Pharmacology, Biochemistry and Behavior 94 (2009) 114–118

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Removal of continuous nicotine infusion produces somatic but not behavioral signs of withdrawal in mice

Andrew J. Kwilasz, Louis S. Harris, Robert E. Vann *

Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia, United States

ARTICLE INFO

Article history:
Received 4 June 2009
Received in revised form 15 July 2009
Accepted 27 July 2009
Available online 4 August 2009

Keywords:
Nicotine dependence
Behavioral dependence
Operant
Somatic
Mice

ABSTRACT

The introduction of transgenic and knockout mice has shaped new interest in developing novel and modified behavioral methods for mice that evaluate the various manifestations of nicotine withdrawal syndromes. This study assessed the disruption of operant baselines during drug withdrawal, an established rat model of nicotine dependence, in mice. Subjects were trained to lever press for food reinforcement during daily operant sessions. After stable operant baselines were established, mice were implanted with osmotic minipumps containing 0 (saline), 6, 12, 24, or 48 mg/kg/day nicotine base. Operant responding was assessed for disruptions in daily sessions throughout the experiment. Somatic signs of withdrawal were assessed after the operant session on day 7, following administration of mecamylamine (1 mg/kg), and on days 12, 13, and 14, following spontaneous removal of nicotine. Spontaneous removal of nicotine increased somatic signs of withdrawal but did not disrupt operant responding. Mecamylamine failed to produce signs of precipitated withdrawal in either procedure. This study demonstrated nicotine dependence in mice during spontaneous removal of nicotine. Moreover, since signs of behavioral withdrawal (i.e. disruptions in operant response rates) were not observed, these findings suggest the importance of considering differences in the apparent manifestations of withdrawal syndromes while evaluating nicotine dependence.

1. Introduction

Withdrawal from tobacco products can produce a variety of symptoms in dependent individuals including irritability, anxiety, concentration difficulties, restlessness, and impatience (Hatsukami et al., 1984) as well as disruption of regular sleep patterns, excessive hunger, and nicotine craving (APA, 1994). This withdrawal syndrome has been implicated in the high relapse rate among tobacco users and can be relieved by nicotine replacement (Stolerman and Jarvis, 1995). Preclinical attempts have been successful in demonstrating attenuation of nicotine withdrawal syndromes in rodents using drugs marketed for humans (Bruijnzeel and Markou, 2003; Cryan et al., 2003; Malin et al., 2006); however, most smokers attempting to quit still remain unsuccessful (see Hughes et al., 2004). Bupropion, for example, has been shown to treat both physical and affective signs of nicotine withdrawal in the rat (Malin et al., 2006) as well as reduce tobacco craving and withdrawal signs in humans (Mooney and Sofuoglu, 2006). This suggests that available human pharmacotherapies lack the ability to completely alleviate withdrawal effects and also implicate a multifaceted tobacco-related withdrawal syndrome in humans.

Rodent models of drug dependence have been used to quantify many of the symptoms of nicotine withdrawal as well as for screening potential pharmacotherapies (see Malin, 2001; O'Dell and Khroyan, 2009). Nicotine withdrawal syndromes have been modeled in the rat using various behavioral procedures such as operant schedules of reinforcement (Carroll et al., 1989; Corrigall et al., 1989; Vann et al., 2006), brain-stimulation reward threshold (Cryan et al., 2003; Epping-Jordan et al., 1998, unpublished data from this laboratory), auditory startle (Acri et al., 1991; Helton et al., 1993; Jonkman et al., 2008), conditioned place preference or aversion (Brielmaier et al., 2008; Torrella et al., 2004; Wilkinson and Bevins, 2008), observational tests (Malin et al., 1992), and locomotor activity (Malin et al., 1992). Moreover, many of these models have predictive validity when evaluating the therapeutic efficacy of drugs used for the treatment of tobacco dependence. For example, bupropion has shown efficacy for relieving the symptoms of nicotine withdrawal in rats using various behavioral models (Bruijnzeel and Markou, 2003; Cryan et al., 2003; Malin et al., 2006).

