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Detrimental effects of acute nicotine on the response-withholding performance of spontaneously hypertensive and Wistar Kyoto rats

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Abstract

Rationale—Attention-Deficit Hyperactivity Disorder (ADHD) is associated with a higher prevalence of smoking, which may be related to potential therapeutic effects of nicotine on ADHD symptoms. Whereas nicotine offers robust improvements in sustained attention, the effects of nicotine on impulsivity are unclear.

Objectives—The present study examined the effects of nicotine on the response inhibition capacity of spontaneously hypertensive rats (SHR), an animal model of ADHD, compared to that of a normotensive control Wistar Kyoto (WKY) using the Fixed Minimum Interval (FMI) schedule of reinforcement.

Methods—Tests were conducted following acute injections of subcutaneous nicotine (0.1 – 0.6 mg/kg). On each FMI trial, the first lever press initiated an inter-response time (IRT); a head entry into a food receptacle terminated the IRT. IRTs longer than 6 s were intermittently reinforced with sucrose.

Results—A model that assumes that only a proportion of IRTs are sensitive to the timing contingencies of the FMI provided a close fit to the data, regardless of strain or treatment. No baseline difference in FMI performance was observed between SHR and WKY. Nicotine reduced the duration of timed IRTs and the duration of latencies to the IRT-initiating lever press similarly for both strains. Nicotine dose-dependently increased the proportion of timed IRTs; the dose-response curve was shifted leftwards in SHR relative to WKY.

Conclusions—These results suggest that nicotine (a) reduces response-inhibition capacity (b) enhances the reinforcement efficacy of sucrose, and (c) dose-dependently enhances attention-like sensitivity to contingencies of reinforcement, through mechanisms that are yet unknown.

Keywords

Nicotine; Impulsivity; Reinforcement; Attention deficit hyperactivity disorder; Spontaneously hypertensive rat; Fixed Minimum Interval schedule; Temporal Regulation; Response inhibition; Motivation

Introduction

Attention-deficit hyperactivity disorder (ADHD) is among the most common childhood psychiatric disorders (Froehlich et al. 2007; Skounti et al. 2007). Barkley (1997) suggested that the core features of ADHD are deficits in response inhibition capacity and sustained attention. Response inhibition capacity refers to the ability to withhold a reinforced response; it is typically assessed in humans using Go/No-Go tasks (e.g., Wodka et al. 2007). Sustained attention refers to the effortful maintenance of responding to a stimulus; it is typically assessed using vigilance tasks (e.g., Stins et al. 2005).

ADHD is associated with tobacco smoking during adolescence (Lambert and Hartsough 1998; Milberger et al. 1997). This link may reflect the ameliorating effect of tobacco on some ADHD-related deficits (Blume et al. 2000; Gehricke et al. 2007; Khantzian 1997; Pomerleau et al. 2000). Because nicotine is the main psychoactive ingredient of tobacco, it is possible that nicotine enhances response inhibition and/or sustained attention.

Effects of nicotine on response inhibition capacity

The effects of nicotine on response inhibition capacity in humans are somewhat disparate. Although acute nicotine appears to enhance the capacity to withhold an ongoing response regardless of smoking or ADHD status (Potter et al. 2012; Potter and Newhouse 2008; Potter and Newhouse 2004), these findings are inconsistent with other data from non-clinical smokers and non-smokers (Bekker et al. 2005; Wignall and de Wit 2011). The effects of acute nicotine on estimates of response inhibition capacity observed in vigilance tasks are also inconsistent: whereas some studies report substantial nicotine-induced enhancement in vigilance-related response inhibition capacity (Myers et al. 2013; Myers et al. 2008), other studies report very mild effects (Levin et al. 1998), effects related only to irrelevant stimuli (Dawkins et al. 2007), and dose-dependent effects (Bekker et al. 2005). Inconsistent effects of acute nicotine have also been observed in biased visual discrimination tasks (Barr et al. 2008; Wignall and de Wit 2011) that are discriminative of ADHD status (Tripp and Alsop 1999).

Unlike humans, acute nicotine administration in rodents consistently decreases response inhibition capacity in a wide range of tasks, including the 5-CSRTT (Bizarro et al. 2004; Blondel et al. 2000; Hahn et al. 2002; Semenova et al. 2007), the differential reinforcement of low rates (DRL) schedule of reinforcement (Kirshenbaum et al. 2011; Kirshenbaum et al. 2009; Kirshenbaum et al. 2008; Popke et al. 2000a; Popke et al. 2000b), the stop-signal task (Kirshenbaum et al. 2011), and the go/no-go discrimination (Kolokotroni et al. 2011). Only the temporal response differentiation task, which involves holding down a lever for a target interval, appears to be insensitive to nicotine-induced premature responding (Popke et al. 2000b).

