Progress in Neuro-Psychopharmacology & Biological Psychiatry 48 (2014) 6–13

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Baseline impulsive choice predicts the effects of nicotine and nicotine withdrawal on impulsivity in rats

Hakan Kayir [a,b,1], Svetlana Semenova [a,1], Athina Markou [a,*]

[a] Department of Psychiatry, School of Medicine, University of California San Diego, La Jolla, CA, USA
[b] Department of Medical Pharmacology, Psychopharmacology Research Unit, Gulhane Military Medical Academy, Ankara, Turkey

ARTICLE INFO

Article history:
Received 9 July 2013
Received in revised form 26 August 2013
Accepted 12 September 2013
Available online 20 September 2013

Keywords:
Delay discounting
Delayed reward
High and low impulsive rats
Wistar rats

ABSTRACT

Impulsive choice, a form of impulsivity, is associated with tobacco smoking in humans. Trait impulsivity may be a vulnerability factor for smoking, or smoking may lead to impulsive behaviors. We investigated the effects of 14-day nicotine exposure (6.32 mg/kg/day base, subcutaneous minipumps) and spontaneous nicotine withdrawal on impulsive choice in low impulsive (LI) and high impulsive (HI) rats. Impulsive choice was measured in the delayed reward task in which rats choose between a small immediate reward and a large delayed reward. HI and LI rats were selected from the highest and lowest quartiles of the group before exposure to nicotine. In non-selected rats, nicotine or nicotine withdrawal had no effect on impulsive choice. In LI rats, chronic nicotine exposure decreased preference for the large reward with larger effects at longer delays, indicating increased impulsive choice. Impulsive choices for the smaller immediate rewards continued to increase during nicotine withdrawal in LI rats. In HI rats, nicotine exposure and nicotine withdrawal had no effect on impulsive choice, although there was a tendency for decreased preference for the large reward at short delays. These results indicate that nicotine- and nicotine withdrawal-induced increases in impulsive choice depend on trait impulsivity with more pronounced increases in impulsive choice in LI compared to HI subjects. Increased impulsivity during nicotine exposure may strengthen the addictive properties of nicotine and contribute to compulsive nicotine use.

1. Introduction

Impulsivity is defined as the predisposition to act prematurely without considering the future outcomes of actions. Impulsivity is a common symptom of several psychiatric disorders, such as attention-deficit/hyperactivity disorder, aggression, and personality disorders (Moeller et al., 2001). Furthermore, trait impulsivity in relatively healthy humans contributes to poor decision making. Impulsivity is not a unitary construct but rather refers to diverse forms of deficits in response inhibition at different stages of the behavior, such as preparation to respond, execution of the behavior, and the assessment of outcomes (Evenden, 1999). At the preparation phase, behaviors initiated without adequate sensory input result in "preparation" or "reflection" impulsivity (Dalley et al., 2011; Evenden, 1999). During the execution of behavior, a failure to inhibit a motor action or stop the initiated behavior causes "impulsive action" (Dalley et al., 2011). Finally, making risky or inappropriate choices, such as preference for small immediate rewards and intolerability of delay associated with large rewards, is termed "impulsive choice," also referred to as increased delay discounting (Dalley et al., 2011).

Impulsive choice has been strongly associated with tobacco smoking and drug dependence in humans (Bickel et al., 1999, 2008; Goldstein and Volkow, 2002; Perry and Carroll, 2008). Individuals with increased delay discounting begin the use of drugs, including nicotine, at an earlier age compared with less impulsive individuals (Kollins et al., 2005; Wulfert et al., 2002). Furthermore, tobacco smokers discounted future monetary rewards to a greater extent than non-smokers (Baker et al., 2003; Bickel et al., 1999; Dallery and Raiff, 2007; Heyman and Gibb, 2006; Mitchell, 2004). A recent meta-analysis of human studies that covered 57 articles and a total of 3329 subjects provided further evidence of increased impulsive choice in smokers and subjects with drug abuse (MacKillop et al., 2011). Nineteen of these studies investigated tobacco smokers, 15 of which found a significant increase in impulsive choices in the currently smoking group. Short-term nicotine abstinence also increased impulsive choices in smokers when the choice was related to smoking but not monetary choices (Mitchell, 2004).

