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Strain Dependency of the Effects of Nicotine and Mecamylamine in a Rat Model of Attention

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Abstract

Rationale—Processes of attention have a heritable component, suggesting that genetic predispositions may predict variability in the response to attention-enhancing drugs. Among lead compounds with attention-enhancing properties are nicotinic acetylcholine receptor (nAChR) agonists.

Objectives—To test, by comparing three rat strains, whether genotype may influence the sensitivity to nicotine in the 5-Choice Serial Reaction Time Task (5-CSRTT), a rodent model of attention.

Methods—Strains tested were Long Evans (LE), Sprague Dawley (SD), and Wistar rats. The 5-CSRTT requires responses to light stimuli presented randomly in one of five locations. The effect of interest was an increased percentage of responses in the correct location (accuracy), the strongest indicator of improved attention.

Results—Nicotine (0.05–0.2 mg/kg s.c.) reduced omission errors and response latency and increased anticipatory responding in all strains. In contrast, nicotine dose-dependently increased accuracy in Wistar rats only. The nAChR antagonist mecamylamine (0.75–3 mg/kg s.c.) increased omissions, slowed responses, and reduced anticipatory responding in all strains. There were no effects on accuracy, which was surprising given the clear improvement with nicotine in the Wistar group.

Conclusions—The findings suggest strain differences in the attention-enhancing effects of nicotine, which would indicate that genetic predispositions predict variability in the efficacy of nAChR compounds for enhancing attention. The absence of effect of mecamylamine on response accuracy may suggest a contribution of nAChR desensitization to the attention-enhancing effects of nicotine.

Keywords

attention; nicotinic; nicotine; mecamylamine; 5-choice serial reaction time; rat; strain; genetic

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Disclosure

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Introduction

Cognitive abilities constitute complex constructs that include perception, attention, working memory, declarative memory, language, and cognitive control (Morris and Cuthbert, 2012). Variation in cognitive phenotypes are influenced by genetic factors (Plomin and Deary, 2015). Constructs associated with attention, in particular, show heritability in healthy human populations (Groot et al., 2004; Polderman et al., 2006), with molecular candidates found in monoamine and cholinergic system genes (Bellgrove and Mattingley, 2008; Barnes et al., 2011). In addition, attention deficits in psychiatric populations show heritability and may contribute to disease vulnerability (Chen et al., 1998; Hatzimanolis et al., 2015). These findings suggest that the attention-enhancing effects of pharmacological treatments, too, may depend on genetic factors. Knowledge about the nature of such influences could help guide drug development and predict individual treatment response.

Among lead compounds with attention-enhancing properties currently under investigation are nicotinic acetylcholine receptor (nAChR) agonists. Cognitive benefits of nAChR agonists, including the prototypical agonist nicotine, are reported most consistently in tests of attention (Stolerman et al., 1995; Heishman et al., 2010), particularly in simple stimulus detection paradigms and vigilance tasks (Hahn, 2015). Such effects have been suggested to be of possible utility in treating cognitive deficits associated with schizophrenia, Alzheimer's disease, and Attention Deficit-Hyperactivity Disorder (Levin and Rezvani, 2002; Singh et al., 2004).

Attention-enhancing effects of nAChR agonists can be measured reliably in the 5-Choice Serial Reaction Time Task (5-CSRTT), a paradigm of attention requiring rodents to detect brief light stimuli presented randomly in one of five apertures, and respond in the correct location. In this paradigm, nicotine and several other nAChR agonists not only reduced omission errors and response latencies in rats, effects which could be explained by non-specific increases in the rate or speed of responding, but also increased response accuracy (Mirza and Stolerman, 1998; Grottick and Higgins, 2000; Hahn et al., 2002a; Hahn et al., 2002b; Hahn et al., 2003a; Hahn et al., 2003b; Grottick et al., 2003; Hahn and Stolerman, 2005; Quarta et al., 2007; Quarta et al., 2012). This measure reflects the percentage of all stimulus-contingent responses made in the correct location and is the clearest indicator of attention. Beneficial effects of nAChR agonists have also been observed in other paradigms of attention, although generally less consistently (Muir et al., 1995; Turchi et al., 1995; Bushnell et al., 1997; McGaughy et al., 1999; Rezvani et al., 2002; Rezvani et al., 2005; Howe et al., 2010).