Effects of nicotine on sustained attention

Acute nicotine appears to reliably enhance sustained attention in individuals with and without ADHD (Conners et al. 1996; Gehricke et al. 2006; Levin et al. 1998; Levin et al. 2000, 2001; Warburton 1992; for review see Heishman et al. 2010). Measures obtained from

rats in the five-choice serial reaction time task (5-CSRTT) suggest that acute nicotine improves sustained attention in outbred rodent models as well (Bizarro et al. 2004; Blondel et al. 2000; Day et al. 2007; Hahn et al. 2002; Mirza and Stolerman 1998; Semenova et al. 2007). Results from a visual signal detection task, another test of vigilance, also support the hypothesis that nicotine improves attention in rodents (Rezvani et al. 2002; Rezvani and Levin 2004).

Human and animal studies are consistent in supporting the ameliorating effects of nicotine on sustained attention, but *not* on response inhibition capacity. In this study, we consider an explanation to the latter negative findings. Nicotine may not appear to enhance response inhibition capacity in past studies due to (a) the animal models used, and/or (b) the method by which response inhibition capacity was assessed in these models.

An animal model of ADHD

The negative effects of nicotine on response inhibition capacity may be due to the choice of animal model in which these effects were tested. Subjects in these studies typically are outbred rats that may not have inhibitory deficits to rescue. The effect of nicotine on response inhibition capacity may be different in animals that model ADHD-related deficits. The spontaneously hypertensive rat (SHR) is the most widely studied animal model of ADHD (Sagvolden 2000; Sagvolden et al. 2009). Despite the prevalent use of this strain, the majority of evidence suggests that sustained attention is not compromised in SHR (Van den Bergh et al. 2006; Thanos et al. 2010; but see Sagvolden and Xu 2008). In contrast, performance in response-withholding paradigms, such as the DRL schedule, consistently shows a reduced response inhibition capacity in SHR compared to normoactive controls (Evenden and Meyerson 1999, Ferguson et al. 2007, Orduña et al. 2009; Sagvolden and Berger 1996, Sanabria and Killeen 2008; van den Bergh et al. 2006). Therefore, despite its limitations as an animal model of ADHD, SHR appears to be an ideal model to test whether or not nicotine enhances response inhibition capacity.

Assessing response inhibition capacity

In tasks like the DRL, the ability to withhold a response for an incentive is confounded with the reinforcing efficacy of the incentive (Doughty and Richards 2002; Hill et al. 2012). Nicotine may appear to reduce response inhibition capacity when in reality it is enhancing the efficacy of a reinforcer. The present study implements a novel response inhibition paradigm that empirically isolates response inhibition capacity from reinforcer efficacy: the fixed minimum interval (FMI) schedule of reinforcement (Hill et al. 2012).

In the FMI schedule, reinforcement is contingent upon withholding a response for a programmed time interval. Intervals are initiated with a lever press (initial response) and terminated with a head entry into the food hopper (terminal response). Head entries made *after* the programmed interval elapses are reinforced. Although this arrangement is similar to the DRL, a key difference is that in the FMI the topography of the initial response and the terminal response are different. In this way, the FMI dissociates the capacity to withhold the terminal response (inferred from the intervals between initial and terminal responses) from the efficacy of the reinforcer in maintaining initial responses (inferred from the intervals

between trial onset and initial response). Such dissociation is not possible with DRL schedules, because initial and terminal responses are identical. Put simply, motivation significantly affects presumed measures of response inhibition capacity in the DRL, but not in the FMI. This difference between FMI and DRL may explain why methylphenidate (MPH), which enhances response inhibition capacity in individuals with ADHD (Aron et al. 2003; Boonstra et al. 2005; DeVito et al. 2009), also enhances response-withholding performance of rats in the FMI (Hill et al. 2012), but not in the DRL (Van den Bergh et al. 2006; Ferguson et al. 2007; Hill et al. 2012; Orduña et al. 2009). In the FMI, acute MPH selectively reduces the interval between trial onset and initial response (Hill et al., 2012); because this interval and the interval between initial and terminal response are confounded in DRL schedules, MPH often induces short intervals between consecutive responses (Emmett-Oglesby et al. 1980; Ferguson et al. 2007; Orduña et al. 2009; Pearl and Seiden 1976; Seiden et al. 1979; but see Hill et al. 2012). We hypothesize that a similar confound explains nicotine-induced response-withholding deficits inferred from DRL performance. Thus, the FMI schedule was expected to reveal a lower baseline response inhibition capacity in SHR relative to a control strain. Also, in agreement with the symptom-amelioration hypothesis of ADHD-related smoking, the FMI was expected to reveal a nicotine-induced enhancement of reinforcer efficacy and inhibitory capacity.

Methods

Subjects

Twelve Spontaneously Hypertensive Rats (SHR/NCrI) served as experimental subjects; 11 Wistar Kyoto rats (WKY/NHsd) served as normoactive controls. Rats arrived on post-natal day (PND) 25, pair-housed by strain. Initially, 10 rats of each strain were received, but 3 WKY died within 3 days of arrival. One rat, left without a cagemate, was added to another pair to make one cage of 3 WKY. Before examining any performance data, a second cohort (4 WKY, 2 SHR) was added to compensate for the attrition. Both cohorts experienced identical procedures throughout the experiment. Shortly upon arrival, the duration of access to food was reduced daily from 24 h to 18 h, 12 h, and finally 1 h. For both SHR and WKY, this feeding regimen yielded weights at the beginning of each session that were, on average, 75.5% of mean ad libitum weights estimated from growth charts provided by the breeders. The average difference in weight between cagemates under food restriction was approximately 9% of their estimated mean ad libitum weights, which was similar to the 10% difference observed when food was freely available. Water was always available in the home cages ad libitum.