Mapping of the mouse genome has facilitated the advancement of new approaches aimed at investigating the biological mechanisms of behavior in mice (Picciotto and Wickman, 1998). Consequently, there has been increased interest in developing novel and modified behavioral techniques for mice, especially with the availability of several nAChR-subunit knockout mice (see Fowler et al., 2008). To date, several behavioral models have distinguished two categories of nicotine withdrawal signs in mice: somatic or physical (Damaj et al.,

* Corresponding author. Department of Pharmacology and Toxicology, Virginia Commonwealth University, 410 North 12th Street, PO BOX 980613, Richmond, VA 23298-0613, United States. Tel.: +1 804 828 8060.
E-mail address: revann@vcu.edu (R.E. Vann).

0091-3057/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2009.07.015

2003) and affective (Jackson et al., 2008; Johnson et al., 2008). The disruption of operant baselines during drug withdrawal, a behavioral model previously established for rats, may reflect a unique withdrawal phenotype not assayed by other models, since drugs that do not typically produce characteristic somatic withdrawal signs, such as tetrahydrocannabinol (Beardsley et al., 1986; Beardsley and Martin, 2000) and phencyclidine (Beardsley and Balster, 1987; Slifer et al., 1984) have been sensitive to this procedure. This procedure may also have particular utility when modified for mice. In this model "behavioral dependence" manifests as disruptions in a reoccurring behavior following the removal of continuous drug administration, providing a sensitive indicator of nicotine dependence (Carroll et al., 1989; Corrigall et al., 1989; Vann et al., 2006).

In an effort to characterize nicotine-induced behavioral dependence in mice, this study simultaneously assessed the disruption of operant responding and the presence of somatic signs in mice during nicotine withdrawal. The ICR mouse was selected for this study since they are an outbred strain, which increases heterogeneity and generalization of results, and have fully functional nAChRs (Kota et al., 2007). Mice were trained to lever press under fixed ratio (FR) 10 schedules of food reinforcement during daily 15-min experimental sessions. Nicotine was then administered subcutaneously via osmotic minipumps. The presence of dependence was tested with challenges of the nicotinic acetylcholine receptor (nAChR) antagonist, mecamylamine, and during spontaneous withdrawal.

2. Method and materials

2.1. Subjects

Male adult ICR mice (25–30 g) obtained from Charles River (Raleigh, NC) were housed individually in clear plastic cages (21×33×18 cm) with plastic tops and wood chip bedding in a temperature-controlled (20–22 °C) vivarium. Water was available ad libitum except during behavioral testing. Training and test sessions were conducted at similar times during the light phase of a 12-h light/dark cycle. Mice were maintained at 85–90% of free-feeding body weights by restricting daily ration of standard rodent chow. Animals used in this study were cared for in accordance with the guideline of the Institutional Animal Care and Use Committee of Virginia Commonwealth University and the 'Guide for the Care and Use of Laboratory Animals' (National Research Council, 1996).

2.2. Apparatus

Eight standard mouse operant conditioning chambers that were sound- and light-attenuated (MED Associates, St. Albans, VT) were used for behavioral training and testing. Each operant conditioning chamber (18×18×18 cm) was equipped with a house light, two levers (left and right), and a recessed food pellet receptacle centered between the levers. A hopper delivered food pellets into the receptacle. Fan motors provided ventilation and masking noise for each chamber. House lights were illuminated during training and testing sessions. A computer with Logic '1' interface (MED Associates) and MED-PC software (MED Associates) controlled schedule contingencies and maintained data. Clear plastic cages (18×28×13 cm) were used for observational studies.