In mouse and rat behavior genetic studies, multiple effects of nicotine displayed strain dependency (Marks et al., 1989; Acri et al., 1995; Faraday et al., 2003; Hamilton et al., 2010). However, few studies have investigated effects of genetic predisposition on the sensitivity to the attention-enhancing effects of nAChR agonists. Beneficial effects on response accuracy in the 5-CSRTT have mostly been reported in Lister Hooded (LH) rats, a strain not available in the United States. A small-N study compared LH and Sprague Dawley (SD) rats (Mirza and Bright, 2001). Nicotine had beneficial effects on 5-CSRTT response accuracy in SD, but detrimental effects in LH rats, the strain showing beneficial effects in

many other studies. LH rats also displayed pronounced rate-suppressant effects, consistent with the fact that all measurements were obtained in drug-naïve animals. Response rate suppression decreases, and beneficial effects of nicotine tend to unfold, after at least one pre-exposure (Grottick and Higgins, 2000; Hahn and Stolerman, 2002). Another study compared SD and Wistar rats and did not observe any significant acute effects of nicotine on response accuracy in either group, although with a somewhat suboptimal dose range (Semenova et al., 2007). A 5-CSRTT study comparing three inbred mouse strains reported no benefits of acute nicotine, while subchronic nicotine slightly improved accuracy in all strains (Pattij et al., 2007). Thus, to date, there are no conclusive data regarding strain differences in the attention-enhancing effects of nicotine.

The present study compared Long Evans (LE), SD, and Wistar rats, three strains commonly used for behavioral studies in the United States, on the attention-enhancing effects of nicotine in the 5-CSRTT. The aim was to determine if a genetic component may exist to these effects. Nicotine provides the ideal tool for the purpose of characterizing attention-enhancing effects of nAChR agonism. Due to its non-selectivity among nAChR subtypes, no potentially important nAChR subtype is spared, and its efficacy in enhancing attention is unsurpassed by other agonists. The effects of nicotine were juxtaposed to the effects of mecamylamine, a nAChR antagonist non-selective among nAChR subtypes. The purpose was to address whether any observed strain differences in the effects of nicotine reflected a difference in sensitivity to change in nAChR tone in either direction.

Materials and Methods

Subjects

Twelve Sprague Dawley (SD) rats (126–143 g at arrival), 12 Long Evans (LE) rats (146–180 g), and 12 Wistar rats (131–163 g), all male, were acquired at the same time and at the same age (6 weeks) from Charles River Laboratories. Subjects from each strain were treated identically throughout the study. The animals were housed individually in the same temperature and humidity controlled room, fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). The animals were maintained on a 12-h light-dark cycle with lights on at 7 a.m. Rats had free access to water and received a food-restricted diet, starting at 8 weeks of age, to maintain them at 85% of their age-appropriate free-feeding weights as determined for each strain. The treatment of animals followed the ‘Principles of Laboratory Animal Care’ (NIH publication No. 86-23, 1996) and was approved by the Institutional Animal Care and Use Committee of the University of Maryland School of Medicine.

Apparatus

Eight operant conditioning chambers measuring 26 cm³ (Med Associates, Inc., Fairfax, VT) were housed in sound-insulated enclosures. The curved rear wall of each chamber contained five 2.5 cm² holes, 2 cm above the grid floor. At the entrance of each hole a photocell monitored interruptions of a beam of infrared light, and at the rear there was a white light-emitting diode. A food trough was located in the opposite wall, equidistant from each

aperture. Illumination was provided by a houselight situated in the top portion of the front panel. The apparatus and data collection were controlled by Med-PC software.

Behavioral Procedure

Rats started 5-CSRTT training at 8 weeks of age. The training procedure was described by Mirza and Stolerma (1998). In the final form of the task, light stimuli of 1 s duration were presented randomly in one of the five holes after an intertrial interval (ITI) of variable duration (1–9 s, average 5 s). A nose-poke into the hole while it was illuminated or within 5 s after the light had terminated (limited hold) was registered as a correct response and resulted in the delivery of a 45-mg food pellet into the trough, followed by 2-s reward retrieval period. A response into any other hole was recorded as an incorrect response and resulted in a time-out of 5 s duration, during which the house light was extinguished. A failure to respond before the end of the limited hold was registered as an omission error. A new trial began with the initiation of an ITI either after a reward retrieval period or after time-outs or limited holds in cases of incorrect responses or omission errors. Responses during ITIs had no programmed consequences. All training and test sessions lasted 30 minutes. Overall, the training took approximately 4 months. Testing started when stable performance of <30% omissions and >50% correct responses was achieved.

The time of day at which training and test sessions were performed was held constant for individual rats but was counterbalanced for the three different strains. Eight rats were trained or tested at the same time, and care was taken to include at least two rats from each strain into each of the five runs. The number of animals from each strain run in each individual testing chamber was also counterbalanced to the degree possible. The chambers were wiped with 70% alcohol after each animal.