Apparatus

Experiments were conducted in 10 MED Associates (St. Albans, VT) modular test chambers (three chambers were 305 mm long, 241 mm wide, and 210 mm high; seven chambers were 305 mm long, 241 mm wide, and 292 mm high), each enclosed in a sound- and light-attenuating box equipped with a ventilating fan. The front and back walls and the ceiling of the 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. A square opening (51 mm sides)

located 15 mm above the floor and centered on the test panel provided access to the hopper (MED Associates, ENV-200-R2M) and was furnished with a head entry detector (ENV-254-CB). Each activation of a dispenser delivered a single 45-mg sucrose pellet (TestDiet, Richmond, IN) to the hopper. A multiple tone generator (MED Associates, ENV-223) was used to produce 3 kHz tones at approximately 75 dB through a speaker (MED Associates, ENV-224AM) centered on the top of the wall opposite to the test panel, 240 mm above the floor of the chamber. Two retractable levers (ENV-112CM) flanked the food hopper, and three-color light stimuli (ENV-222M) were mounted above each lever and could be illuminated yellow, green, and red. Lever presses were recorded when a force of approximately 0.2 N was applied to the end of the lever. The ventilation fan mounted on the rear wall of the sound-attenuating chamber provided masked noise of approximately 60 dB. The test chambers could be dimly illuminated by a houselight located behind the wall opposite to the test panel. Experimental events were arranged via a Med-PC® interface connected to a PC controlled by Med-PC IV® software.

Procedure

Figure 1 describes the sequence of events rats were exposed to. Sessions were conducted once daily, 7 days a week. Training initiated with autoshaping, consisting of pairing lever insertion with the delivery of a sucrose pellet. Once all rats were responding reliably to the lever, FMI training began. During FMI sessions, reinforcement was contingent upon the rat successfully waiting a given interval of time. The waiting interval was initiated by a lever press and terminated with a head entry into the food hopper. All terminal responses resulted in the retraction of the lever and a 5.5-s blackout period, after which the lever was reinserted and the next trial began. Each session ended after 60 min or after 150 sucrose pellets were delivered, whichever happened first. For a detailed description of training and the arrangement of sessions, see Mika et al. (2012).

At the onset of FMI training, the criterial waiting time (t) was set to 0.5 s. Each correct response increased t by 1.25%; t was carried over from one session to the next until $t = 6$ s, and remained constant thereafter. Once the 6-s criterion had been established, a conjunctive variable interval (VI) 9-s schedule was introduced and gradually increased across sessions, to a VI 30-s schedule. The conjunctive VI 30-s schedule was implemented to reduce the between-subject variability in rate of reinforcement that would otherwise result from unequal performance (for details, see footnote 1). When there were no noticeable upward or downward trends in the proportion of correct responses in four consecutive days, as determined by visual inspection of the data, the treatment phase began.

¹The VI schedule was implemented as follows: A timer ran throughout the session. Reinforcement became available when the timer completed a specified interval, with one exception: if the interval elapsed after the initial response, reinforcement was not available until the subsequent trial. After each reinforcer, the timer was reset and a new interval was specified. If a correct response was made before reinforcement became available, the rat was exposed to the 3kHz tone, but sucrose reinforcement was withheld. Intervals were specified by sampling without replacement from a 12-item Fleschler-Hoffman distribution (Fleschler & Hoffman, 1962). The VI-schedule requirement progressed in daily succession (9, 15, 20, 30 s), until all rats were performing at VI 30-s and $t = 6$ s. The VI schedule was implemented to reduce the between-subject variability in rate of reinforcement that would otherwise result from unequal performance. With this control in place, differences in performance could be reliably attributed to the experimental manipulation and not to differences in rate of reinforcement.

Nicotine and pre-feeding treatments

Prior to PND 52, when treatment commenced, all rats were drug naïve. Treatment consisted of *either* a subcutaneous (s.c.) injection of saline, 0.1, 0.3, or 0.6 mg/kg of nicotine, 10 min prior to session, or ad libitum access to food in the home cage during the hour leading up to session start. Treatment was implemented twice per week, with at least 2 rest days between treatments. This drug regimen was chosen because neither tolerance nor sensitization effects were evidenced in a similar regimen implemented by Kirshenbaum et al. (2008) using DRL 4.5-s and Sprague Dawley rats. Within this range of doses, acute s.c. nicotine disrupts DRL performance (Kirshenbaum et al., 2008), timing (Hinton and Meck, 1996), improves performance in 5-CSRTT (Bizarro and Stolerman 2003; Hahn et al. 2003), induces place preference, and enhances social rewards (Thiel et al. 2009).