2.3. Procedures

2.3.1. Lever press training

Each mouse was trained to lever press on a single lever according to a FR1 schedule of reinforcement, during which a food pellet reinforcer was delivered after every lever press. Reinforced lever press assignment was based on preference of the mouse that was assessed during an initial two-lever training session and typically resulted in nearly equal left and right lever choices by a group of mice. The FR value was gradually increased to the final FR10 schedule of reinforcement in which 10 consecutive responses were required for the delivery of reinforcement. Daily 15 min training sessions were held Monday–Friday until stable baselines were established under FR10 conditions. Baseline stability was determined according to a three-session response rate criterion requiring the response rates of three consecutive sessions to be within +/−20% of the mean response rate for the three sessions. Levers were wiped with diluted isopropyl alcohol between sessions to minimize olfactory cues.

2.3.2. Mecamylamine dose effect determination

Once lever press behavior was stable a mecamylamine dose effect curve was conducted. Mice were tested with saline, or 1, 3, or 5.6 mg/kg mecamylamine ($n=6$) to determine a dose that did not alter operant responding for subsequent challenge tests. To habituate the mice to the injection procedure, saline injections (15 min pre-session) were administered for five days prior to mecamylamine tests.

2.3.3. Continuous nicotine infusion

Mice were surgically implanted with osmotic minipumps (Alzet Model 1002; Alza, Palo Alto, CA) filled with either (−)-nicotine (6, 12, 24, 48 mg/kg/day) or sterile physiological saline for 12 days. Minipumps were implanted in a subcutaneous pocket on the back of each mouse under 2% isoflurane anesthesia. Mice used to conduct the mecamylamine dose effect curve were used in experiment 1. Stable lever press behavior was reestablished according to baseline stability criterion, then mice were matched on response rates, and assigned to 0 (saline), 24, or 48 mg/kg/day nicotine administration groups ($n=8$). Experiment 2 was similar to experiment 1 except a mecamylamine dose effect was not conducted. For this study, once stable baseline response rates were established, mice were assigned to 0 (saline), 6, or 12 mg/kg/day nicotine administration groups ($n=8$).

2.3.4. Operant precipitated withdrawal

Mice were tested in daily operant conditioning sessions for 7 consecutive days following minipump implantation. On the 7th day following implantation, 1 mg/kg mecamylamine was administered (s.c.) 15 min prior to the start of the operant conditioning session. This pretreatment time was selected based on previous studies. Saline was administered on all other days.

2.3.5. Operant spontaneous withdrawal

Daily operant conditioning sessions continued following the precipitated withdrawal test. On day 12, minipumps were removed 4 h prior to the start of the operant conditioning session. Testing continued on days 13 and 14.

2.3.6. Observation of somatic signs

Mice were observed for somatic withdrawal signs on days 7, 12, 13, and 14 using a modified version of methods previously described by Damaj et al. (2003). Immediately following operant conditioning sessions, mice were placed in clear plastic cages and observed for 10 min. Typical somatic withdrawal signs counted included grooming, head shakes, paw tremors, backing, and body tremors. Observers were blind to treatments during observational studies.

2.4. Drugs

(−)-Nicotine base and mecamylamine hydrochloride (Sigma Chemicals Co., St. Louis, MO, USA) were dissolved in saline. Nicotine doses are expressed in terms of the base. Nicotine was continuously administered at an infusion rate of ~0.25 µl/h for 12 days via osmotic minipumps. Mecamylamine was administered 15 min prior to operant testing at a volume of 0.1 ml/10 g.

2.5. Data analysis

The number of correct lever presses was recorded during each session. Non-contingent lever presses were also recorded however were typically low in number and thus not presented. Response rate (responses/min) was calculated for each day by dividing the mean total number of correct lever presses by the session length in min +/− the S.E.M. Somatic withdrawal signs were tallied and compiled as the mean total number of somatic signs +/− the S.E.M. recorded during the 10 min observation period.

3. Results

Mean response rate data for the acute administration of mecamylamine are shown in Fig. 1. A one-way ANOVA indicated that response rates from the mecamylamine tests resulted in significant differences in rates of responding as a function of dose ($p<0.05$). Post hoc tests revealed that 5.6 mg/kg mecamylamine significantly reduced operant responding compared to responding during saline tests. Based on the results of this test, a dose of 1 mg/kg mecamylamine was chosen for subsequent challenge tests since it was a log dose lower than the dose that produced rate suppression.