Despite the considerable number of human studies, it remains unclear whether increased impulsivity, including impulsive choice, is a cause or consequence of nicotine dependence or whether impulsivity and nicotine dependence are both consequences of a shared biological mechanism. Studies in humans cannot easily determine the direction of causality of these two behaviors (i.e., tobacco smoking and impulsivity), mainly because such evaluations necessitate long-term follow-up

Abbreviations: HI, high impulsive; LI, low impulsive; ITI, intertrial interval; AUC, area under the curve; ANOVA, analysis of variance; s, second(s); min, minute(s); h, hour(s).

* Corresponding author at: Department of Psychiatry, Mail Code 0603, School of Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603, USA. Tel.: +1 858 534 1572; fax: +1 858 534 9917.
E-mail address: amarkou@ucsd.edu (A. Markou).

[1] These authors contributed equally to this work.

0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.09.007

assessments that begin from the early years of adolescence and continue into adulthood. In this context, animal studies are important tools for understanding the neurobiological basis of the development of nicotine dependence in subjects that exhibit high or low levels of impulsivity before nicotine exposure.

A procedure that assesses impulsive choice is a delayed reward (i.e., delay discounting) task that has been used to evaluate cognitive impulsivity in both humans and experimental animals (Evenden and Ryan, 1996). In this task, impulsivity is defined and measured as the preference for a smaller immediate reinforcer over a larger delayed reward (Ainslie, 1975; Evenden, 1999). Acute nicotine administration increased impulsive choices in rats (Anderson and Diller, 2010; Dallery and Locey, 2005; Kelsey and Niraula, 2013; Kolokotroni et al., 2011), whereas exposure to chronic nicotine and nicotine withdrawal had mixed effects on impulsive choice behavior in rats (see Discussion for details). Differences in baseline trait impulsivity may play a role in differential responses to chronic nicotine exposure and nicotine withdrawal, a hypothesis that was explored in the present study.

The present study investigated the effects of chronic nicotine treatment and nicotine withdrawal on impulsive choice in a general population of Wistar rats and rats selected for high and low baseline levels of impulsivity. Outbred Wistar rats were used in the present study because outbred rat strains best reflect the human population and are most suitable for the detection of individual differences because of a higher degree of genetic and phenotypic heterogeneity than inbred rat strains. A discrete-trial delayed reward task with predefined delay times for larger reinforcers was used in the present study to evaluate impulsive choice behavior. The rats were chronically exposed to nicotine via subcutaneous osmotic minipumps. Chronic nicotine administration via minipumps provides a stable nicotine blood concentration that mimics the regular nicotine exposure experienced by long-term tobacco smokers (Ulrich et al., 1997). Nicotine withdrawal was induced by removal of the osmotic minipumps. Control rats were treated with saline via osmotic minipumps. We hypothesized that exposure to chronic nicotine and nicotine withdrawal will have differential effects on impulsivity in subjects with high and low levels of trait impulsivity.

2. Materials and methods

2.1. Animals

Male Wistar rats (Charles River, Raleigh, NC), weighing 200–225 g upon arrival in the laboratory, were housed two per cage on a 12 h/12 h reverse light/dark cycle (lights off at 8:00 AM). During behavioral training and testing, the rats were food-deprived and received 16 g/rat/day of food, including the food received in the experimental chamber. The rats were fed 1 h after the experimental session. Water was available *ad libitum* in the home cage. Behavioral tests were performed during the dark phase of the light/dark cycle. The animals were treated in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care and the National Research Council's Guide for Care and Use of Laboratory Animals. All experiments were approved by the Institutional Animal Care and Use Committee of the University of California San Diego.