FMI 6-s sessions were conducted daily. (–)Nicotine hydrogen tartrate (Sigma-Aldrich, St. Louis, MO) was dissolved in saline, and sodium hydroxide was added until the pH of the solution was approximately 7.2. Nicotine dose was calculated as the base, and injection volume was based on body weight at the time of injection. All animals experienced two determinations of each dose and two pre-feeding (PF) sessions. Each animal received each treatment (dose or PF) once (cycle 1) and then again in the same order (cycle 2). Treatment order within each cycle was counterbalanced across animals.

FMI with minimal delay

Once the two cycles of treatment were completed, two daily FMI 6-s sessions were conducted in the absence of nicotine. Immediately following, 15 daily sessions were conducted in which the criterial time was reduced to 0.5 s (FMI 0.5-s). No injections were administered until the 15th day, when all rats received 0.6 mg/kg nicotine immediately prior to the FMI session. The purpose of this condition was to determine whether selected effects of nicotine on FMI 6-s performance were dependent on the 6-s waiting period.

Dependent measures

The primary dependent measures were median latency to initial lever press, and selected parameters of the distribution of inter-response times (IRTs), computed for each rat over individual sessions. Latencies are the intervals between lever presentation (start of the trial) and initial lever press. Latencies were classified into two categories based on the outcome of the previous trial: (1) post-R latencies: those following correct reinforced trials, and (2) post-N latencies: those following non-reinforced trials, including those following trials in which a correct response went unreinforced because the conjunctive VI had not elapsed, as well as those following incorrect responses (i.e., $IRT < t$).

IRT refers to the time elapsed between the initial lever press and the terminal head entry. The Temporal Regulation model was applied to estimate parameters of the distribution of IRTs (Mika et al. 2012; Sanabria and Killeen 2008). The model assumes that, at the beginning of every trial, rats sometimes enter a *timing state* with probability P . When in a timing state, rats produce IRTs that are gamma-distributed, centered close to the criterial FMI interval (here, 6 s). When rats are not in a timing state, they produce IRTs at a constant average rate, and as such, non-timing IRTs are exponentially distributed. Thus, according to

the Temporal Regulation model, a mixture of two distributions, one gamma and one exponential, underlie the distribution of IRTs:

$$\begin{aligned} Pr(\text{IRT}=t|t<\delta) &= 0 \\ Pr(\text{IRT}=t|t \geq \delta) &= P\Gamma(t-\delta; n, c) + (1-P)(1/K)\exp(-(t-\delta)/K). \end{aligned} \quad (1)$$

In Equation 1, the probability of entering a timing state, P , is the mixture weight of a gamma distribution with shape parameter n and scale parameter c . Both distributions, gamma and exponential, are shifted rightwards to account for the minimum time required to complete an IRT, δ . Thus, the mean duration of timed IRTs is $nc + \delta$ and the mean duration of non-timed IRTs is $K + \delta$. Our analysis was primarily concerned with estimates of P and of the rescaled mean of the gamma distribution, $\theta = (nc + \delta) / 6$ s. If the mean timed IRT is shorter or longer than the 6-s criterial time, estimates of θ are, respectively, less than or greater than 1. Estimates of θ served as indices of response inhibition capacity (Sanabria and Killeen, 2008).

Data Analysis

IRTs and latencies were collected on every treatment day, on the day preceding each treatment (*no-treatment days*), and on the last 2 experimental days (FMI 0.5-s on no-treatment and on 0.6 mg/kg nicotine). Median latencies and estimates of θ were log-transformed. The proportion of correct IRTs (i.e., $\text{IRT} > 6$ s), the proportion of correct IRTs reinforced (i.e., reinforced IRTs / total IRTs), and estimates of P were log-odds transformed. These transformations follow suggestions on the estimation of population parameters in a similar model by Cheung, Neisewander and Sanabria (2012). All dependent measures are reported as back-transformed mean $\pm$ SEM. P and θ were estimated for each rat using the method of maximum likelihood (Myung 2003).

Analysis of variance (ANOVA)—ANOVA was implemented to establish the statistical significance of the effects of strain (SHR vs. WKY) and nicotine dose (vehicle vs. 0.1 vs. 0.3 vs. 0.6 mg/kg) on proportions of correct IRTs and correct IRTs reinforced. The effects of strain, nicotine dose, pre-feeding, schedule (FMI 6-s vs. 0.5-s) and treatment cycle (first vs. second) were examined on rate of reinforcement, median latencies and estimates of P and θ , using a significance threshold of $\alpha = .05$. When sphericity was violated according to Mauchly's test, a Huynh-Feldt correction was implemented. Only significant main effects or interaction effects were followed by post hoc 2-tailed t-tests. Significant cycle effects were followed by a separate ANOVA in each cycle. Only significant effects are reported.

Nicotine effects—Separate $2 \times 2 \times 4$ (strain $\times$ cycle $\times$ dose) mixed-design ANOVAs were conducted on median latencies and estimates of P and θ to establish the dose effects of nicotine on these dependent measures, and whether those effects were modulated by strain and treatment cycle.