The following behavioral measures are reported

Percentage of correct responses (accuracy): $100 \times [\text{correct responses}/(\text{correct} + \text{incorrect responses})]$. Accuracy was not calculated when less than 10 responses had been emitted. Response accuracy is a measure of response choice that is based only on responses that have been emitted and does not take into account omission error trials. It is not influenced by the overall rate or speed of responding. Thus, accuracy is interpreted as the main index of stimulus detection and attention.

Percentage of omission errors: $100 \times (\text{omission errors}/\text{stimuli presented})$. Errors of omission are influenced by stimulus detection, but also by the general rate of responding.

Latency of correct responses: the mean time between stimulus onset and a nose-poke in the correct hole. The latency was not determined if less than 10 responses had been emitted.

Anticipatory responses: total number of responses in ITIs. Unpunished anticipatory responses, as in the present version of the task, have no direct influence on reward payoff. The measure would reflect general rate-increasing or -decreasing drug effects on non-contingent responding.

Experimental Design

Test sessions were conducted twice a week with training sessions on the other weekdays. Test days were always preceded by at least one training day. Task parameters in test sessions were identical to those in training sessions.

Two separate experiments tested the effects of either nicotine (0, 0.05, 0.1 & 0.2 mg/kg) or mecamylamine (0, 0.75, 1.5 & 3 mg/kg). Drug or vehicle was administered s.c. 10 minutes before each test session. No injections were given on training days. Both experiments adopted a within-subject design. Thus, each rat was tested with each dose of nicotine or mecamylamine and vehicle in a sequence that was randomized for each individual animal. In the nicotine experiment, each dose level was repeated three times in a randomized sequence of 12 test sessions. In the experiment testing mecamylamine, each dose was tested twice over a sequence of 8 tests. The purpose of repeated testing was to increase the reliability of the measurements. Measurements were averaged for each dose. The nicotine and mecamylamine experiments were separated by a 2-week period during which rats were trained daily but no drugs were given.

Drugs

(–)-Nicotine tartrate (MP Biomedical, Solon, OH) was dissolved in isotonic saline, and the pH was adjusted to 7 with NaOH solution. Mecamylamine hydrochloride (Sigma Aldrich, St. Louis, MO) was dissolved in isotonic saline. All injections were given subcutaneously (s.c.) into the flank at a volume of 1 ml/kg. All doses are expressed as those of the base.

Data analysis

Each of the above performance measures was analyzed separately by 2-factor ANOVA with strain as a between-subjects factor and nicotine dose or mecamylamine dose as a within-subject factor. These analyses were followed by 1-factor ANOVA for repeated measures within each strain when appropriate. Note that SEMs plotted in the figures were adjusted to remove within-group between-subject variability (Cousineau, 2007; Morey, 2008). This method essentially subtracts out interindividual variance in the *average* performance across dose levels to only reflect variance related to interindividual differences in drug effect, the focus of this study. Effects of $\alpha < 0.05$ (two-tailed) were considered statistically significant.

Results

Nicotine

Figure 1 shows nicotine dose-response curves for each of the four performance indices. Each data point in Figure 1 represents the average over three test days.

Two-factor ANOVA with strain as a between-subjects factor and nicotine dose as a within-subject factor revealed a main effect of dose on omission errors, latency of correct responses and anticipatory responses [$F(3,99) > 19.6$, $P < 0.001$ in all three cases], but not on response accuracy [$P > 0.5$]. As can be seen from Figure 1, nicotine reduced omission errors and response latency and increased anticipatory responding in all strains. In contrast, the figure suggests that nicotine increased response accuracy in Wistar rats only. Statistically, this was

reflected by only a trend towards an interaction [$F(6,99)=1.80$, $P=0.106$; post-hoc strain $\times$ linear nicotine dose contrast $F(2,33)=2.99$, $P=0.064$], although one-factor ANOVA within each strain confirmed a robust effect of nicotine on accuracy only in Wistar rats [$F(3,33)=6.03$, $P=0.002$], and not in LE [$P>0.8$] or SD rats [$P>0.8$].

