Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 87 (2007) 360–368
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Chronic nicotine administration improves attention while nicotine withdrawal induces performance deficits in the 5-choice serial reaction time task in rats

Svetlana Semenova [a], Ian P. Stolerman [b], Athina Markou [a,*]

[a] *Department of Psychiatry School of Medicine University California San Diego 9500 Gilman Drive, M/C 0603 La Jolla, California 92093-0603, USA*
[b] *Section of Behavioural Pharmacology Institute of Psychiatry PO49 King's College London, De Crespigny Park London SE5 8AF, UK*

Received 4 January 2007; accepted 16 May 2007
Available online 23 May 2007

Abstract

Nicotine appears to enhance attention, while nicotine withdrawal leads to attentional deficits in humans that are ameliorated with nicotine administration. However, there has been much debate as to whether nicotine improves performance under baseline conditions, or only ameliorates attentional deficits. Thus, we studied the effects of acute and chronic nicotine administration and nicotine withdrawal on attentional performance in the 5-choice serial reaction time task (5-CSRTT) in Wistar and Sprague Dawley (SD) rats under baseline conditions. Wistar rats performed with higher accuracy compared to SD rats. Acute nicotine administration induced small increases in accuracy and correct responses, impulsivity and speed of responding, and decreases in omission errors. These effects were more pronounced in less accurate rats or after task modifications were implemented to disrupt the rats' performance. Chronic nicotine administration *via* minipumps consistently increased accuracy during days 4–6 of nicotine infusion after the effect of nicotine on impulsivity during days 1–3 dissipated. By contrast, nicotine withdrawal induced decreases in correct responses, and increases in omissions and latencies to respond, but had no effect on accuracy. These results provide evidence that chronic, but not acute, nicotine administration induced accuracy improvement under baseline conditions, while nicotine withdrawal produced some limited performance deficits.

Keywords: Attention; Nicotine; 5-choice serial reaction time task; Nicotine withdrawal; Strain; Rat

1. Introduction

Nicotine has been shown to enhance cognition in humans especially in tasks involving attentional processes (Koelega, 1993; Levin et al., 2006; Rezvani and Levin, 2001; Stolerman et al., 1995). Further, nicotine-induced improvements in performance in various cognitive tasks, including attentional tasks, have been demonstrated in smokers after a period of abstinence (Bates et al., 1995; Bell et al., 1999; Ernst et al., 2001; Foulds et al., 1996; Snyder et al., 1989; Snyder and Henningfield, 1989; Warburton and Mancuso, 1998) and in patients with different psychiatric and neurological disorders, such as Alzheimer's disease, attention deficit and hyperactivity disorder and schizophrenia (Levin et al., 1996; Sahakian et al., 1989; White and Levin, 2004). Thus, it has been argued that nicotine-induced cognitive enhancement in these populations reflects the reversal of cognitive deficits characteristic of both nicotine withdrawal and/or the neuropsychiatric disease states.

The effects of nicotine in non-abstinent smokers or non-smokers have been inconsistent. Some studies demonstrated cognitive improvements in smokers in the absence of withdrawal effects (Warburton and Arnall, 1994). In non-smokers nicotine enhanced motor responses in brief tests of attention (Kerr et al., 1991) and performance in tests of sustained attention (Foulds et al., 1996; Levin et al., 1998; Mumenthaler et al., 1998). In contrast, other studies reported that nicotine either had no effect or impaired performance in non-smokers or non-abstinent smokers in tasks measuring sustained or selective attention (Heishman and Henningfield, 2000; Heishman et al., 1993; Hindmarch et al.,

* Corresponding author. Tel.: +1 858 534 1572; fax: +1 858 534 9917.
E-mail address: amarkou@ucsd.edu (A. Markou).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.05.009

1990). These inconsistencies in the human data may be attributed to differences in nicotine dose used, route of nicotine delivery or the fact that only one nicotine dose was used in some studies and thus the nicotine effect may have been missed. Further, it is well documented that infrequent nicotine administration or initial exposure to cigarettes can induce dysphoria in non-smokers that may interfere with performance in these tasks (Foulds et al., 1997; Heishman and Henningfield, 2000; Heishman et al., 1993; Hindmarch et al., 1990; Perkins et al., 1993); smokers develop tolerance to the dysphoric effects of nicotine, perhaps allowing the beneficial effects of nicotine on cognition to emerge. Therefore, systematic investigations of cognitive and attentional improvements after acute and chronic nicotine administration are needed to determine whether indeed nicotine may improve performance under baseline conditions when there is no underlying deficit that could be reversed. Studies in rats permit such systematic evaluations to be undertaken under controlled conditions.

The 5-choice serial reaction time task (5-CSRTT) is now among the most widely used tests of attentional function in experimental animals (Robbins, 2002). This task is analogous to the continuous performance test and Leonard's 5-choice serial reaction time task used in humans to assess sustained attention (Mirsky and Rosvold, 1960). This operant task requires localization of brief visual stimuli presented randomly in one of five locations. In the 5-CSRTT, a large number of correct target detections indicates good attentional performance as reflected by high response accuracy accompanied by few omission errors and a relatively fast speed of responding. Additional measures of performance, such as premature responses (impulsive behavior), and perseverative responses (compulsive behavior), provide measures of inhibitory response control (for review, Robbins, 2002). When nicotine was administered under the standard task conditions, used by Trevor Robbins and colleagues (Carli et al., 1983), the most robust nicotine effects were increases in impulsivity and speed of responding, while detection of improvements in accuracy in *unimpaired* experimental animals has proven to be challenging (Blondel et al., 2000; Grottick and Higgins, 2000; Muir et al., 1995). Therefore, changes to the task (*e.g.*, limited use of time-outs as punishment for incorrect or inappropriate responding, trials initiated automatically and not by the subject) were introduced by Ian Stolerman and colleagues (Hahn et al., 2002b; Mirza and Stolerman, 1998) to reduce the number of different behavioral contingencies controlling performance and thereby allow a greater focus on stimulus detection. This approach was adapted because each additional contingency provides a potential substrate for drug action that may obscure the effects on attention. In this modified task nicotine produced small improvements in several measures of the attentional performance of unimpaired rats, and also reversed the effects of an auditory distractor stimulus (Hahn et al., 2002a,b).