Pre-feeding effects—Separate $2 \times 2 \times 2$ (strain $\times$ cycle $\times$ feeding status: not pre-fed at vehicle vs. pre-fed) mixed-design ANOVAs were conducted on median latencies and estimates of P and θ to establish the effects of pre-feeding on these dependent measures, and whether such effects were modulated by strain and treatment cycle. This analysis was

intended to identify effects related to a potential nicotine-induced reduction in appetite (Dandekar et al. 2011; Wellman et al. 2005). Nicotine effects that matched pre-feeding effects were discounted as potentially related to appetite reduction and not to performance enhancement.

Schedule effects on latencies—Separate $2 \times 2 \times 2$ (strain $\times$ schedule: FMI 0.5-s vs. 6-s on 0.6 mg/kg in second cycle; treatment: no-treatment vs. treatment day) mixed-design ANOVAs were conducted on post-R and post-N latencies to establish whether strain and nicotine effects on latency were modulated by the length of the criterial waiting time. Only the second cycle of 0.6 mg/kg FMI 6-s treatment was used in this comparison to minimize the confound between schedule and order effects (FMI 6-s was implemented before FMI 0.5-s, see Figure 1).

Stability of rate of reinforcement—Rate of reinforcement was measured as the number of reinforcers obtained per 60-min session. Although the maximum number of reinforcers obtainable in a session was 150 pellets, no rat reached this limit in any experimental session. The conjunctive VI schedule was expected to keep rate of reinforcement relatively constant across experimental manipulations. Stability of rate of reinforcement was tested by conducting a $2 \times 2 \times 4$ (strain $\times$ cycle $\times$ dose) and a $2 \times 2 \times 2$ (strain $\times$ cycle $\times$ feeding status) mixed-design ANOVAs, with reinforcers per session as the dependent measure.

Coefficient of variation—The estimation of the coefficient of variation (CV) of timed IRTs is often included as part of the analysis of FMI performance (Sanabria and Killeen 2008). Higher CV is indicative of less precise timing (Sanabria and Killeen 2008). In this study we monitored CV across manipulations, but do not report it because baseline timing is not less precise in SHR than in WKY (Orduña et al. 2009; Orduña et al. 2008; Sanabria and Killeen 2008). This null finding was replicated here in the vehicle condition, $CV_{SHR} = 0.18 \pm 0.01$, $CV_{WKY} = 0.20 \pm 0.01$. Thus, SHR does not appear to be an adequate model of timing deficits in ADHD (Toplak et al. 2006); effects of nicotine in this domain are, therefore, uninterpretable.

Results

Temporal Regulation Parameters

In all conditions the distribution of IRTs were well described by a mixture of two underlying distributions, one gamma (timed IRTs) and one exponential (non-timed IRTs) (Eq. 1). Figure 2 illustrates the goodness-of-fit of this model to performance under vehicle and under the highest dose of nicotine, 0.6 mg/kg.

Nicotine effects—A significant main effect of nicotine dose was observed on the proportion of correct IRTs, $F(3,63) = 4.23$, $p = .009$. Post hoc paired-sample t-tests revealed that all doses of nicotine reduced the proportion of correct IRTs, from an average of 51% at baseline to 33–36% under nicotine; $t(22)$ ranged between 2.25, $p = .035$, and 3.00, $p = .007$. No significant effect of nicotine dose or strain was observed on the proportion of correct IRTs reinforced, which was on average 54%.

Figure 3 shows the effects of strain and dose on estimates of θ and P . A significant main effect of dose on θ estimates was observed, $F(3, 63) = 4.64$, $p = .005$. Post hoc paired-samples t -tests revealed that, relative to vehicle, all doses of nicotine significantly reduced θ ; $t(22)$ ranged between 2.58, $p = .017$, and 3.31, $p = .003$. Significant strain $\times$ dose interaction effects on estimates of P were observed, $F(3, 63) = 5.05$, $p = .003$. Post hoc t -tests on P revealed that it was (a) significantly higher for SHR than WKY on 0.1 mg/kg nicotine, $t(21) = 2.33$, $p = .030$, (b) significantly higher for SHR on 0.1 and 0.3 mg/kg nicotine than on vehicle, $t(11) = 4.41$, $p = .001$, and $t(11) = 4.05$, $p = .002$, respectively, and (c) significantly higher for WKY on 0.3 and 0.6 than on vehicle, $t(10) = 2.79$, $p = .019$, and $t(10) = 2.64$, $p = .024$. Overall, these results suggest that nicotine reduced response inhibition capacity, but dose-dependently increased the sensitivity to the temporal contingencies of reinforcement, requiring a lower dose for the latter improvement in SHR.

Pre-feeding effects—Figure 3 shows the effects of pre-feeding (PF) on estimates of θ and P . A significant strain $\times$ cycle $\times$ feeding status interaction effect was observed on θ estimates, $F(1, 21) = 5.61$, $p = .028$. A separate analysis was conducted on θ estimates at each cycle. No significant effect of strain or feeding status was observed on θ in either cycle, suggesting that the 3-way interaction effect on θ was an effect of cycle modulated by strain and feeding status. No significant effects of strain, cycle, or feeding status were observed on P .