Figure 1 suggests that the effects of nicotine on anticipatory responding were weaker in Wistar rats than in LE or SD rats. The strain $\times$ dose interaction for this measure, too, was only a trend [$F(6,99)=1.48$, $P=0.19$], although one-factor ANOVA within each strain confirmed a significant main effect of nicotine dose in LE [$P<0.001$] and SD rats [$P<0.001$], but not in Wistar rats [$P>0.1$]. The effects of nicotine on omission errors also appeared weaker in Wistar rats; however, there was no strain $\times$ dose interaction [$P>0.4$], and the effects of nicotine were significant in LE [$P<0.001$], SD [$P=0.003$], and Wistar [$P=0.015$] rats. Similarly, the effects of nicotine on response latency did not interact with strain [$P>0.6$] and were significant in LE [$P=0.004$], SD [$P<0.001$], and Wistar [$P<0.001$] rats.

There were no significant main effects of strain on any measure, but a trend was seen on response accuracy [$F(2,33)=3.03$, $P=0.062$; $P>0.2$ for the other variables]. We controlled for the potential influence of baseline differences in response accuracy between strains by including as a covariate each animal's average accuracy of all training sessions surrounding test sessions (from one week before the first to one week after the last test session, including all intermediate training sessions). This approach avoided the use of data that formed part of the analysis of nicotine effects. A linear mixed model was used to allow the testing of a full factorial model including the covariate. In this model, there no longer was any effect of strain ($P>0.3$), but the strain $\times$ nicotine dose interaction was significant [$F(6,30)=2.93$, $P<0.03$].

Mecamylamine

Figure 2 shows mecamylamine dose-response curves for each performance index. Each data point in Figure 2 represents the average over two test days.

Two-factor ANOVA revealed a main effect of mecamylamine on omission errors, latency of correct responses and anticipatory responses [$F(3,99)>16.6$, $P<0.001$ in all three cases], but not on response accuracy [$P>0.5$]. As can be seen from Figure 2, the largest dose of mecamylamine (3 mg/kg) robustly increased omission errors, slowed response latency, and reduced anticipatory responding in each strain, with some more subtle effects also at 1.5 mg/kg. The effects of mecamylamine interacted with group on omission errors [$F(6,99)=3.47$, $P=0.004$] and anticipatory responding [$F(6,99)=2.26$, $P<0.05$]; the rate-suppressant effects of the largest dose of mecamylamine on these measures were reduced in LE rats as compared with the other two strains, although they were highly significant in all strains. There was no strain $\times$ dose interaction on response accuracy or latency [$P>0.3$ in both cases]. There were also no main effects of Group on any measure [all $P>0.4$].

Discussion

The present study provides evidence to support strain differences in the attention-enhancing effects of nicotine. While Wistar rats displayed a dose-related increase in response accuracy

after systemic administration of nicotine, no such effect was seen in LE or SD rats. All three strains showed reductions in omission errors and correct response latency with each dose of nicotine. These latter two measures can be affected by general rate- and speed-enhancing effects of nicotine associated with its stimulant properties. Response accuracy, however, is not confounded by such effects, reflecting the accuracy of stimulus-contingent responses, and is the performance index most closely related to attention. On this measure, the interaction between the three strains and the four dose levels trended towards statistical significance (linear contrast $P=0.064$), and was found to be significant when accounting for interindividual variance in baseline accuracy derived from training sessions. Independent analysis of nicotine effects in each strain demonstrated clear improvement in Wistar rats ($P<0.002$) and a complete absence of effect in LE and SD rats ($P_s>0.8$). The results suggest that genetic predisposition modulates the sensitivity to the attention-enhancing effects of nicotine.

Nicotine increased anticipatory responding in the intertrial interval, responses that had no programmed consequences. This increase was robust in LE and SD rats, but was observed only as a non-significant trend in Wistar rats, thus representing the inverse to the pattern seen on response accuracy. This may suggest a reduced susceptibility of Wistar rats to the general response rate-increasing effects of nicotine, which may have helped uncover its attention-enhancing effects. Strain differences in the locomotor responses to nicotine (which may or may not translate to response rate-related effects in the present paradigm) have been reported (Iyaniwura et al., 2001; Faraday et al, 2003); however, Wistar rats have not been directly compared to SD or LE rats. Baseline differences cannot account for either of the strain differences in nicotine effect reported here. Accuracy in the saline condition was lower in Wistar rats than in LE rats but higher in Wistar than SD rats. Similarly, anticipatory responses of Wistar rats were numerically between the other two strains. Furthermore, accounting statistically for potential baseline differences on accuracy strengthened the strain x nicotine dose interaction.

