



Behavioral effects of nicotine withdrawal in adult male and female rats

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ABSTRACT

Nicotine withdrawal may differ between men and women but clinical reports are inconsistent. Two experiments were conducted to examine behavioral effects of nicotine withdrawal in male and female adult rats in dimly-lit and brightly-lit environments. Ninety-six Sprague–Dawley male and female rats received 7 days continuous subcutaneous infusion via ALZET osmotic minipumps filled with saline or 3.16 mg/kg/day nicotine hydrogen tartrate expressed as base. Behavioral observations were made before, during, and after drug administration. During observations, occurrences of empty-mouth-chewing, whole-body-shakes, abnormal grooming, abnormal posture/movement, diarrhea, ptosis, eyeblinks, and any other abnormal behaviors were counted. Cessation of nicotine administration upon pump removal caused a significant increase in withdrawal behaviors in males and females in both environments. In the dimly-lit environment, females showed more withdrawal behavior than males; there was no sex difference in the brightly-lit environment. Males that had received nicotine displayed more withdrawal behavior in the brightly-lit environment than in the dimly-lit environment, while females that had received nicotine displayed similar amounts of withdrawal behavior in both environments. Behavioral symptoms of withdrawal may be more affected by the environment in male rats than in female rats. These experiments are the first to compare nicotine withdrawal in adult male and female rats.

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1. Introduction

Cigarette smoking is the leading cause of preventable death in the United States, and leads to significant health consequences, including cardiovascular diseases, cancers, and respiratory diseases (Centers for Disease Control [CDC], 2007). Despite these health consequences, one out of every five adults in the U.S. smokes cigarettes (CDC, 2007). People continue to smoke cigarettes largely because of nicotine, a highly addictive drug that plays a major role in reinforcing the maintenance of tobacco use (Grenhoff and Svensson, 1989; Grunberg et al., 2000; Henningfield and Benowitz, 1995; Koob and LeMoal, 2008; United States Department of Health and Human Services [USDHHS], 1988).

Cessation of nicotine administration results in nicotine withdrawal symptoms and behaviors in humans and animals. Marked nicotine withdrawal in humans lasts for approximately 10 days, and symptoms include tension, irritability, headaches, and increased appetite. Body weight gain and craving for cigarettes last for roughly a year (e.g., Hughes et al., 1990; Koob and LeMoal, 2008; Shiffman et al., 2006; USDHHS, 1988). The occurrence of withdrawal symptoms upon cessation of drug administration provides a useful measure of addiction. Malin et al. (1992) developed an animal model to examine nicotine withdrawal in rats. Previous work from the Malin group was

focused on morphine dependence, in which it was discovered that some of the most widespread and useful models of morphine dependence were those in which rats spontaneously exhibited quantifiable unusual behaviors during abstinence (Gianutsos et al., 1975; Malin et al., 1988). With the aim of developing a laboratory model of nicotine withdrawal, the Malin group conducted extensive pilot studies in which they took various physiological measurements and recorded all countable behavioral events before, during, and after nicotine infusion (Malin, 2001). They identified certain behaviors, termed “somatic behavioral signs,” as being selectively elevated during the withdrawal phase, particularly whole body shakes, abnormal grooming, abnormal posture or movement, ptosis (slackening of the jaw), empty-mouth chewing/teeth chattering, eyeblinks, and diarrhea.

Several lines of evidence support the validity of the present model as a representation of nicotine withdrawal syndrome (Kenny and Markou, 2001). First, when nicotine is chronically administered and then withdrawn from rats, they display more somatic behavioral signs than when these same subjects were nicotine naive, immediately prior to the termination of nicotine administration, after the recovery from withdrawal, or compared to saline-treated control rats (Malin et al., 1992). Second, the severity of the somatic behavioral signs was proportional to the amount of nicotine to which the animal was exposed, with animals receiving higher concentrations of nicotine displaying more behavioral signs. Third, nicotine administration reverses withdrawal behavioral signs in rats undergoing nicotine

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withdrawal, which demonstrates that tonic activation of nicotinic cholinergic receptors (nAChR), which are upregulated when addiction develops, is critical to prevent the somatic behavioral symptoms (Malin et al., 1992). In addition, administration of bupropion, a compound that is clinically efficacious in the treatment of nicotine dependence, reverses both somatic and affective signs of nicotine withdrawal (Cryan et al., 2003).

Malin's rodent model of nicotine withdrawal has proven to be reliable with rats and mice because it has produced consistent results across a number of experiments of nicotine withdrawal from the Malin group (1993, 1994, 1996, 1998; Malin, 2001) and other laboratories (Carboni et al., 2000; Epping-Jordan et al., 1998; Hildebrand et al., 1997, 1998; Kota et al., 2007, 2008; O'Dell et al., 2004; Phillips et al., 2004; Watkins et al., 2000). Additional somatic signs of nicotine withdrawal reported include escape attempts, foot licks, genital licks, and writhes (e.g., O'Dell et al., 2004; Skjei and Markou, 2003). Some work with rodent models has been focused on individual differences, specifically age differences, and their effect on nicotine withdrawal (Kota et al., 2007, 2008; O'Dell et al., 2004, 2006). However, no published studies have used this model to examine nicotine withdrawal in female rats.