Latencies

Nicotine effects—Figure 4 (left) shows the effects of strain and dose on post-R and post-N latencies. Significant effects of dose on post-R and post-N latencies were observed [post-R: $F(3, 63) = 19.83$, $p < .001$; post-N: $F(3, 63) = 28.16$, $p < .001$]. Post hoc paired-sample t -tests revealed that all doses of nicotine significantly shortened post-R and post-N latencies relative to vehicle; $t(22)$ ranged between 2.36, $p = .027$, and 8.21, $p < .001$. No significant effect of strain was observed. Thus, regardless of strain or of the outcome in the preceding trial, even the lowest dose of nicotine was effective in reducing the time between trial onset and first lever press.

Pre-feeding effects—Figure 4 (PF) shows the effects of strain and feeding status on post-R and post-N latencies. Significant main effects of feeding status on post-R and post-N latencies were observed [post-R: $F(3, 63) = 20.08$, $p < .001$; post-N: $F(3, 63) = 62.20$, $p < .001$]. All latencies were roughly 2 s longer when rats were pre-fed. No significant strain $\times$ feeding status interaction effect was observed. Thus, regardless of strain or of the outcome of the preceding trial, pre-feeding increased the time between trial onset and first lever press.

Schedule effects—Figure 4 (right) shows the effects of an s.c. injection of 0.6 mg/kg on FMI 0.5-s and FMI 6-s performance. Significant main effects of schedule and nicotine were observed in both post-R [respectively: $F(1, 21) = 61.56$, $p < .001$; $F(1, 21) = 27.92$, $p < .001$] and post-N latencies [respectively: $F(1, 21) = 4.58$, $p = .044$; $F(1, 21) = 51.06$, $p < .001$]. No significant effect of strain or interaction effect was observed. These results suggest that the nicotine-induced shortening of latencies was not schedule-dependent, and was observable even when reinforcement was minimally delayed.

Stability of Rate of Reinforcement

A significant strain $\times$ dose effect on rate of reinforcement was observed, $F(3,63) = 2.84$, $p = .045$. Post hoc paired-sample t -tests revealed that WKY obtained fewer reinforcers under 0.6 mg/kg nicotine than under vehicle, $t(10) = 3.29$, $p = .008$. This means that the effect of nicotine on WKY performance was confounded with the effects of reduced rate of reinforcement only at the highest dose. At other doses in WKY and all doses in SHR, these effects were not confounded.

A significant strain $\times$ cycle $\times$ feeding status effect on rate of reinforcement was observed, $F(1,21) = 310.42$, $p = .004$. Post hoc t -tests were conducted separately in each cycle. Post hoc comparisons revealed that, in the second cycle, pre-feeding substantially reduced the rate of reinforcement of WKY relative to no pre-feeding, $t(10) = 2.98$, $p = .014$, and relative to pre-fed SHR, $t(21) = 2.97$, $p = .007$.

Discussion

Nicotine and response inhibition capacity

The acute administration of nicotine reduced estimates of θ similarly for SHR and WKY (Figure 3). This result suggests that acute nicotine reduces response inhibition capacity in both strains. Although this finding is inconsistent with our expectations, it is consistent with nicotine-induced reductions in IRTs observed in DRL studies using Sprague Dawley rats (Kirshenbaum et al. 2008, 2009, 2011). Performance in DRL schedules cannot be readily interpreted in terms of response inhibition capacity, because it is also sensitive to reinforcer-efficacy manipulations (e.g., reinforcer magnitude; Doughty and Richards 2002). In contrast, estimates of θ are not significantly sensitive to changes in reinforcer efficacy via pre-feeding (Figure 3). Yet, nicotine also appears to reduce θ , suggesting that the effect of nicotine on DRL performance may not be solely explained on the basis of enhanced reinforcer efficacy.

An alternative account of our results would suggest that reduced estimates of θ resulted from a faster internal clock under acute nicotine (Hinton and Meck 1996). Intervals trained without nicotine may be perceived as being longer under nicotine, thus yielding shorter timed IRTs when nicotine was acutely administered. The accelerative effects of nicotine on timing, however, have only been demonstrated using the peak interval method (Hinton and Meck 1996; Meck 2007), which is vulnerable to confounding motivational effects (Galtress and Kirkpatrick 2009; Ludvig et al. 2011; Plowright et al. 2000; Sanabria et al. 2009). Timing estimates that are more robust to motivational manipulations, such as those obtained from the temporal bisection procedure (Galtress and Kirkpatrick, 2010), do not suggest an accelerative effect of nicotine on the internal clock (Ward et al. 2009). These findings do not support an explanation of nicotine-induced effects on θ based on timing mechanisms.

Neither changes in reinforcer efficacy nor changes in rate of reinforcement can explain nicotine-induced reductions in estimates of θ . Pre-feeding did not have a significant effect on estimates of θ (Figure 3), but it increased latencies, an effect opposite that of nicotine. The robustness of θ to the pre-feeding manipulation suggests that, consistent with prior findings (Mechner and Guevrekian 1962), mean timed IRTs are robust against changes in reinforcer efficacy. Relative to baseline, rate of reinforcement was significantly lower only

for WKY at the highest dose of nicotine. The stability of rate of reinforcement in both strains across most conditions was primarily due to the conjunctive VI schedule of reinforcement that imposed a minimum (but variable) amount of time between reinforcers. The limited effect of nicotine on rate of reinforcement cannot account for reductions in estimates of θ in both strains at every dose of nicotine. Thus, it appears that nicotine-induced reductions in estimates of θ reflect a nicotine-induced reduction in the capacity of both SHR and WKY to withhold a reinforced response.

