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Suppressive and enhancing effects of nicotine on food-seeking behavior

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ABSTRACT

The present study examined how systemic low doses of nicotine affect the microstructure of reinforced food-seeking behavior in rats. Rats were first given an acute saline or nicotine treatment (0.1–0.6 mg/kg, with an inter-injection interval of at least 48 h), and then a chronic saline or nicotine treatment (0.3 mg/kg/day for 10 consecutive days). Immediately after each injection, rats were required to press a lever five times to obtain food that was available at unpredictable times (on average every 80 s) with constant probability. Acute nicotine dose-dependently suppressed behavior prior to the delivery of the first reinforcer, but enhanced food-reinforced behavior afterwards. These effects were primarily observed in the time it took rats to initiate food-seeking behavior. Enhancing effects were also observed in the microstructure of food-seeking behavior, with lower nicotine doses (0.1–0.3 mg/kg) increasing the rate at which response bouts were initiated, and higher doses (0.3–0.6 mg/kg) increasing within-bout response rates. A pre-feeding control suggests that changes in appetite alone cannot explain these effects. Over the course of chronic nicotine exposure, tolerance developed to the suppressive, but not to the enhancing effects of nicotine on food-seeking behavior. These results suggest that (a) lower doses of nicotine enhance the reward value of food and/or food-associated stimuli, (b) higher doses of nicotine enhance motoric activity, and (c) ostensive sensitization effects of nicotine on behavior partially reflect a tolerance to its transient suppressive motoric effects.

1. Introduction

Tobacco use is linked to diseases of nearly all organs of the body, and to 480,000 deaths per year in the United States [1]. The main addictive component that maintains tobacco dependence is nicotine [2]. Among other functions, nicotine appears to enhance the reinforcing properties of non-nicotinic stimuli, including food rewards [3–9]. Nicotine-induced changes in food-seeking behavior may explain body weight changes often associated with tobacco use [10]. Although smokers have a lower average body weight than nonsmokers, this difference reverses once smokers quit smoking [11–13]. Similarly, rats also have low body weights while on nicotine, but gain substantial weight once nicotine is discontinued [14]. Given these effects, it is particularly important to establish how nicotine affects motivated food-seeking behavior, which may help identify key contributors to the pervasive use of nicotine [15,10].

Although nicotinic enhancement of non-nicotine stimuli and rewards is well documented (e.g., see [3] for a review), such effects may vary depending on the schedule of reinforcement. Nicotine induces a substantial dose-dependent, but transient, reduction in response rate on both variable-ratio (VR) and variable-interval (VI) schedules of reinforcement [16]. However, nicotine-induced behavioral suppression is typically followed by increased locomotor activity [17,18]. In VI schedules, nicotine-induced suppression of response rate is also typically followed by a dose-dependent increase in response rate. In response-withholding tasks, such as differential reinforcement of low response rates (DRL) and fixed-minimum interval (FMI) schedules of reinforcement, nicotine appears to disrupt performance such that rats are less capable of withholding a reinforced response [19–21]. Similar disruptive effects are observed in fixed-interval (FI) schedules of reinforcement, wherein response withholding is not required but often emerges [22]. A disinhibition of reinforced responding is also observed under fixed-ratio (FR) schedules of reinforcement [9].

The suppressive effect of nicotine on food-seeking behavior may reflect the malaise typically induced by nicotine at high doses [23]. Such suppressive effect is observed not only in VR and VI schedules of reinforcement, but also in spontaneous locomotion [17,24]. This effect may be analogous to the initial effects of nicotine in humans, which are typically aversive, but disappear with continued exposure [25–27].

The enhancing effect of nicotine on food-seeking behavior is also observed in nicotine-experienced humans. Under fasting conditions, nicotine increases caloric intake and reduces habituation to food-associated cues [28–30,11]. Despite the prevalence of these enhancing effects in the literature, it is unclear what components of food-seeking are

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modulated by the administration of nicotine.

In animal models, nicotine may affect food-seeking behavior by altering the reward value of food and associated stimuli, the learned association between food-obtaining responses and food, and/or the motoric capacity to produce the food-obtaining response. The purpose of this study was to determine the relative contribution of these factors to nicotine-induced changes of food-reinforced behavior. There are various models that aim at dissociating the contribution of each of these factors to instrumental performance. Some of these models are based on constraints imposed either on the behavioral expression of arousal [31,32], or on the consumption of the incentive [33]. Although various aspects of these models have been validated, they are not without limitations. Most importantly, these models account only for averaged data, neglecting key behavioral processes that are only visible in the stochastic variability of behavioral data. The methods of the present study aim at overcoming some of these limitations.

In the present study, inferences on reward value, response-outcome association, and motor capacity are drawn from the bout structure of instrumental behavior [34–39]. This structure is particularly visible in tandem variable-time (VT) FR schedules of reinforcement, in which the probability of reinforcing a train of responses is low and constant over time. Fig. 1 shows a schematic of how responding is organized in each VI trial. Following the onset of cues signaling imminent food, rats wait some time before emitting their first response (latency) and then fluctuate in and out of bouts of responding. Previous work has revealed that the bout-initiation rate is the only parameter of bout structure sensitive to changes in reinforcer efficacy and rate [40,35,41,36,38,39]. Other parameters are uniquely sensitive to other manipulations: mean bout length is particularly sensitive to schedule requirements [42,39], and within-bout response rate and response duration reflect the capacity to complete a response [35,36,43]. Latencies, in contrast, appear to be sensitive to various manipulations [39].