In the present study, we explored further the potential task-dependent effects of acute and chronic nicotine on attention under baseline conditions in the widely used Wistar and Sprague Dawley (SD) rat strains as some studies suggested that the effects of nicotine in the 5-CSRTT are strain-dependent (Didriksen and Christensen, 1993; Mirza and Bright, 2001). The use of two versions of the task allowed us to examine whether differences in the task parameters may facilitate the detection of nicotine-induced enhancements in performance. Finally, we explored the effects of nicotine withdrawal on attentional performance.

2. Materials and methods

2.1. Subjects

Male Wistar and Sprague Dawley rats (Charles River; 200–250 g at the beginning of the experiments) were housed in groups of two in a humidity- and temperature-controlled vivarium on a 12 h light/dark cycle. A food restriction schedule of 20 g/rat per day was maintained throughout the training and testing period. Rats had *ad libitum* access to water throughout the course of the studies except during testing. Training and testing occurred during the dark cycle. All subjects were treated in accordance with the National Institutes of Health guidelines. All experimental protocols and animal facilities were in accordance with the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) and approved by the institutional animal care and use committee.

2.2. Drugs

Nicotine bitartrate (Sigma, St. Louis, MO) was dissolved in saline and subcutaneously (s.c.) delivered by 7-day osmotic pumps (3.16 mg/kg/day base or 9 mg/kg/day nicotine salt) or injected acutely at the doses of 0.017–0.14 mg/kg calculated as nicotine base (*i.e.* 0.05–0.4 mg/kg salt).

2.3. Apparatus

All testing was conducted in a set of 12 'nine-hole' test boxes (Med Associates, St. Albans, VT). Each box consisted of a 25.5 width × 28.4 length × 28.7 height cm chamber enclosed in a soundproofed box with a ventilator fan providing air circulation and producing low level background noise. A 2.5 W, 24 V white house light was positioned on one wall of the chamber and was illuminated during each experimental session. The concavely curved rear wall of the chamber contained nine 2.5 cm^2 square apertures, 4 cm deep and 1.4 cm above floor level. Each aperture had a vertical infrared beam crossing the entrance that illuminated a photoelectric cell. Illumination of each aperture was provided by a 2.5 W bulb located at the rear of the aperture. Alternate apertures were blocked by a metal cover leaving five apertures open to register the subjects' responses. Food pellets were delivered to a magazine tray, located on the wall opposite to the curved wall that contained the five apertures. The distance from each aperture to the magazine feeder was 28.4 cm. Each apparatus was controlled by and provided data collected through a MedAssociates interface to a PC computer.

2.4. The 5-CSRTT procedures

The 5-CSRTT procedures used in the present studies were similar to the procedure originally developed by Robbins and colleagues (Carli et al., 1983) and a modified version of the same procedure designed by Stolerman and colleagues (Hahn et al.,

2002b). The Robbins procedure will be described first as the majority of studies reported here used this procedure. Initially, the subjects were given the opportunity to become familiar with the test box, feeding regimen, and response apertures prior to training and testing. This habituation was accomplished by allowing rats to retrieve free food pellets from the magazine feeder and the five response apertures during two 20 min sessions. Two additional sessions with pellets dispensed every 20 s for 20 min in the magazine feeder preceded further training on the task.

2.4.1. Final Test Schedule (as used by Robbins and colleagues)

Each test session of the 5-CSRTT commenced with the illumination of the chamber by the house light and the delivery of a free food pellet. The collection of this pellet from the feeder started the first trial. After a fixed inter-trial interval (ITI) of 5 s, the light at the rear of one of the response apertures was illuminated for 0.75 s. Responses in this aperture within 5 s of illumination of the hole, the limited hold, were recorded as correct responses and were rewarded by the delivery of a food pellet to the magazine feeder. The latencies to correct response were measured from the initiation of the illumination of the aperture to the breaking of the appropriate beam of light. An additional response in an aperture after a correct response and before the food collection was recorded as a perseverative response and punished with a 5 s time-out period. Further responding in the apertures during the time-out restarted this time-out period. Time-out periods were denoted by the extinction of the house light, leaving the test chamber in total darkness. The magazine feeder latency was measured as the time from breaking the correct beam of light until the entry to the feeder to collect a food pellet. Responses in a non-illuminated hole were recorded as incorrect responses and were punished by a time-out period (5 s), as were failures to respond within the 5 s limited hold period, which were recorded as omissions. Other responses in the apertures during the ITI or time-out periods were also recorded and punished by a time-out period (5 s). A response in the feeder after the delivery of food or after a time-out period initiated the next trial; a feeder response after a premature response restarted the same trial.

Each test session was terminated after either the completion of 100 trials or 30 min, whichever occurred first. During each session the stimulus light was presented an equal number of times in each of the five holes. Training started with the stimulus duration set at 30 s and the limited hold set at 60 s. These variables were altered on subsequent sessions until the final set of task parameters was implemented (stimulus duration, 0.75 s; limited hold, 5 s). Rats were trained until they had reached criterion performance (>70% accuracy and <20 omissions) and stable baselines (<10% variation in accuracy over 5 consecutive days).

2.4.2. Modified Final Test Schedule (as used by Stolerman and colleagues)

A version of the 5-CSRTT based on the procedures described by Hahn et al. (2002b) was used in Experiment 2; it incorporated the following differences from the original Robbins procedure. Omission errors, premature responses and perseverative responses were not punished by time-outs. Trials were initiated automatically and not by the subject. In addition the time-out period was 2 s (instead of 5 s), the stimulus duration was 1 s (instead of 0.75 s) in the final phase of training and testing, and the session length of 30 min was independent of the number of trials completed. These modifications were previously described in detail and the significance of these changes was discussed in Hahn et al. (2002b).