Given that nicotine reduces response inhibition capacity so consistently in rodent models, it is unclear why the effects of nicotine on response inhibition capacity appear to vary so much among human studies. The key to these inconsistencies may be the underlying processes assessed by divergent methodologies. For instance, nicotine-induced improvements in human response-inhibition capacity are primarily observed in the stop-signal task and in the Stroop task (Potter et al. 2012; Potter and Newhouse 2008; Potter and Newhouse 2004; Wignall and de Wit 2011). In these tasks, the behavior to be withheld is prepotent because it is either already initiated (stop signal task) or because it is strongly associated with a present stimulus (Stroop task). In contrast, most rodent paradigms, including DRL and FMI schedules, are based on behavior that is potentiated by its consequences. Nicotine has detrimental effects on performance in analogous tasks in humans, such as the biased visual discrimination task used by Barr et al. (2008).

The absence of strain effects on estimates of θ at baseline tempers our interpretation of the measure of response inhibition capacity obtained from FMI performance. To the extent that θ reflects response inhibition capacity, and SHR models inhibitory deficits associated with ADHD, lower estimates of θ would be expected in SHR relative to WKY. This difference between strains has been observed systematically in the DRL (Ferguson et al. 2007, Orduña et al. 2009; Sagvolden and Berger 1996, Sanabria and Killeen 2008; van den Bergh et al. 2006), but was not observed in the present study using the FMI. It is thus likely that procedural differences between FMI and DRL schedules are responsible for these divergent results. Various features of the FMI—the longer resting period between withholding trials, the response-initiated nature of these trials, the separation of initial and terminal responses—may facilitate the response-withholding performance of SHR.

Nicotine and reinforcer efficacy

Mechner and Guevrekian (1962) demonstrated that FMI latencies, but not IRTs, are sensitive to reinforcer deprivation. Our results are consistent with those findings, showing that pre-feeding increased latencies regardless of strain and of the outcome of the preceding trial (i.e., post-R vs. post-N; Figure 4, left). These results support the interpretation of changes in latencies as reflecting changes in reinforcer efficacy. The reduction in latencies following nicotine administration (Figure 4, left) thus suggests that nicotine enhanced the reinforcing efficacy of sucrose pellets. These data are consistent with reports of nicotine-induced enhancement of reinforcer efficacy for appetitive reinforcers or food-related cues (see Donny et al. 2011) in both rats (Grimm et al. 2012; Raiff and Dallery 2006; Wing and Shoaib 2010) and humans (Epstein et al. 1992; Perkins 1992).

In principle, however, it is possible that the reduction in latencies following nicotine administration reflects a nicotine-induced reduction in the sensitivity to the delay of reinforcement. Prior research (Morgan 1972) and the positive relationship between latencies and FMI target time (0.5 s vs. 6 s; Figure 4), support the notion that latencies are sensitive to delay of reinforcement. If nicotine effects on latencies were mediated by changes in sensitivity to delay of reinforcement, it would be expected that the elimination of the delay of reinforcement would also eliminate the effect of nicotine on latencies. Contrary to that expectation, however, nicotine produced shorter latencies even in FMI 0.5 s, when delay to reinforcement was minimal (Figure 4, right panels). Such effect supports the hypothesis that changes in latencies induced by nicotine reflect changes in reinforcer efficacy and not in sensitivity to the delay of reinforcement.

Nicotine and sensitivity to timing contingencies

In all conditions the distribution of IRTs were well described by a mixture of two underlying distributions, one gamma (timed IRTs) and one exponential (non-timed IRTs) (Eq. 1, Figure 2). Generally, more than 90% of the IRTs were timed, signified by parameter P . The remaining 10% of intervals ($1-P$) appear to be produced absent of the control of the timing contingencies, as they are produced at a constant rate. Although it has not been explicitly evaluated in the FMI schedule, this loss of control by the contingencies of reinforcement may be attributed to lapses in attention (Killeen et al. 2013; Sagvolden et al. 1998).

In the present study, the proportion of timed intervals did not differ significantly at baseline (vehicle) between SHR and WKY (Figure 3, bottom). This lack of significant baseline differences has also been observed in paradigms designed to assess sustained attention in rodents, such as the 5-CSRTT (van den Bergh et al. 2006) and the visual stimulus position discrimination task (Thanos et al. 2010). The evidence available suggests that the SHR is not an adequate model of ADHD-related deficits in sustained attention.