The present study separately analyzed latencies and run rates (Fig. 1) to identify the locus of the behavioral effect of passively administered nicotine. Run rates were further analyzed to identify potential nicotine-induced changes in bout-initiation rate, within-bout response rate, and response duration, which would indicate changes in reward value, response-outcome association, and motoric capacity.

2. Methods

2.1. Subjects

Twelve male Sprague Dawley rats (Charles River Laboratories, Hollister, CA) served as subjects. Rats arrived on post-natal day (PND) 61 and were immediately pair housed. Rats experienced a 12:12 h light cycle, with lights on at 1900 h. All behavioral training was conducted during their active phase (the dark phase of the cycle). Behavioral training and food restriction began on PND 62. Access to food was reduced daily from 24, to 18, 12, and finally 1 h a day. Chow was placed on the homecages of the rats 30 min after the end of an experimental session during the dark phase of the cycle (the 30-min interval was meant to minimize interference of food anticipation on task performance). At the beginning of the next session, weights were, on average, 85% of *ad libitum* weights estimated from growth charts provided by the breeder. Water was always available in home cages. All animal handling procedures used during this study followed National Institutes for Health guidelines and were approved by the Arizona State University Institutional Animal Care and Use Committee.

2.2. Apparatus

Experiments were conducted in 12 MED Associates (ST. Albans, VT, USA) modular test chambers (6 chambers were 305 mm long, 241 mm wide, and 210 mm high; 6 chambers were 305 mm long, 241 mm wide, and 292 mm high), each enclosed in a sound- and light-attenuating box equipped with a ventilation fan that provided masking noise of approximately 60 dB. The front and back walls and the ceiling of test chambers were made of Plexiglas; the front wall was hinged and served as a door to the chamber. One of the two aluminum side panels served as a test panel. The floor consisted of thin metal bars positioned above a catch pan. The reinforcer receptacle was a square opening (51-mm sides) located 15 mm above the floor and centered on the test panel. The receptacle provided access to a dipper (ENV-202M-S) fitted with a cup (ENV-202C) that could hold 0.01 cc of a liquid reinforcer (33% sweetened condensed milk diluted in tap water; Kroger, Cincinnati, OH). The receptacle was furnished with a head entry detector (ENV-254-CB). A multiple tone generator (ENV-223) produced a 15-kHz tone at approximately 75 dB through a speaker (ENV-224 AM), which was centered on the top of the wall opposite the test panel and 240 mm above the floor of the chamber. Two retractable levers (ENV-112CM) flanked the reinforcer receptacle. Lever presses were recorded when a force of approximately 0.2 N was applied to the end of the lever. Three-color light stimuli (ENV–222 M) were mounted above each lever; they could be illuminated yellow, green, and red. A house light located behind the wall opposite to the test panel could dimly illuminate the test chambers. Experimental events were arranged via a MED PC® interface connected to a PC controlled by MED-PC IV® software

2.3. Drugs

Nicotine hydrochloride tartrate (Sigma, St. Louis, MO, USA) was

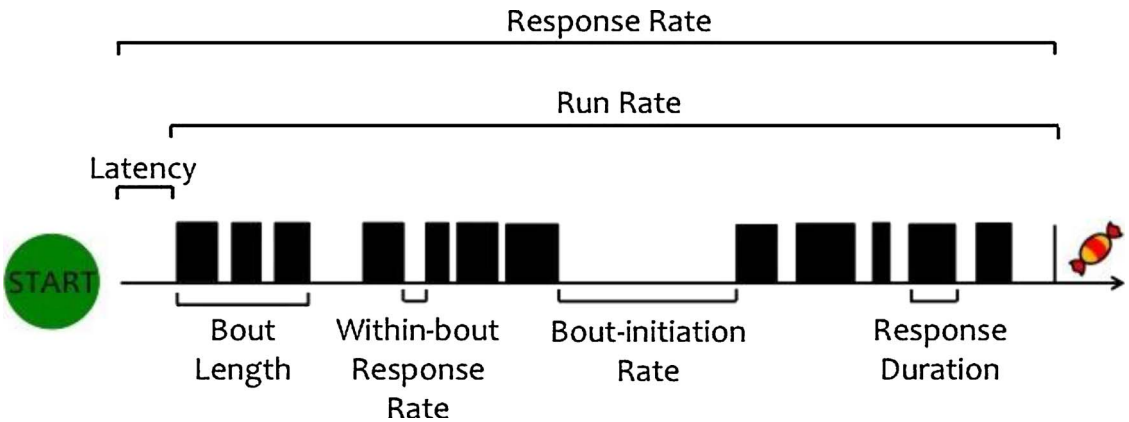

Fig. 1. The microstructure of response rate found in a typical VI trial. Response rate is composed of latency and run rate, where response rate ≈ run rate × (1–mean latency/VI requirement), assuming independence of latency and run rate. Run rate is composed of bout length, within-bout response rate, bout-initiation rate, and response duration. Each component is differentially sensitive to changes in motivation, response-outcome learning, and motoric capacity; see text for details.