2.4.3. Measures of task performance:

1. Accuracy (%): the number of correct responses/(number of correct+number of incorrect responses)×100.
2. Correct responses are defined as nose-poke responses during the limited hold period in the same aperture as the stimulus light presentation.
3. Incorrect responses are defined as the nose-poke responses during the limited hold period in a different aperture from the one where the stimulus light was presented.
4. Omissions are defined by the absence of a nose-poke response during the limited hold period in any of the response apertures.
5. Premature responses are defined as responses in the apertures during the ITI periods.
6. Perseverative responses are defined as responses in the apertures after a correct response and before collection of the food reward.
7. Speed of responding was assessed by two measures. The latency to respond correctly was measured from the onset of the visual stimulus to the response in the aperture where the light appeared. The second measure was the latency to respond incorrectly and was measured from the onset of the visual stimulus to the response in any wrong hole where the light did not appear during that trial.
8. Magazine latency or reward latency was measured from the time of a correct response until the collection of the food pellet from the magazine feeder.

2.5. Experimental designs

2.5.1. Experiment 1: The effects of acute nicotine treatment on performance in the standard 5-CSRTT in Wistar and SD rats

After the establishment of stable performance in the 5-CSRTT (see above), rats (Wistar rats $n=10$; SD rats $n=9$) were injected with nicotine (s.c., 0, 0.017, 0.035, 0.07 and 0.14 mg/kg calculated as base, corresponding to 0, 0.1, 0.2 and 0.4 mg/kg of nicotine salt). Injections took place 10 min before the session, using a within-subject Latin-square design. To minimize disruptive/aversive effects of the first exposure to nicotine, rats received two subcutaneous injections of 0.07 mg/kg of nicotine base in the home cage 1 week before the initiation of the Latin-square.

2.5.2. Experiment 2: The effects of acute nicotine treatment on performance in the modified 5-CSRTT in Wistar rats

After the establishment of stable performance in the 5-CSRTT (see above), naïve Wistar rats ($n=12$) were injected with nicotine (s.c., 0, 0.017, 0.035, 0.07 and 0.14 mg/kg base, corresponding to 0, 0.1, 0.2 and 0.4 mg/kg, nicotine salt) 10 min before the session using a within-subject Latin-square design. As in Experiment 1, rats received two subcutaneous injections of 0.07 mg/kg of nicotine base in the home cage 1 week before the initiation of the

Latin-square design. Only Wistar rats were tested in the modified 5-CSRTT task as their attentional performance was superior to that of the Sprague Dawley rats. We hypothesized that a task that leads to degraded performance compared to the standard task may reveal enhancing effects of nicotine in performance.

2.5.3. Experiment 3: The effects of chronic nicotine treatment and spontaneous nicotine withdrawal on 5-CSRTT performance in Wistar rats using the standard 5-CSRTT

After the establishment of stable performance in the standard 5-CSRTT (see above), naïve Wistar rats were prepared with 7-day osmotic minipumps (model 2ML1, Alza Co., Palo Alto, CA) delivering 3.16 mg/kg/day base (9 mg/kg/day nicotine salt; $n=11$) or saline ($n=11$). During the 7 day period of exposure to the minipumps, the rats' behavior was assessed daily in the 5-CSRTT. On day 7, the minipumps were removed and the rats' behavior in the 5-CSRTT was assessed at 12 h and at 24 h intervals thereafter for 7 days.

2.6. Data analyses

Correct and incorrect responses and omissions were expressed as a percentage of the number of trials completed to facilitate comparisons between measures obtained in the "standard" and "modified" tasks. In the "standard" task, rats completed all allowed 100 trials (*e.g.*, correct responses + incorrect responses + omissions = 100), while in the "modified" task there was no limit in the number of trials and there was only a limit in the session duration (30 min) during which rats on average completed approximately 220 trials.

All data from all measures obtained in Experiments 1 and 2 were analyzed by repeated measures ANOVAs with treatment (*i.e.*, nicotine dose) as the within-subjects factor. Data obtained in Experiment 3 were analyzed by 2-way ANOVAs with treatment (2 levels: nicotine or saline exposure) as a between-subject factor and day of chronic nicotine exposure or day of nicotine withdrawal as within-subject factors. Statistical analyses performed on the chronic nicotine and nicotine withdrawal data included the day before pump implantation as baseline and days 1–6 or days 4–6 of chronic nicotine exposure and days 1–5 of withdrawal. Withdrawal day 1 was measured at 12 h after the removal of the nicotine/saline-containing minipumps. All *post-hoc* comparisons were conducted using the Newman–Keuls test, after statistically significant effects were shown in the overall ANOVAs. Group comparisons of Wistar and SD rats' performance under baseline conditions in the standard and/or modified tasks were made using *t*-test. The level of significance was set at the $p<0.05$ level.

3. Results

3.1. Experiment 1: The effects of acute nicotine treatment on performance in the standard 5-CSRTT in Wistar and SD rats

Under baseline conditions (*i.e.*, after saline treatment), Wistar rats exhibited higher accuracy of responding, and emitted more correct responses and fewer incorrect responses compared to SD rats (see Table 1). There were no differences in omissions, premature and perseverative responses or speed of responding between strains.

Due to initial strain differences in performance in the 5-CSRTT, the acute effects of nicotine were analyzed separately for each strain. In Wistar rats (see Table 1), nicotine administration had no effect on accuracy [$F(4,36)=1.94$, n.s.]; however, there was a strong tendency for increased correct responses [$F(4,36)=2.44$, $p<0.064$, n.s.] and decreased omissions only at the highest nicotine dose used of 0.14 mg/kg base [$F(4,36)=1.31$, n.s.]. Nicotine administration decreased latency to correct response [$F(4,36)=2.83$, $p<0.05$] at the dose of 0.14 mg/kg and had no effect on latency to incorrect response or reward latency. Finally, there was a significant main effect of nicotine treatment on premature responses [$F(4,36)=2.84$, $p<0.05$], but there was no effect on perseverative responses.

In SD rats (see Table 1), there was a significant effect of nicotine on accuracy [$F(4,32)=2.68$, $p<0.05$]. Visual inspection of the data revealed biphasic effects of nicotine on accuracy. Specifically, a low nicotine dose (0.017 mg/kg) tended to decrease accuracy mainly due to increases in incorrect responses, while a higher nicotine dose (0.14 mg/kg) increased the number of correct responses [$F(4,32)=3.11$, $p<0.05$]. There were no significant main effects of nicotine treatment on omissions or latencies to correct and incorrect responses, reward latency, or premature and perseverative responses.