Other potential factors that could account for strain differences were controlled to the degree possible. All animals were acquired and shipped at the same time, at the same age, from the same breeder, and were housed and cared for in the same room. The time of day at which the animals were trained and tested, as well as the experimental chambers, were counterbalanced between strains. However, potential confounding factors introduced before shipment cannot be entirely excluded. For example, we have no information about the number of litters that each strain originated from, whether they were housed in the same or different colony rooms, and to what degree housing conditions were equated between rooms. While there is no indication that any of these factors differed between strains or would affect the attention-enhancing effects of a nAChR agonist, the possibility also cannot be entirely discounted.

Strain selectivity of the attention-enhancing effects of nicotine would have important implications for the clinical development of nAChR agonists for treating attentional deficits. First, identifying the biological elements that mediate this heritability would be extremely informative about the neuropharmacological mechanisms mediating the attention-enhancing effects of nAChR agonists. If the relevant genetic differences were found to be affecting, for

example, a specific neurotransmitter system modulated by nAChRs, this would direct drug development efforts towards (or away from) nAChRs expressed by this system. Second, strain selectivity suggests that genetic predispositions can affect the clinical efficacy of nAChR agonists when treating attentional deficits. Thus, identifying the relevant genetic markers could help predict treatment response on an individual basis. Both applications of the present findings warrant follow-up genetic studies to pinpoint the relevant biological mechanisms.

Mecamylamine robustly increased omission errors, slowed response latency, and reduced anticipatory responding at the largest dose tested (3 mg/kg), with more subtle effects also at the middle dose (1.5 mg/kg). The rate-suppressant effects of the largest dose of mecamylamine on omission errors and anticipatory responding, although significant in all groups, were weaker in LE rats as compared with the other two strains. In vitro, doses of mecamylamine in the μM range have been shown to exert antagonism also at NMDA and 5-HT₃ receptors (Papke et al., 2001; Clarke et al., 1994; Drisdell et al., 2008), but based on behavioral effect comparisons of systemic and intracerebroventricular doses (Decker and Majchrzak, 1992), these concentrations appear to substantially exceed those tested in the present study.

There was no effect of mecamylamine on response accuracy in any strain. Given the robust increase in accuracy with the nAChR agonist nicotine in the Wistar group, the absence of a significant decrease with a nAChR antagonist at a dose range bordering response rate suppression is puzzling. It beckons the question whether the enhancement seen with nicotine really is the result of an increase in nAChR tone, or if nAChR desensitization following agonist exposure may have contributed to this effect as described for several other behavioral effects of nicotine (Picciotto et al., 2008). Several studies found paradoxical performance-enhancing effects of very low doses of nAChR antagonists (Terry et al., 1999; Levin and Caldwell, 2006; Hahn et al., 2011; Levin et al., 2013), and the slight decrease in nAChR tone may mimic effects of desensitization of some nAChR subtypes. This may point to a contribution of nAChR desensitization to the attention-enhancing effects of nAChR agonists, although other as of yet unexplored mechanisms may also underlie this type of effect. Any strain differences in the effects of nicotine may thus be related to different sensitivities to any such mechanism. Future studies will address this possibility, and may identify nAChR subtypes contributing to attentional enhancement by activation vs. deactivation.

Research is also warranted to specify the genetic differences underlying the strain-selectivity of the attention-enhancing effects of nicotine shown here. Identifying the neuropharmacological mechanisms associated with this heritability would move us further along the path of developing effective, and potentially individually tailored, nAChR-based therapies for attentional deficits. Finally, the present results identified the Wistar strain as a rat strain suitable for preclinical studies of the attention-enhancing effects of nAChR agonism reported in human subjects.

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Fig. 1.

Effects of nicotine on performance in Long Evans rats (LE; N=12), Sprague Dawley rats (SD; N=12) and Wistar rats (N=12). Bars reflect the mean performance in 30-min test sessions, averaged over three repeat-sessions. Error bars reflect SEMs, adjusted to remove within-group between-subject variability (Cousineau, 2007; Morey, 2008) to reflect a within-subjects standard error. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ in paired t-tests comparing performance after nicotine to performance after vehicle, Bonferroni-adjusted for three comparisons. Please note that scales do not start at zero in the graphs on the left.

Fig. 2.

Effects of mecamlamine on performance in Long Evans rats (LE; N=12), Sprague Dawley rats (SD; N=12) and Wistar rats (N=12). Bars reflect the mean performance in 30-min test sessions, averaged over two repeat-sessions. Error bars reflect SEMs, adjusted to remove within-group between-subject variability (Cousineau, 2007; Morey, 2008). *P<0.05, **P<0.01, ***P<0.001 in paired t-tests comparing performance after mecamlamine to performance after vehicle, Bonferroni-adjusted for three comparisons. Please note that scales do not start at zero in the graphs on the left.