The operant response rate data for the saline, 6, and 12 mg/kg/day nicotine groups (upper panel) and saline, 24, and 48 mg/kg/day nicotine groups (lower panel) are shown in Fig. 2. Repeated measures ANOVA conducted on response rates collected in consecutive daily operant sessions for baseline and the 14 days of the experiment from the saline, 6, and 12 mg/kg/day groups, and the saline, 24, and 48 mg/kg/day groups failed to reveal significant differences in rates of responding as a function of days for both contingent and non-contingent levers ($p>0.05$).

The effects of precipitated and spontaneous withdrawal of continuous nicotine administration on somatic withdrawal signs are shown in Figs. 3 and 4, respectively. Mecamylamine challenges failed to increase somatic signs of nicotine withdrawal in any group on day 7 of nicotine administration ($p>0.05$, Fig. 3). In contrast, somatic signs of nicotine dependence were significantly increased in the 24 and 48 mg/kg/day nicotine administration groups compared to saline 4 and 24 h after the removal of continuous nicotine administration ($p<0.05$, Fig. 4). The most prevalent sign observed was paw tremors, which were dose dependently significant at 4 and 24 h in the 24 and 48 mg/kg/day nicotine administration groups compared to saline ($p<0.05$). Other signs observed included backing, writhing, head shakes, and body tremors.

Two days after minipump removal in the 24 and 48 mg/kg/day nicotine administration groups, somatic signs of spontaneous nicotine withdrawal were similar to those of saline-treated animals (Fig. 4). Somatic signs of spontaneous nicotine withdrawal were dose dependent since no changes were observed at the two lowest doses, 6 and 12 mg/kg/day nicotine administration.

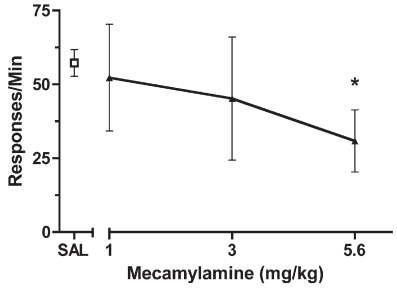

Fig. 1. The effects of mecamylamine challenges on mean rates of responding for mice trained to lever press under a FR10 schedule of food reinforcement. Brackets through the symbols indicate SEMs. Asterisks (*) indicate a significant decrease ($p<.05$) in response rates compared to rates of responding obtained during saline tests.

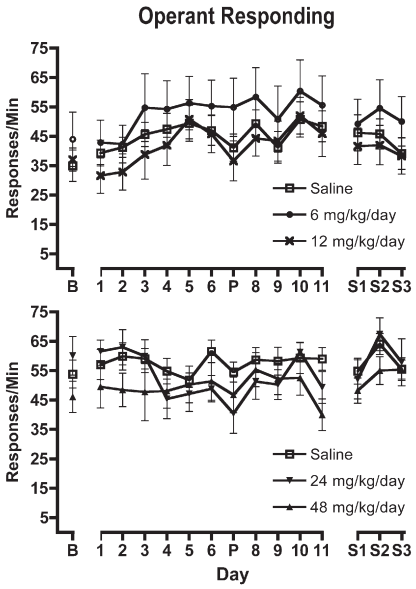

Fig. 2. The effects of mecamylamine challenges and spontaneous removal of nicotine following continuous nicotine administration on mean rates of responding for mice trained to lever press under a FR10 schedule of food reinforcement ($n=8$). "P" represents 1 mg/kg mecamylamine administered (s.c.) 15 min prior to the operant session. "S" represents spontaneous removal of nicotine 4 h (1), 24 h (2), and 48 h (3) prior to the operant session. Squares represent saline control animals. Circles represent 6 mg/kg/day, X's represent 12 mg/kg/day, downward triangles represent 24 mg/kg/day, and upward triangles represent 48 mg/kg/day nicotine administration. Values represent the mean (±S.E.M.).