3.2. Experiment 2: The effects of acute nicotine treatment on performance in the modified 5-CSRTT in Wistar rats

The implemented modifications in the 5-CSRTT procedure resulted in poorer performance compared to the rats' performance in the standard 5-CSRTT procedure (see Table 1). Group comparisons (*t*-test, $p<0.05$) showed that there was a significant decrease in accuracy and correct responses, while incorrect responses, omissions and latency to correct responses were significantly increased compared to the rats' performance in the traditional 5-CSRTT after saline treatment (*i.e.*, baseline conditions).

Acute nicotine administration produced some improvements of performance in the modified 5-CSRTT (see Table 1). ANOVAs revealed a significant increase in correct responses [$F(4,44)=4.82$, $p<0.01$] and a significant decrease in omissions [$F(4,44)=3.08$, $p<0.05$] when nicotine was administered at the dose of 0.14 mg/kg (*post-hoc* test, $p<0.05$). However, nicotine treatment did not have a significant effect on accuracy [$F(4,44)=2.13$, $p<0.09$, n.s.] or on incorrect and premature responses. The speed of responding was increased as reflected in a significant decrease in the latencies to correct responses [$F(4,44)=4.15$, $p<0.01$] at the 0.035 and 0.14 mg/kg nicotine doses, although there was no effect on the latency to incorrect responses.

3.3. Experiment 3: The effects of chronic nicotine treatment and spontaneous nicotine withdrawal on 5-CSRTT performance in Wistar rats using the standard 5-CSRTT parameters

3.3.1. Chronic nicotine treatment

ANOVA and *post-hoc* analyses revealed that chronic nicotine delivery for 7 days had biphasic effects on premature

Table 1
The effects of acute nicotine treatment on Sprague Dawley and Wistar rats' performance in the standard and a modified version of the 5-CSRTT

Measure	Saline	Nicotine doses (base, mg/kg)			
		0.017	0.035	0.07	0.14
Sprague Dawley rats (n=9, standard task)					
% Accuracy	79.79±1.74@	75.71±1.79	79.64±1.98	80.03±2.65	80.65±1.76
% Correct responses	72.18±2.79@	71.44±2.10	75.11±2.46	74.00±2.75	77.56±2.14*
% Incorrect responses	18.57±1.55@	23.11±1.71	19.53±1.98	18.92±2.40	18.56±1.64
% Omissions	8.55±2.08	5.13±1.19	4.82±1.17	6.03±1.17	3.89±1.02
Premature responses	21.33±4.45	22.11±6.13	23.22±5.98	29.00±7.55	21.11±5.17
Perseverative responses	15.67±3.74	13.89±2.93	18.11±3.74	19.89±6.15	14.11±4.15
Correct response latency	0.63±0.04	0.66±0.04	0.64±0.04	0.65±0.03	0.59±0.04
Incorrect response latency	1.2±0.12	1.31±0.09	1.16±0.09	1.21±0.23	1.16±0.14
Reward latency	1.97–0.29	2.16–0.42	1.79–0.16	1.75–0.16	1.78–0.22
Wistar rats (n=10, standard task)					
% Accuracy	87.46±2.05	84.13±2.67	82.95±1.63	87.86±1.89	87.23±1.91
% Correct responses	80.78±2.02	77.41±3.31	75.50±2.85	81.12±2.28	82.84±2.57
% Incorrect responses	11.61±1.94	14.53±2.48	15.3±1.23	11.32±1.77	12.05±1.79
% Omissions	7.61±1.10	8.06±2.37	9.20±2.00	7.56±2.08	5.11±1.63
Premature responses (†)	12.30±2.45	13.50±3.1	11.50±2.34	11.30±2.88	21.20±5.79
Perseverative responses	10.40±1.85	8.10±2.07	9.50±1.66	7.60±1.73	11.10±1.27
Correct response latency	0.69±0.03	0.69±0.03	0.67±0.03	0.65±0.02	0.63±0.03*
Incorrect response latency	1.50±0.12	1.37±0.14	1.52±0.12	1.58±0.18	1.30±0.16
Reward latency	1.74–0.21	1.55–0.15	2.06–0.46	1.67–0.21	1.55–0.18
Wistar rats (n=12, modified task)					
% Accuracy	75.20±3.31&	75.52±3.81	75.66±3.02	72.83±3.79	78.53±2.64
% Correct esponses	56.33±3.69&	59.09±2.59	59.84±4.52	56.60±3.97	68.98±3.30**
% Incorrect responses	18.53±2.31&	20.03±3.59	19.62±2.84	21.78±3.43	19.11±2.63
% Omissions	25.14±3.81&	20.88±2.79	20.54±5.39	21.62±4.50	11.91±3.63*
Premature responses	119.92±19.26	124.5±21.49	149.00±26.3	149.8±32.6	180.58±37.25
Correct response latency	0.88±0.05&	0.87±0.03	0.79±0.03*	0.90±0.06	0.79±0.04*
Incorrect response latency	1.57±0.13	1.62±0.08	1.64±0.18	1.74±0.19	1.30±0.15

Data are presented as mean±s.e.m. *, $p<0.05$; **, $p<0.01$, comparison between saline- and nicotine-treated rats (Newman–Keuls test); @, $p<0.05$, comparison between saline-treated Sprague Dawley and Wistar rats' performance in the standard task (*t*-test); &, $p<0.05$, comparison of saline-treated Wistar rats' performance in the standard and modified tasks (*t*-test). (†) indicated a significant main effect of nicotine treatment in the ANOVA. In the modified task, reward latency and perseverative responses have not been recorded due to task specifics (*e.g.*, automatic trial initiation).

responses (see Fig. 1; day×treatment interaction: $F(6,120)=3.17$, $p<0.01$). *Post-hoc* analyses showed a significant increase in premature responses on day 1 of nicotine delivery; this effect slowly dissipated and by day 4 and on subsequent days of nicotine delivery the numbers of premature responses for nicotine- and saline-treated rats were almost identical.