Nevertheless, the effects of nicotine on P may be informative. It was observed that P increased following nicotine administration, tracing an inverted-U dose response function that peaked at a lower dose for SHR (0.1 mg/kg) than for WKY (0.3 mg/kg; Figure 3). This effect suggests that, relative to WKY, SHR required a lower dose of nicotine to increase the proportion of timed IRTs. If P were to be interpreted in terms of attentional processes, these results would be the opposite of what would be expected. This is because the SHR, compared to WKY, has fewer $\alpha 4\beta 2$ nicotinic receptors (Wigstrand et al. 2011), which appear to mediate the enhancement of sustained attention in rodents induced by nicotine (Rezvani et al. 2011; Young et al. 2013). Other nicotinic receptor subunits potentially involved in attentional processes, such as $\alpha 7$ (Leiser et al. 2009), do not vary significantly in number between SHR and WKY (Wigstrand et al. 2011) and may therefore mediate the effect of nicotine on estimates of P . Nonetheless, the involvement of $\alpha 7$ receptors in sustained attention in rats is disputable (Grottick and Higgins 2000; Shoaib and Bizarro 2005). Furthermore, estimates of P do not appear to increase with MPH treatment in rats (Hill et al. 2012), even though past research has shown that MPH enhances sustained attention in both rats (Paine et al. 2007) and humans (Epstein et al. 2006; Riccio et al. 2001). A potential explanation to these seemingly contradictory findings requires that nicotine and

MPH enhance sustained attention through different mechanisms (Levy and Hobbes 1996; McGaughy et al. 1999), and *P* indexes a nicotine-sensitive attention-like process that is not necessarily mediated by $\alpha 4\beta 2$ nicotinic receptors. Although it is yet unclear what neural processes are indexed by *P*, these processes are likely to have implications in the research and treatment of attentional deficits.

Conclusion

This investigation provides the first evidence, in an animal model of ADHD, for nicotine-induced reduction in response inhibition capacity that is not confounded with reinforcer-efficacy effects. In particular, our data suggests that nicotine hinders the capacity of rats to withhold a response that has been instrumentally reinforced. This result undermines the hypothesis that smoking among individuals with ADHD is facilitated by an ameliorating effect of nicotine on response inhibition deficits.

Acute nicotine increased the degree to which rats responded to reinforcement contingencies. This effect peaked at a lower dose for the animal model of ADHD (0.1 mg/kg) than for its control (0.3 mg/kg). Along with observations from past research and pre-feeding manipulations, it suggests that the mechanism by which nicotine enhances the sensitivity to reinforcement contingencies involve neither $\alpha 4\beta 2$ nicotinic receptors—which are often involved in sustained attention—nor motivational mechanisms on which MPH appear to operate (Levy and Hobbes 1996). Future research may unveil the specific mechanisms supporting this effect.

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Fig. 1.

Timeline of events. Rats arrived at the facility on PND 25; after an acclimation period, they began lever training on PND 30. FMI training started on PND 40, and once performance stabilized on the FMI 6-s schedule, the treatment phase began on PND 57. During treatment, rats were injected with saline, three different doses of nicotine (0.1, 0.3, 0.6 mg/kg), and pre-fed in counterbalanced order. Rats were subjected to each treatment twice, with the second cycle beginning on PND 74. On PND 92, the criterial waiting time for the FMI schedule was reduced from 6 s to 0.5 s. After 14 days of experience with FMI 0.5-s, all animals received 0.6 mg/kg nicotine immediately prior to session (PND 106).

Fig. 2.

Mean cumulative frequency distributions of IRTs produced by SHR (top) and WKY (bottom) after s.c. injections of vehicle (circles) and 0.6 mg/kg nicotine (downward triangles). Data are organized in 39 bins, each containing approximately equal number of IRTs. Dotted lines are fits of the Temporal Regulation (TR) model of response inhibition capacity (Eq. 1).

Fig. 3.

Mean estimates of θ (top) and P (bottom) for SHR (solid circles) and WKY (open circles) rats across vehicle (Veh), 0.1, 0.3, and 0.6 mg/kg s.c. nicotine (left of vertical dashed line) and pre-feeding (PF; right of vertical dashed line). *Significant difference between dose and Veh. §Significant simple main effect of strain at a dose level. †Significant difference between dose and Veh in SHR. ‡Significant difference between dose and Veh in WKY. Symbols are repeated with lower p-values (i.e., * $p < .050$, ** $p < .010$, *** $p < .001$). A significant strain $\times$ cycle $\times$ feeding status interaction effect was observed on θ , but no significant main or interaction effect of strain or feeding status on θ were observed in either cycle. All doses of nicotine reduced estimates of θ relative to Veh. Nicotine increased estimates of P in a dose-dependent manner and differentially across strains. The nicotine dose-response curve of P was shifted leftwards in SHR relative to WKY.

Fig. 4.

Mean median latencies to the initial lever press across nicotine and pre-feeding (PF) treatment conditions (left panel) and across FMI schedules (right panel; FMI 6-s data is from cycle 2) for SHR (solid circles) and WKY (open circles) rats. “Post-R” denotes the latencies following reinforced trials; “Post-N” denotes latencies following non-reinforced trials.

*Significant difference between dose and Veh. #Significant main effect of FMI schedule, %Significant main effect of nicotine relative to no-treatment (day preceding injection). Symbols are repeated with lower p-values (i.e., * $p < .050$, ** $p < .010$, *** $p < .001$). Nicotine and shorter FMI target time reduced median post-R and post-N latencies; pre-feeding increased median post-R and post-N latencies.