4. Discussion

The recent introduction of transgenic and knockout mice has facilitated the investigation of the molecular specificity of behavioral models of nicotine dependence (Picciotto and Wickman, 1998). These techniques have proven to be invaluable for elucidating the different mechanisms underlying the various symptoms of nicotine dependence and have enormous potential as tools for further classification of these symptoms. For example, β4 (Salas et al., 2004) and α5-knockout mice

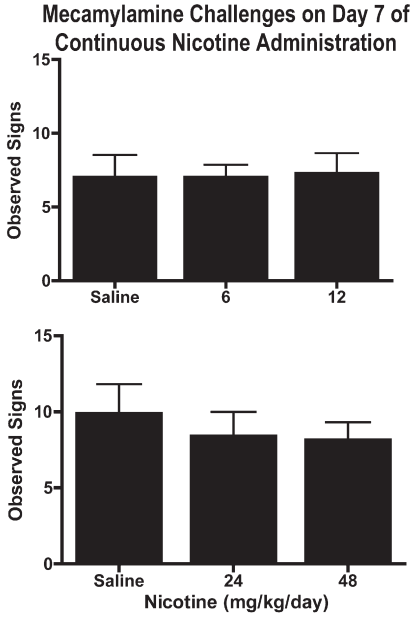

Fig. 3. The effects of mecamylamine challenges (1 mg/kg) following 7 days of continuous nicotine administration on mean somatic signs of withdrawal in mice ($n=8$). Values represent the mean (±S.E.M.).

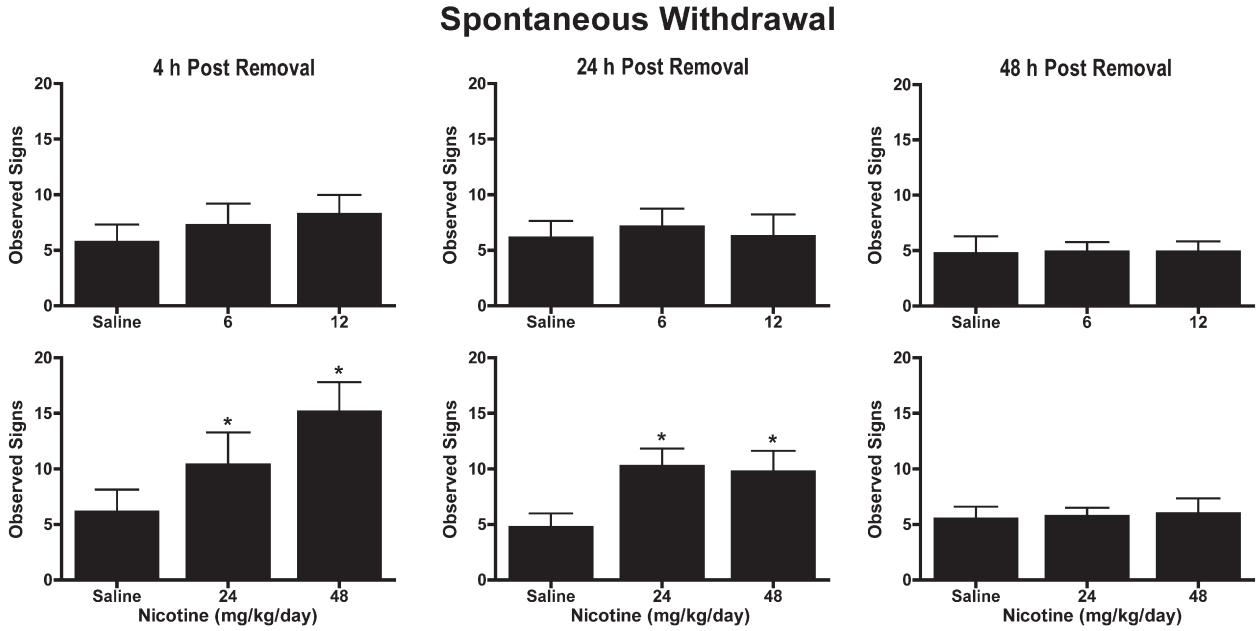

Fig. 4. The effects at 4 h, 24 h, and 48 h after spontaneous removal of nicotine on somatic signs of withdrawal in mice following 12 days of continuous nicotine administration. Values represent the mean (±S.E.M.). The asterisks (*) indicate significant increases ($p<.05$) in somatic signs of nicotine-treated compared to saline-treated mice.