It is known that increases in premature responding are often correlated with decreases in accuracy (Hahn et al. 2002b). Therefore, data for nicotine on accuracy were analyzed separately for the period after its effects on premature responding had dissipated. An ANOVA was performed on data obtained from the baseline and days 4–6 of nicotine delivery; this analysis showed that there was a significant improvement in accuracy [day×treatment interaction $F(3,60)=3.14$, $p<0.05$]. This improvement in accuracy was attributable to a trend for increase in correct responses [day×treatment interaction: $F(3,60)=2.47$, $p<0.07$, n.s.] and a significant decrease in incorrect responses (day×treatment interaction: $F(3,60)=3.19$, $p<0.05$) during days 4–6 of nicotine delivery. There was a significant main effect of nicotine on omissions [day×treatment interaction $F(6,120)=3.71$, $p<0.01$]; however, *post-hoc* analyses did not reveal significant differences between nicotine- and saline-treated rats on any specific day of exposure to the minipumps. Further, the speed of responding was increased during chronic nicotine delivery, reflected in significant day×treatment interaction effects for the latency to correct [$F(6,120)=4.58$, $p<0.001$] and incorrect responses [$F(6,120)=3.12$, $p<0.01$]. *Post-hoc* analyses revealed a significant decrease in latencies to both correct and incorrect response on day 1 of nicotine delivery (Newman–Keuls *post-hoc* test; see Fig. 1). Reward latency was not affected by chronic nicotine treatment [day×treatment interaction: $F(6,120)=0.82$, n.s.]. The mean reward latency values during days 1–6 of chronic nicotine/saline delivery varied from 1.44±0.14 s to 1.73±0.32 s in saline-treated rats and from 1.38±0.11 s to 1.56±0.18 s in nicotine-treated rats.

3.3.2. Nicotine withdrawal

After minipump removal, rats underwent nicotine/saline withdrawal that was observed for 8 consecutive days (see Fig. 1). Nicotine withdrawal had no effect on accuracy of responding [day×treatment interaction: $F(5,100)=1.57$, n.s.]. However, there was a dramatic decrease in correct responses [day×treatment interaction: $F(5,100)=10.01$, $p<0.0001$] and a dramatic increase in omissions [day×treatment interaction:

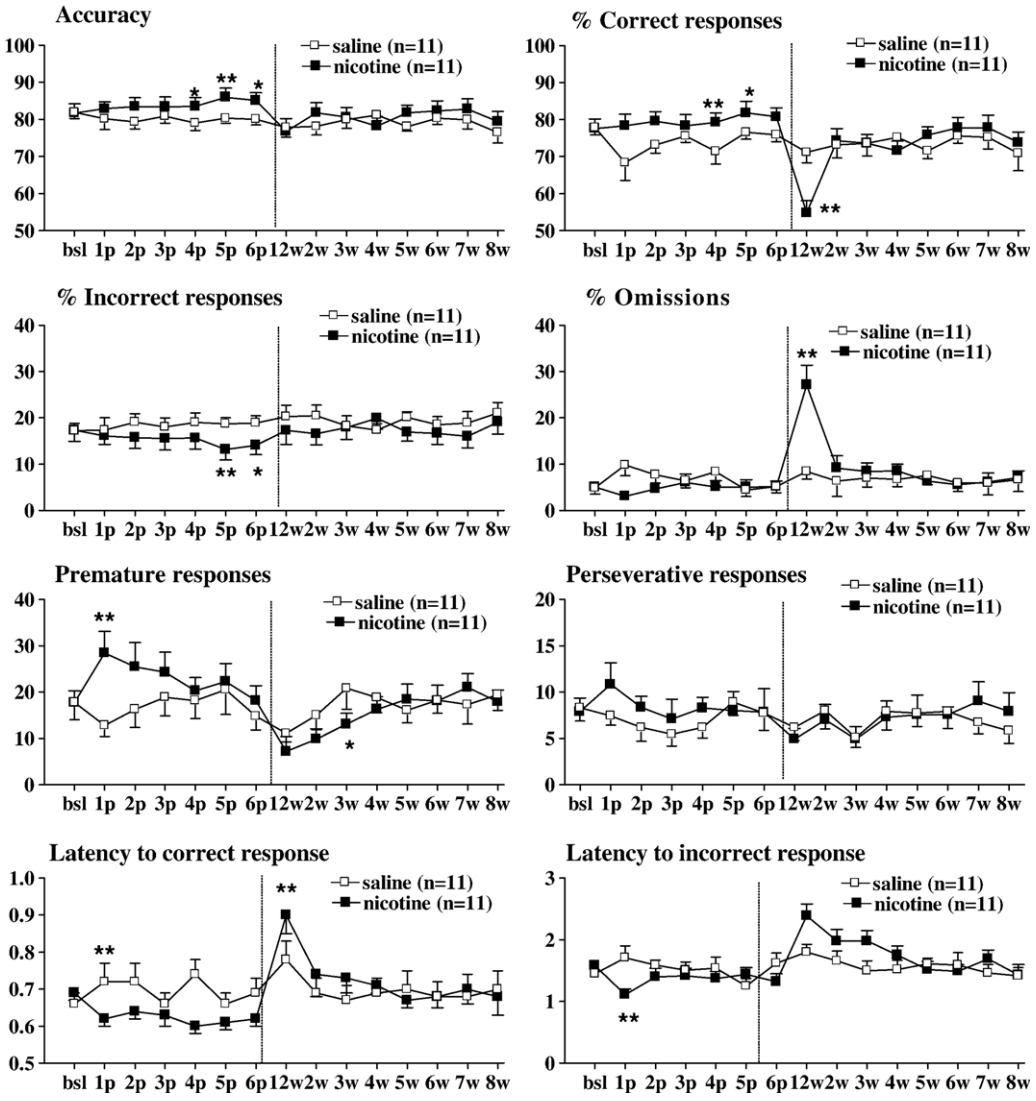

Fig. 1. The effects of chronic nicotine treatment and nicotine withdrawal on performance in the standard 5-CSRTT in Wistar rats. Data are presented as mean±s.e.m. Asterisks denote statistically significant differences between nicotine- and saline-treated rats (*, $p<0.05$; **, $p<0.01$, Newman–Keuls *post-hoc* test). Bsl: baseline; p: days of exposure to nicotine/saline through osmotic minipumps; w: days of nicotine/saline withdrawal.