2.2. Apparatus

All of the tests were conducted in a set of 12 nine-hole operant boxes (Med Associates, St. Albans, VT). Each box consisted of a 25.5 cm width × 28.4 cm length × 28.7 cm height chamber placed in a soundproof enclosure with a ventilator fan that provided air circulation and produced low levels of background noise. A 2.5 W, 24 V white houselight was positioned on one wall of the chamber and illuminated during each experimental session. Each testing chamber contained a curved wall with nine holes equipped with 3 W cue lights located at the rear panel and a photocell emitter and detector pair located at the entrance of each hole. Metal inserts covered every other hole, leaving open holes 1, 3, 5, 7, and 9. Food pellets (45 mg, Noyes Precision Pellets, New Brunswick, NJ) were delivered via a food dispenser into a pellet receptacle located in the center of the opposite wall. The pellet receptacle was also equipped with a cue light and photocell emitter and detector pair. Each apparatus was controlled by and provided data collected through a Med Associates (Med Associates, St. Albans, VT) interface to a computer. Behavioral training and baseline assessments in the delayed reward task were conducted 5 days per week (Monday–Friday), and behavioral testing during chronic nicotine/saline exposure and withdrawal was conducted daily (i.e., 7 days per week).

2.3. Delayed reward procedure

The delayed reward procedure used in the present study was similar to the procedure originally developed by Evenden and Ryan (1996) for two-lever boxes and modified by van Gaalen et al. (2006) for the five-hole chambers. In a discrete-trial choice procedure, the rats choose between one food pellet delivered immediately and four food pellets delivered after a delay.

On day 1, the rats were habituated to the chambers for 20 min. During habituation, the cue lights in holes 3 and 7 were illuminated, and food pellets were placed in each illuminated hole. On day 2, a 20-min session began with the illumination of the cue lights in holes 3 and 7, and one pellet was delivered into the pellet receptacle every 20 s, independent of the rats' responses. On day 3, training on a fixed-ratio 1 (FR1) schedule of reinforcement was initiated. For the FR schedule, at the beginning of the session, the cue lights in holes 3 and 7 were illuminated, and nosepoking at either hole was rewarded with one pellet. The session was terminated after a maximum of 100 pellets were earned or 30 min elapsed, whichever occurred first. The intertrial interval (ITI) was 20 s, and the limited hold to make a response was 10 s. The rats were then trained to nosepoke into the hole in the center position (hole 5) to initiate a trial. A nosepoke in hole 5 resulted in the presentation of the cue lights in holes 3 and 7. Nosepoking in either illuminated hole during a 10 s limited hold period was rewarded with one pellet. If the rat did not respond within the limited hold period, then the house light was switched on for 5 s, and the same trial was initiated with the illumination of hole 5. The ITI was 20 s. Nosepoking in a non-illuminated hole was recorded but had no consequences. The session was terminated after a maximum of 100 pellets were earned or after 34 min elapsed, whichever occurred first. During the subsequent training sessions, the ITI was gradually increased from 20 to 100 s, and the session duration was also increased from 34 to 100 min. The duration of the final training and testing sessions was fixed at 100 min, together with increasing the ITI to 100 s. Thus, the maximal number of pellets obtained during a session decreased to 85 and 60 pellets when the ITI was increased to 70 and 100 s, respectively.

During the next phase, holes 3 and 7 were designated as small (one pellet) and large (four pellets) reward holes, respectively. The position associated with the small and large rewards was the same for each individual subject and counterbalanced across rats. The hole opposite the initial preferred side was designated the large reward hole for each subject. The session was initiated with illumination of the cue light in hole 5. When the rat nosepoked in hole 5, the cue light was extinguished while the cue lights in holes 3 and 7 were illuminated. During a 10 s limited hold period, nosepoking in hole 3 or 7 was rewarded with one or four pellets, consistent with the size of the reward designated for each hole. If the rat did not respond within the limited hold period, then the house light was turned on for 5 s, and the same trial was initiated. The ITI was 100 s. Nosepoking in non-illuminated holes was recorded but had no consequence. The session was terminated after 60 trials or 100 min, whichever occurred first. The rats were trained under these conditions until they preferred the large reward for at least 50 trials. After reaching this criterion of performance, the delayed reward training was initiated.