(Jackson et al., 2008) display significantly less somatic signs during nicotine withdrawal compared to wild type animals, whereas a role for β2 nAChR subunits has been implicated in the affective signs of nicotine withdrawal (Jackson et al., 2008). Other behaviors associated with nAChR subtypes have also been characterized (see Fowler et al., 2008). Collectively these studies support the contention that tobacco dependence is a grossly complex disorder with a variety of symptoms mediated through a multitude of different nAChR receptor subtypes, which is likely to result in various manifestations of tobacco dependence in humans.

The goal of this study was to characterize nicotine-induced behavioral dependence in mice by simultaneously assessing the disruption of operant behavior, an established rat model of nicotine dependence (Carroll et al., 1989; Corrigall et al., 1989; Vann et al., 2006), and the presence of somatic withdrawal signs, a formerly characterized mouse observational model of nicotine withdrawal (Damaj et al., 2003). In this study, mecamylamine challenges (1 mg/kg) failed to precipitate disruptions of operant behavior or increases in somatic signs of nicotine withdrawal following 7 days of continuous nicotine administration. In these same mice, somatic signs of nicotine withdrawal were observed after removal of 12 days of continuous nicotine administration. This occurred in 24 and 48 but not in 6 or 12 mg/kg/day continuous infusion nicotine-treated mice. Operant baselines were not disrupted during spontaneous withdrawal. These results suggest that mice displaying physical dependence upon nicotine, as inferred by characteristic somatic signs of nicotine withdrawal, displayed no detectable evidence of nicotine behavioral dependence, as inferred by disruptions in operant behavior.

Previous studies in rats have demonstrated that the disruption of operant behavior during precipitated and spontaneous drug withdrawal, termed "behavioral dependence," is an objective, sensitive, and quantitative measure of the presence of drug dependence (Schuster and Thompson, 1969). This phenotype may represent a class of withdrawal symptoms distinct from characterized somatic and affective withdrawal signs, since it has been demonstrated under experimental conditions not to induce signs of physical dependence (Slifer et al., 1984) with drugs such as tetrahydrocannabinol (Beardsley et al., 1986; Beardsley and Martin, 2000), phencyclidine (Beardsley and Balster, 1987), and nicotine (Carroll et al., 1989; Corrigall et al., 1989; Vann et al., 2006). Although the disruption of operant behavior was not observed in this study, it has been observed in two previous studies using intracranial self-stimulation procedures (Johnson et al., 2008; Stoker et al., 2008). Taken together, these findings exemplify the importance of model sensitivity to the various symptoms of nicotine withdrawal and establish that when appropriate conditions are met, behavioral dependence upon nicotine can be induced in mice.

Preclinical studies have often examined nicotine withdrawal in rats using 7 days of nicotine administration to induce dependence (see Malin, 2001). The findings from our study suggest that 7 days of nicotine administration is insufficient to induce dependence in mice observable by the presence of somatic or operant behavioral signs of precipitated withdrawal. A possible explanation for the lack of precipitated withdrawal, although unconfirmed in this study, is that the dose of mecamylamine administered (1 mg/kg) was insufficient to effectively block the action of nicotine at nAChRs or that insufficient levels of nicotine were administered. Support for these are demonstrated by Kota et al. (2007) that precipitated withdrawal with a higher dose of mecamylamine (2 mg/kg) after 8 days of nicotine administration and Damaj et al. (2003) that precipitated withdrawal with 1 mg/kg mecamylamine following 14 days of nicotine administration.