$F(5,100)=9.44$, $p<0.0001$] at the 12 h withdrawal time point (Newman–Keuls *post-hoc* test). Nicotine withdrawal had no effect on incorrect, premature and perseverative responses, on latencies to correct and incorrect responses, and latency to reward retrieval. The mean reward latency values during nicotine/saline withdrawal varied from 1.45±0.12 s to 1.59±0.1 s in saline-withdrawing rats and from 1.44±0.07 s to 1.85±0.25 s in nicotine-withdrawing rats.

4. Discussion

In the standard 5-CSRTT, Wistar rats performed more accurately compared to SD rats (accuracy 87.46% and 79.8%, respectively) due to a significantly higher number of correct responses and significantly lower number of incorrect responses in the Wistar rats; while the number of omissions, premature and perseverative responses and speed of responding were similar between strains under baseline conditions. Previous reports have also described strain differences in accuracy, such that SD rats were less accurate compared to Lister Hooded rats (accuracy approximately 60 and 80%, respectively) in the 5-CSRTT (Blondel et al., 2000; Mirza and Bright, 2001; Mirza and Stolerman, 1998). In Wistar rats, the implemented modifications in the task resulted in lower baseline attentional performance compared to performance in the standard task, reflected in significant decreases in accuracy, and correct and incorrect responses, and increases in omissions and latency to correct response. SD rats were not trained or tested on the modified task as they exhibited significantly lower level of correct responses and accuracy compared to Wistar rats in the standard task. Thus, there was concern that in the modified task, SD rats' low baseline performance would preclude meaningful evaluation of the effects of manipulations.

Acute nicotine (0.14 mg/kg) administration induced small increase in accuracy/correct responses in SD, but not Wistar rats; this dose also tended to decrease omissions in both strains and increased speed of responding in Wistar rats. Further, in

Wistar rats trained and tested in the modified task, nicotine administration (0.14 mg/kg) increased speed of responding, impulsivity (*i.e.*, premature responses), and correct responses (but not accuracy). This pattern of results suggests that acute nicotine administration may optimize rather than improve attentional performance. The decreases in response latency and omissions after acute nicotine administration are consistent with previous observations (Blondel et al., 2000; Grottick et al., 2001; Mirza and Stolerman, 1998; Stolerman et al., 2000; van Gaalen et al., 2006). Increases in accuracy appeared harder to detect except when demanding task conditions resulted in slight performance deteriorations (Bizarro et al., 2004; Grottick et al., 2001; Hahn et al., 2002b; Mirza and Stolerman, 1998). Additionally, an initial low level of accuracy may be important for detecting improvements in performance with nicotine as it has been shown that acute nicotine administration induced a 20% increase in accuracy only in less accurate SD rats, but not in Lister Hooded rats (Mirza and Bright, 2001). Similar in the present study the effect of nicotine on accuracy was more pronounced in the SD compared to Wistar rats.

In human studies, baseline-dependent differences in the influence of nicotine on behavioral and attentional/cognitive task performance have been reported (Perkins, 1999). For example, in non-smokers, nicotine treatment (7 mg nicotine patch) induced improvements on some measures of sustained attention in the low attention group and some decrement in working memory in the high attention group (Poltavski and Petros, 2006). Further, an inverted U-shaped dose–effect relationship has been observed for nicotine on cognitive tasks (Newhouse et al., 2004), suggesting that the same nicotine dose will induce less improvement or possibly performance deterioration in subjects already showing optimal performance.

The main finding of the present study is that chronic continuous nicotine administration for 7 days through osmotic minipumps improved accuracy in Wistar rats after its effect on impulsivity (*i.e.*, increased premature responses on days 1–3 of nicotine delivery) dissipated. Consistent with our findings, an acute nicotine challenge increased accuracy of responding in the absence of changes in other performance parameters after chronic nicotine exposure in Lister Hooded rats in the standard 5-CSRTT (Grottick and Higgins, 2000). In another experiment, chronic nicotine administration increased accuracy, decreased omissions and response latencies in Lister Hooded rats that were selected for performing below criterion (Grottick and Higgins, 2000). Finally, in the modified 5-CSRTT, initial doses of nicotine disrupted performance (*i.e.*, increased omission errors and decreased premature responses) in Lister Hooded rats tested under conditions that increased attentional demands (*i.e.*, increased ITI and reduced stimulus duration compared to baseline conditions (Hahn and Stolerman, 2002)). However, when tolerance developed to these disruptive effects of nicotine, further administration of the drug revealed attentional improvements reflected in increased accuracy, decreased omissions and increased speed of responding (Hahn and Stolerman, 2002).

Interestingly, accuracy improvements were seen during several consecutive days (days 4–6) of nicotine delivery and tolerance did not develop to this beneficial effect of nicotine. Consistent with these findings, studies in humans showed that nicotine administered *via* skin patches induced attentional improvement that did not diminish during 4 weeks of administration in patients with mild to moderate Alzheimer's disease (White and Levin, 1999). Further, nicotine-induced improvements in short-term recognition memory became stronger with the development of acute tolerance to some of the initial adverse effects of nicotine (Perkins et al., 1994).