In the U.S. men are more likely to smoke cigarettes (23.9%) than women (18.1%) (CDC, 2007), and men smoke more cigarettes than women (Grunberg et al., 1991; Perkins, 1996). Yet, women report less success quitting smoking than do men (Perkins, 2001; Swan et al., 1997; Wetter et al., 1999). Some investigators report more self-reported nicotine withdrawal symptoms in women than men (e.g. Shiffman, 1979) but others report no gender differences in withdrawal (e.g., Hughes and Hatsukami, 1992; Svikis et al., 1986). No reports indicate greater withdrawal symptoms in men than women. It has been noted that the studies in which women self-report greater withdrawal severity than men were retrospective (Hughes et al., 1990). Pomerleau et al. (1994) conducted a retrospective and prospective study of self-reported nicotine withdrawal symptoms in women and men. Women reported more withdrawal than men retrospectively, but there were no gender differences in reported withdrawal symptom severity in the prospective portion of the study (i.e., while in withdrawal). Based on the available literature, it is unclear whether there are sex differences in nicotine withdrawal in humans.

Research on nicotine's effects in rodent models reports sex differences depending on the measures studied. For example, female rats are more sensitive than male rats to effects of nicotine on body weight, feeding, pre-pulse inhibition of the acoustic startle reflex, antinociception, and behavioral sensitization (Chiari et al., 1999; Craft and Milholland, 1998; Faraday et al., 1999; Grunberg et al., 1986; Harrod et al., 2004). However, female rats are less sensitive to the discriminative effects of nicotine (Schechter and Rosencrans, 1971). Studies in mice suggest that females are less sensitive to nicotine-induced suppression of Y-maze activity, nicotine-induced increase in active avoidance learning, withdrawal from nicotine, and nicotine's positive and rewarding effects (Hatchell and Collins, 1980; Kota et al., 2007, 2008; Yilmaz et al., 1997). However, nicotine withdrawal effects have not been directly compared in male and female mice, and sex differences in nicotine withdrawal have not been investigated in a rat model.

Environment may also be an important variable to examine with regard to nicotine withdrawal. Smoking-related stimuli, smoking-related activities, and environmental context may be more important, especially for women (Parrott and Craig, 1995; Perkins, 1996). In addition, the extent to which a given environment is stressful or not may be relevant to nicotine withdrawal because stress is associated with increased smoking (e.g., George et al., 2007; Grunberg and Baum, 1985; Jarvik et al., 1977; Kassel et al., 2003; Pomerleau and Pomerleau, 1987; Schachter et al., 1977).

Details about the environmental conditions in which withdrawal behavioral observations were conducted were not reported in

previous withdrawal research (e.g., Kota et al., 2007, 2008; Malin et al., 1993, 1994, 1996, 1998; Malin, 2001; O'Dell et al., 2004). However, it was revealed in personal communications with Malin and O'Dell that the behavioral observations took place in a brightly-lit room in cages without bedding. In the present research, nicotine withdrawal in adult male and female rats was examined in two different environments. The animal model allowed for random assignment of subjects to drug groups, manipulation of environment, and assessment of nicotine withdrawal based on observed behaviors.

2. Experiment 1: adult females and males observed in a dimly-lit environment in cages with bedding

2.1. Overview

The purpose of this experiment was to examine the effect of nicotine withdrawal in male and female adult rats in a dimly-lit environment in cages with bedding. Withdrawal behaviors identified by Malin et al. (1992) were observed and recorded before, during, and after administration of nicotine via osmotic minipumps. In the present experiment, the observation room was dark to be similar to the home-cage environment. The observation cages contained bedding material and were identical to home cages, and the observations were made during the rats' dark, active phase. There were four behavioral observation sessions during the course of the experiment. Observations were conducted once weekly during the baseline and nicotine phases, and twice during the cessation phase: the first withdrawal behavioral observation occurred at 20 h post pump removal, and the second observation occurred at 44 h post pump removal. The present experiment was a 2 (male, female) × 2 (nicotine, saline) mixed model with repeated measures. The dependent variables were observed withdrawal behaviors and open field locomotor activity.

2.2. Subjects

Subjects were 24 female and 24 male Sprague–Dawley rats obtained from Charles River Laboratories (Wilmington, MA). Animals were individually housed in standard polycarbonate shoebox cages (42 × 20.5 × 20 cm) on hardwood chip bedding (Pine-Dri). Animals had continuous access to rodent chow (Harlan Teklad 18% Protein Rodent Diet 2018) and water during all phases of the study in the home cages. Housing rooms were maintained at 23 °C at 50% humidity on a 12 hour light/dark cycle (lights off at 0800 h). Rats were approximately 70 days old at the start of the experiment—an age in rats that is analogous to young adulthood (Douglas et al., 2004). At the beginning of the experiment, the females weighed an average of 186.5 g and the males weighed an average of 303.7 g. This experimental protocol was approved by the USU Institutional Care and Use Committee and was conducted in full compliance with the NIH Guide for Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1985).

2.3. Methods

2.3.1. Baseline phase

The baseline phase lasted for one week (7 days) after the rats' arrival. In the first two days after arrival, rats were gentled by being held and petted for 2 min each so that they would become accustomed to handling by humans, and were acclimated to the activity chambers. Daily collection of estrous samples began on the third day of the baseline phase for females. On the sixth day, locomotor activity was measured by placing the rats into individual electronic physical activity monitoring chambers of the Omnitech/Accuscan Electronics Digiscan infrared photocell system (Test box model RXYZCM [16 TAO]; Omnitech/Accuscan Electronics, Columbus, OH) for 1 h to measure open field locomotor activity. Baseline behavioral observations were conducted on the seventh day of the baseline phase.

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