Phenotypic variance in mouse strain sensitivities to continuous nicotine exposure also may account for the lack of effect observed during our precipitated withdrawal study. This study and the two studies referenced above suggest that an 8-day minimum exposure period in ICR mice may be required to produce nicotine dependence. Strain variations and sensitivity to nicotine withdrawal have been reported by Damaj et al. (2003) who demonstrated that C57/BL/6J mice were highly sensitive to nicotine withdrawal compared to 129/SvEv mice and by Stoker et al. (2008) who demonstrated differences between C57/BL/6J and BALB/cByJ strains in the affective signs of nicotine withdrawal. One study, using CD-1 mice, found increases in somatic signs of precipitated withdrawal after 6 days of 25 mg/kg/day nicotine administration (Balerio et al., 2004). These studies collectively provide evidence that variability in the sensitivity to displaying the signs of nicotine withdrawal exists between mouse strains and additionally implies the inherent difficulty of modifying preclinical techniques for use with other species or strains.

In an effort to better understand the numerous parameters underlying the symptoms of tobacco dependence in humans, novel

and modified behavioral methods of detecting nicotine dependence, particularly in mice, must continue to be developed and evaluated. In general, models used for studying the induction of nicotine dependence, as inferred by signs of withdrawal, are sensitive to the measure of dependence, type of withdrawal (spontaneous versus precipitated), species and strain of subject used, and duration as well a magnitude of nicotine exposure. This study demonstrates an established rat operant model of drug dependence, the disruption of operant behavior during drug withdrawal, is insensitive to signs of behavioral dependence in ICR mice physically dependent upon nicotine under this particular dosing regimen. To shape a more complete understanding of the multifaceted symptomology associated with nicotine dependence, future research must focus on the modification, development, and/or characterization of behavioral methods that have the potential to be sensitive to the multifaceted manifestations of nicotine dependence and withdrawal in mice.

Acknowledgments

This research was supported in part by NIDA DA-005274 and DA 7-8859.