Nicotine withdrawal induced performance deficits in Wistar rats as reflected in a dramatic decrease in correct responses, increased omissions and decreased speed of responding. Nicotine withdrawal had no effect on response accuracy. However, there was a ~10% decrease in accuracy in nicotine-withdrawing rats when comparing the last day of chronic nicotine delivery (85.1±2.2%) with the 12 h withdrawal time point (76.7±2. 6%) indicating that nicotine-induced accuracy improvements were no longer evident after cessation of nicotine administration. This finding is consistent with recent data showing that spontaneous nicotine withdrawal increased omissions and induced only a modest non-significant decrease in response accuracy; these effects were greater during dihydro-β-erythroidine-, but not mecamylamine-, precipitated or spontaneous nicotine withdrawal in Lister Hooded rats (Shoaib and Bizarro, 2005). In the present study, decreases in correct responses were dramatic during nicotine withdrawal but there were no effects of nicotine withdrawal on incorrect responses and, thus, no effects on accuracy. Interestingly, these small performance deficits were short-lasting and observed only at 12 h (present study) or 10–16 h (Shoaib and Bizarro, 2005) of nicotine abstinence. Similarly, in nicotine-dependent individuals nicotine abstinence impaired attentional and cognitive abilities within 12 h of smoking cessation (Bell et al., 1999; Ernst et al., 2001).

Interestingly, in the 5-CSRTT impaired attentional accuracy, increased omissions and slower latencies to respond have been observed following repeated withdrawal from self-administered amphetamine (Dalley et al., 2005b), cocaine or heroin (Dalley et al., 2005a). However, attentional performance deficits induced by these drugs of abuse were more pronounced and long-lasting than the deficits induced by nicotine in the present study and in that of (Shoaib and Bizarro, 2005). These findings are consistent with previous results showing more severe affective symptoms of withdrawal (*i.e.*, elevations in brain reward thresholds) from cocaine (Markou and Koob 1991), opiates (Schulteis et al., 1994), and amphetamine (Lin et al., 1999; Paterson et al., 2000) than from nicotine (Epping-Jordan et al., 1998; Harrison et al., 2001; Semenova and Markou, 2003).

In summary, the present study provided additional evidence that the effects of acutely administered nicotine on attentional performance under baseline conditions are small although they include increases in accuracy, correct responses, impulsivity and speed of responding as well as decreases in omissions. These effects of acute nicotine administration were more pronounced in less accurate rats or after task modifications were implemented that resulted in lower baseline performance. By contrast, chronic nicotine administration induced clear

improvement of attentional performance in Wistar rats after the initial effects of nicotine on impulsivity dissipated, and then the effects lasted until the end of nicotine treatment. Further, the present data show that performance deficits during spontaneous nicotine withdrawal, including some attentional deficits, are small, but detectable. Thus, changes in attentional performance during chronic nicotine delivery and nicotine withdrawal could provide the basis for further investigations of the neural mechanisms underlying these phenomena, as well as provide tools for the discovery of treatments for attentional symptoms of nicotine withdrawal and other neuropsychiatric disorders.

Acknowledgements

This work was supported by NIMH grant MH62527 to AM. The authors would like to thank Dr. Amanda Harrison and Mr. Richard Sharp for their excellent assistance with setting up the 5-CSRTT in our laboratory, including equipment set-up and programming, Ms. Jessica Benedict and Ms Chelsea Onifer for technical assistance, and Mr. Mike Arends for editorial assistance.

References

Bates T, Mangan G, Stough C, Corballis P. Smoking processing speed and attention in a choice reaction time task. Psychopharmacology (Berl) 1995;120:209–12.

Bell SL, Taylor RC, Singleton EG, Henningfield JE, Heishman SJ. Smoking after nicotine deprivation enhances cognitive performance and decreases tobacco craving in drug abusers. Nicotine Tob Res 1999;1:45–52.

Bizarro L, Patel S, Murtagh C, Stolerman IP. Differential effects of psychomotor stimulants on attentional performance in rats: nicotine amphetamine caffeine and methylphenidate. Behav Pharmacol 2004;15:195–206.

Blondel A, Sanger DJ, Moser PC. Characterisation of the effects of nicotine in the five-choice serial reaction time task in rats: antagonist studies. Psychopharmacology (Berl) 2000;149:293–305.

Carli M, Robbins TW, Evenden JL, Everitt BJ. Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav Brain Res 1983;9:361–80.

Dalley JW, Laane K, Pena Y, Theobald DE, Everitt BJ, Robbins TW. Attentional and motivational deficits in rats withdrawn from intravenous self-administration of cocaine or heroin. Psychopharmacology (Berl) 2005a;182:579–87.

Dalley JW, Theobald DE, Berry D, Milstein JA, Laane K, Everitt BJ, Robbins TW. Cognitive sequelae of intravenous amphetamine self-administration in rats: evidence for selective effects on attentional performance. Neuropsychopharmacology 2005b;30:525–37.

Didriksen M, Christensen AV. Differences in performance in three strains of rats in a 5-choice serial reaction time task. Pharmacol Toxicol 1993;72:66–8.

Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. Nature 1998;393:76–9.

Ernst M, Heishman SJ, Spurgeon L, London ED. Smoking history and nicotine effects on cognitive performance. Neuropsychopharmacology 2001;25:313–9.

Foulds J, Stapleton J, Swettenham J, Bell N, McSorley K, Russell MA. Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. Psychopharmacology (Berl) 1996;127:31–8.

Foulds J, Stapleton JA, Bell N, Swettenham J, Jarvis MJ, Russell MA. Mood and physiological effects of subcutaneous nicotine in smokers and never-smokers. Drug Alcohol Depend 1997;44:105–15.

Grottick AJ, Higgins GA. Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. Behav Brain Res 2000;117:197–208.

Grottick AJ, Wyler R, Higgins GA. A study of the nicotinic agonist SIB-1553A on locomotion and attention as measured by the five-choice serial reaction time task. Pharmacol Biochem Behav 2001;70:505–13.

Hahn B, Shoaib M, Stolerman IP. Effects of dopamine receptor antagonists on nicotine-induced attentional enhancement. Behav Pharmacol 2002a;13:621–32.

Hahn B, Shoaib M, Stolerman IP. Nicotine-induced enhancement of attention in the five-choice serial reaction time task: the influence of task demands. Psychopharmacology (Berl) 2002b;162:129–37.

Hahn B, Stolerman IP. Nicotine-induced attentional enhancement in rats: effects of chronic exposure to nicotine. Neuropsychopharmacology 2002;27:712–22.

