute response to amphetamine as compared to low responders [9]. Furthermore, adult mice classified as high and low novelty seekers based on their performance in a novel environment task demonstrated differences in the ability of a sub-threshold dose of cocaine (1 mg/kg) to elicit a CPP, with high novelty seekers demonstrating a preference for a cocaine-paired environment following conditioning, but no preference in the low novelty seekers [10]. Rats classified as high responders to novelty have also been demonstrated to learn to self-administer cocaine faster, and self-administer more cocaine, than their low responder counterparts [11]. Thus, novelty-seeking can be an effective predictor of subsequent drug responses.

Although susceptibility to the abuse of psychostimulants such as cocaine and amphetamine has been examined, few studies have sought to characterize behavioral predictors of nicotine dependence, despite tobacco use being a substantial health problem and the leading risk factor in preventable deaths worldwide. For example, Pastor et al. [12] examined whether the acute locomotor response to nicotine would affect the subsequent establishment of a nicotine CPP in rats classified as either low or high nicotine responders. The authors demonstrated that in low responders, pre-exposure to nicotine failed to induce a CPP following a conditioning regimen that normally results in a conditioned preference (four nicotine exposures), and only showed CPP after extensive conditioning sessions (seven nicotine exposures). In contrast, high nicotine responders failed to show a preference at any conditioning regimen. Thus, pre-exposure to nicotine resulted in an impairment in reinforcement that was greater in high responders. In contrast, rats classified as high responders based on novelty-induced locomotion demonstrated more reliable nicotine self-administration and a higher break point than their low responder counterparts [13]. Thus, the ability to predict subsequent nicotine responding based on differences in the acute locomotor response to the drug or novelty-induced locomotion remains unclear.

The purpose of this study was to examine the ability of basal locomotor activity to predict the acute and sensitized locomotor response to nicotine in animals classified as having low and high basal activity. We also employed a sub-threshold conditioning procedure to assess the effects of nicotine pre-exposure on nicotine CPP in animals separated based on their initial basal locomotor activity level.

2. Methods

2.1. Subjects

Male C57Bl/6N mice (Charles River, Germany) aged 10–14 weeks old at the start of experiments served as subjects. Mice were single-housed in a temperature-controlled (21 °C) environment maintained on a 12-h light-dark cycle (lights on at 6 a.m.). Food and water was available ad libitum. All experiments were performed in accordance with EU guidelines on the care and use of laboratory animals and were approved by the local animal care committee (Regierungspräsidium, Karlsruhe, Germany). All behavioral testing was conducted during the light phase between 0800 h and 1700 h.

2.2. Drugs

Nicotine hydrogen tartrate salt (Sigma-Aldrich, Germany) was dissolved in physiological saline (0.9% NaCl) for intraperitoneal (IP) injection of 0.5 mg/kg (10 ml/kg) based on free base weight (final solution adjusted to approximately pH 7 using NaOH).

2.3. Apparatus

2.3.1. Locomotor activity

Locomotor activity was assessed in eight TruScan activity monitors (Coulbourn Instruments, USA). Each monitor consists of a clear acrylic plastic test cage (27 × 27 × 39 cm) placed inside a monitoring unit that records via computer ambulatory beam interruptions from infrared photocell emitter/detector pairs evenly spaced along each axis.

2.3.2. Conditioned place preference

Nicotine conditioned place preference was assessed in two Panlab place preference boxes (Panlab, Spain). Each box consists of two chambers (20 × 18 × 25 cm) with distinct visual and tactile cues separated by a clear acrylic rectangular corridor. Sessions are monitored via video-tracking system (Ethovision 2.0, Noldus, The Netherlands), which determines spatial placement within sessions.

2.4. Behavioral procedures

2.4.1. Locomotor activity

Mice ($n = 20$) were habituated to the locomotor activity monitors during a single 60 min session. Previous work from our lab has demonstrated that a single habituation session reduces novelty-induced locomotion in our experimental setting; in other words, locomotor activity levels during subsequent sessions remain consistent [14]. Following this habituation session, mice received a saline injection (10 ml/kg), immediately followed by a 60-min exposure to the locomotor chamber. Activity during this trial was determined to be a measure of basal locomotion, and mice were separated into two groups based on a median split of the total distance traveled (cm) during this session. Thus, mice below the median distance traveled were characterized as having low basal activity (low), and mice above the median distance traveled were characterized as having high basal activity (high). The following day, all mice were administered nicotine (0.5 mg/kg IP) and immediately given a 60-min session in the locomotor chambers to determine the acute locomotor effect of the drug. In a separate experiment, a group of control mice ($n = 16$) were given a single habituation trial followed by two consecutive days of saline (10 ml/kg) injections.

2.4.2. Conditioned place preference

Ten days following the test of the acute locomotor response to nicotine (or saline in control animals), all mice underwent nicotine CPP. Nicotine CPP was assessed using a biased design, in which animals were conditioned to nicotine in their non-preferred environment, in three phases: pre-test, conditioning, and post-test. During the pretest, mice were injected with saline (IP, 10 ml/kg) and placed into the apparatus for a 30-min test of initial preference to the distinct environments. During conditioning, which entailed two trials per day (one nicotine, one saline) on two consecutive days (total two pairings nicotine, two pairings saline), mice received nicotine (0.5 mg/kg IP) immediately prior to 15-min conditioning trials in their non-preferred compartment or saline (10 ml/kg IP) immediately prior to 15-min trials in their preferred compartment. On the day following the last conditioning trial, mice were injected with saline (10 ml/kg IP) and given a 30-min drug-free test of preference, during which mice had access to both compartments.