References

Acri JB, Grunberg NE, Morse DE. Effects of nicotine on the acoustic startle reflex amplitude in rats. Psychopharmacology 1991;104:244–8.
APA. Diagnostic and statistical manual of mental disorders. Washington DC: American Psychiatric Press; 1994.
Balerio GN, Aso E, Berrendero F, Murtra P, Maldonado R. Delta9-tetrahydrocannabinol decreases somatic and motivational manifestations of nicotine withdrawal in mice. Eur J Neurosci 2004;20:2737–48.
Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. J Pharmacol Exp Ther 1987;242:203–11.
Beardsley PM, Martin BR. Effects of the cannabinoid CB(1) receptor antagonist, SR141716A, after Delta(9)-tetrahydrocannabinol withdrawal. Eur J Pharmacol 2000;387: 47–53.
Beardsley PM, Balster RL, Harris LS. Dependence on tetrahydrocannabinol in rhesus monkeys. J Pharmacol Exp Ther 1986;239:311–9.
Brielmaier JM, McDonald CG, Smith RF. Nicotine place preference in a biased conditioned place preference design. Pharmacol Biochem Behav 2008;89:94-100.
Bruijnzeel AW, Markou A. Characterization of the effects of bupropion on the reinforcing properties of nicotine and food in rats. Synapse 2003;50:20–8.
Carroll ME, Lac ST, Asencio M, Keenan RM. Nicotine dependence in rats. Life Sci 1989;45:1381–8.
Corrigall WA, Herling S, Coen KM. Evidence for a behavioral deficit during withdrawal from chronic nicotine treatment. Pharmacol Biochem Behav 1989;33:559–62.
Cryan JF, Bruijnzeel AW, Skjei KL, Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. Psychopharmacology (Berl) 2003;168:347–58.
Damaj MI, Kao W, Martin BR. Characterization of spontaneous and precipitated nicotine withdrawal in the mouse. J Pharmacol Exp Ther 2003;307:526–34.
Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. Nature 1998;393:76–9.
Fowler CD, Arends MA, Kenny PJ. Subtypes of nicotinic acetylcholine receptors in nicotine reward, dependence, and withdrawal: evidence from genetically modified mice. Behav Pharmacol 2008;19:461–84.
Hatsukami DK, Hughes JR, Pickens RW, Svikis D. Tobacco withdrawal symptoms: an experimental analysis. Psychopharmacology (Berl) 1984;84:231–6.
Helton DR, Modlin DL, Tizzano JP, Rasmussen K. Nicotine withdrawal: a behavioral assessment using schedule controlled responding, locomotor activity, and sensorimotor reactivity. Psychopharmacology 1993;113:205–10.
Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction 2004;99:29–38.
Jackson KJ, Martin BR, Changeux JP, Damaj MI. Differential role of nicotinic acetylcholine receptor subunits in physical and affective nicotine withdrawal signs. J Pharmacol Exp Ther 2008;325:302–12.
Johnson PM, Hollander JA, Kenny PJ. Decreased brain reward function during nicotine withdrawal in C57BL6 mice: evidence from intracranial self-stimulation (ICSS) studies. Pharmacol Biochem Behav 2008;90:409–15.
Jonkman S, Risbrough VB, Geyer MA, Markou A. Spontaneous nicotine withdrawal potentiates the effects of stress in rats. Neuropsychopharmacology 2008;33: 2131–8.
Kota D, Martin BR, Robinson SE, Damaj MI. Nicotine dependence and reward differ between adolescent and adult male mice. J Pharmacol Exp Ther 2007;322:399–407.
Malin DH. Nicotine dependence: studies with a laboratory model. Pharmacol Biochem Behav 2001;70:551–9.
Malin DH, Lake JR, Newlin-Maultsby P, Roberts LK, Lanier JG, Carter VA, Cunningham JS, Wilson OB. Rodent model of nicotine abstinence syndrome. Pharmacol Biochem Behav 1992;43:779–84.
Malin DH, Lake JR, Smith TD, Khambati HN, Meyers-Paal RL, Montellano AL, Jennings RE, Erwin DS, Presley SE, Perales BA. Bupropion attenuates nicotine abstinence syndrome in the rat. Psychopharmacology (Berl) 2006;184:494–503.
Mooney ME, Sofuoglu M. Bupropion for the treatment of nicotine withdrawal and craving. Expert Rev Neurother 2006;6:965–81.
O'Dell LE, Khroyan TV. Rodent models of nicotine reward: what do they tell us about tobacco abuse in humans? Pharmacol Biochem Behav 2009;91:481–8.
Picciotto MR, Wickman K. Using knockout and transgenic mice to study neurophysiology and behavior. Physiol Rev 1998;78:1131–63.
Salas R, Pieri F, De Biasi M. Decreased signs of nicotine withdrawal in mice null for the beta4 nicotinic acetylcholine receptor subunit. J Neurosci 2004;24:10035–9.
Schuster CR, Thompson T. Self administration of and behavioral dependence on drugs. Annu Rev Pharmacol 1969;9:483–502.
Slifer BL, Balster RL, Woolverton WL. Behavioral dependence produced by continuous phencyclidine infusion in rhesus monkeys. J Pharmacol Exp Ther 1984;230:399–406.
Stoker AK, Semenova S, Markou A. Affective and somatic aspects of spontaneous and precipitated nicotine withdrawal in C57BL/6J and BALB/cByJ mice. Neuropharmacology 2008;54:1223–32.
Stolerman IP, Jarvis MJ. The scientific case that nicotine is addictive. Psychopharmacology (Berl) 1995;117:2-10 discussion 14–20.
Torrella TA, Badanich KA, Philpot RM, Kirstein CL, Wecker L. Developmental differences in nicotine place conditioning. Ann N Y Acad Sci 2004;1021:399–403.
Vann RE, Balster RL, Beardsley PM. Dose, duration, and pattern of nicotine administration as determinants of behavioral dependence in rats. Psychopharmacology (Berl) 2006;184:482–93.
Wilkinson JL, Bevins RA. Intravenous nicotine conditions a place preference in rats using an unbiased design. Pharmacol Biochem Behav 2008;88:256–64.