Harrison AA, Liem YT, Markou A. Fluoxetine combined with a serotonin-1A receptor antagonist reversed reward deficits observed during nicotine and amphetamine withdrawal in rats. Neuropsychopharmacology 2001;25:55–71.

Heishman SJ, Henningfield JE. Tolerance to repeated nicotine administration on performance subjective and physiological responses in nonsmokers. Psychopharmacology (Berl) 2000;152:321–33.

Heishman SJ, Snyder FR, Henningfield JE. Performance subjective and physiological effects of nicotine in non-smokers. Drug Alcohol Depend 1993;34:11–8.

Hindmarch I, Kerr JS, Sherwood N. Effects of nicotine gum on psychomotor performance in smokers and non-smokers. Psychopharmacology (Berl) 1990;100:535–41.

Kerr JS, Sherwood N, Hindmarch I. Separate and combined effects of the social drugs on psychomotor performance. Psychopharmacology (Berl) 1991;104: 113–9.

Koelega HS. Stimulant drugs and vigilance performance: a review. Psychopharmacology (Berl) 1993;111:1-16.

Levin ED, Conners CK, Silva D, Hinton SC, Meck WH, March J, Rose JE. Transdermal nicotine effects on attention. Psychopharmacology (Berl) 1998;140: 135–41.

Levin ED, Conners CK, Sparrow E, Hinton SC, Erhardt D, Meck WH, et al. Nicotine effects on adults with attention-deficit/hyperactivity disorder. Psychopharmacology (Berl) 1996;123:55–63.

Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization pharmacological specification and anatomic localization. Psychopharmacology (Berl) 2006;184:523–39.

Lin D, Koob GF, Markou A. Differential effects of withdrawal from chronic amphetamine or fluoxetine administration on brain stimulation reward in the rat–interactions between the two drugs. Psychopharmacology (Berl) 1999;145: 283–94.

Markou A, Koob GF. Postcocaine anhedonia: an animal model of cocaine withdrawal. Neuropsychopharmacology 1991;4:17–26.

Mirsky AF, Rosvold HE. The use of psychoactive drugs as a neuropsychological tool in studies of attention in man. New York: Wiley; 1960.

Mirza NR, Bright JL. Nicotine-induced enhancements in the five-choice serial reaction time task in rats are strain-dependent. Psychopharmacology (Berl) 2001;154:8-12.

Mirza NR, Stolerman IP. Nicotine enhances sustained attention in the rat under specific task conditions. Psychopharmacology (Berl) 1998;138: 266–74.

Muir JL, Everitt BJ, Robbins TW. Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist ondansetron. Psychopharmacology (Berl) 1995;118:82–92.

Mumenthaler MS, Taylor JL, O'Hara R, Yesavage JA. Influence of nicotine on simulator flight performance in non-smokers. Psychopharmacology (Berl) 1998;140:38–41.

Newhouse PA, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol 2004;4:36–46.

Paterson NE, Myers C, Markou A. Effects of repeated withdrawal from continuous amphetamine administration on brain reward function in rats. Psychopharmacology (Berl) 2000;152:440–6.

Perkins KA. Baseline-dependency of nicotine effects: a review. Behav Pharmacol 1999;10:597–615.

Perkins KA, Grobe JE, Epstein LH, Caggiula A, Stiller RL, Jacob RG. Chronic and acute tolerance to subjective effects of nicotine. Pharmacol Biochem Behav 1993;45:375–81.

Perkins KA, Grobe JE, Fonte C, Goettler J, Caggiula AR, Reynolds WA, et al. Chronic and acute tolerance to subjective behavioral and cardiovascular effects of nicotine in humans. J Pharmacol Exp Ther 1994;270:628–38.

Poltavski DV, Petros T. Effects of transdermal nicotine on attention in adult non-smokers with and without attentional deficits. Physiol Behav 2006;87:614–24.

Rezvani AH, Levin ED. Cognitive effects of nicotine. Biol Psychiatry 2001;49:258–67.

Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl) 2002;163: 362–80.

Sahakian B, Jones G, Levy R, Gray J, Warburton D. The effects of nicotine on attention information processing and short-term memory in patients with dementia of the Alzheimer type. Br J Psychiatry 1989;154:797–800.

Schulteis G, Markou A, Gold LH, Stinus L, Koob GF. Relative sensitivity to naloxone of multiple indices of opiate withdrawal: a quantitative dose–response analysis. J Pharmacol Exp Ther 1994;271:1391–8.

Semenova S, Markou A. Clozapine treatment attenuated somatic and affective signs of nicotine and amphetamine withdrawal in subsets of rats exhibiting hyposensitivity to the initial effects of clozapine. Biol Psychiatry 2003;54: 1249–64.

Shoaib M, Bizarro L. Deficits in a sustained attention task following nicotine withdrawal in rats. Psychopharmacology (Berl) 2005;178:211–22.

Snyder FR, Davis FC, Henningfield JE. The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend 1989;23:259–66.

Snyder FR, Henningfield JE. Effects of nicotine administration following 12 h of tobacco deprivation: assessment on computerized performance tasks. Psychopharmacology (Berl) 1989;97:17–22.

Stolerman IP, Mirza NR, Hahn B, Shoaib M. Nicotine in an animal model of attention. Eur J Pharmacol 2000;393:147–54.

Stolerman IP, Mirza NR, Shoaib M. Nicotine psychopharmacology: addiction cognition and neuroadaptation. Med Res Rev 1995;15:47–72.

van Gaalen MM, Brueggeman RJ, Bronius PF, Schoffelmeer AN, Vanderschuren LJ. Behavioral disinhibition requires dopamine receptor activation. Psychopharmacology (Berl) 2006;187:73–85.

Warburton DM, Arnall C. Improvements in performance without nicotine withdrawal. Psychopharmacology (Berl) 1994;115:539–42.

Warburton DM, Mancuso G. Evaluation of the information processing and mood effects of a transdermal nicotine patch. Psychopharmacology (Berl) 1998;135:305–10.

White HK, Levin ED. Chronic transdermal nicotine patch treatment effects on cognitive performance in age-associated memory impairment. Psychopharmacology (Berl) 2004;171:465–71.

White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology (Berl) 1999;143:158–65.