Psychopharmacology (2011) 217:75–82
DOI 10.1007/s00213-011-2258-8

ORIGINAL INVESTIGATION

# Selective nicotinic receptor antagonists: effects on attention and nicotine-induced attentional enhancement

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Received: 24 November 2010 / Accepted: 7 March 2011 / Published online: 25 March 2011
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**Abstract**
*Rationale* The question of the subtype(s) of the nicotinic acetylcholine receptor (nAChR) mediating the attention-enhancing effects of nicotine is still unsettled. While early studies pointed towards subtypes other than the homomeric α7 nAChR, pro-cognitive effects of α7 nAChR agonists have since been demonstrated.
*Objectives* This study tested whether the performance-enhancing effects of nicotine in a rodent model of attention could be reversed by the α4β2, α4β4, α3β2, and α2β2 nAChR antagonist dihydro-β-erythroidine (DHβE), or the α7 antagonist methyllycaconitine (MLA).
*Methods* In repeated tests, 12 rats trained to perform the 5-choice serial reaction time task were systemically injected with nicotine or vehicle in the presence of increasing doses of DHβE or MLA.
*Results* DHβE did not antagonize the attention-enhancing effects of nicotine reflected by measures of accuracy and omission errors, suggesting that its previously reported antagonism of nicotine effects on latency and anticipatory responses specifically reflected the stimulant effects of nicotine. MLA dose-dependently reversed the reduction in omission errors by nicotine. In the absence of nicotine, low doses of MLA (0.4 and 1.3 mg/kg) not previously tested on attention improved response accuracy, resulting in an inverted U-shape dose–response function.
*Conclusions* nAChR subtypes involved in the performance-enhancing effects of nicotine appear to vary depending on the function assessed. Our findings suggest a greater involvement of α7 nAChRs in the effects of nicotine on attention than first suggested by preclinical studies, with different optimal receptor tones for aspects of stimulus detection and response readiness to task stimuli.

**Keywords** Nicotine · Dihydro-beta-erythroidine · Methyllycaconitine · Attention · 5-choice serial reaction time · Alpha 7 · Antagonism

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## Introduction

Nicotine improves attention in healthy and cognitively impaired individuals (Rezvani and Levin 2001; Newhouse et al. 2004; Heishman et al. 2010). These effects have been replicated in rodent models of attention (Grilly et al. 2000; Hahn et al. 2002a; Hahn and Stolerman 2002; Grottick et al. 2003; Rezvani et al. 2005), thereby facilitating their pharmacological characterization. To determine which subtypes of the nicotinic acetylcholine receptor (nAChR) mediate the attention-enhancing effects of nicotine, previous studies aimed at reproducing them with different nAChR agonists or blocking them with antagonists that display varying binding profiles across nAChR subtypes (McGaughy et al. 1999; Blondel et al. 2000; Grottick and Higgins 2000; Hahn et al. 2003b; Young et al. 2004; Rezvani et al. 2009; Howe et al. 2010). nAChRs are pentameric cation channels composed of α2-8 and β2-4 subunits in the vertebrate

central nervous system. Different combinations of these subunits display distinct pharmacological and pharmacokinetic properties and distinct neuroanatomical distributions (Gotti et al. 2009). The ability to selectively target the nAChR subtype(s) mediating the effects of nicotine on attention would allow isolation of the desired effects with potential clinical benefit.

Dihydro-β-erythroidine (DHβE) is a competitive nAChRs antagonist that displays high affinity at α4β2, α4β4, α3β2, and α2β2 receptors but not at α3β4 and α7 receptors (Harvey et al. 1996; Harvey and Luetje 1996; Chavez-Noriega et al. 1997). Methyllycaconitine (MLA) is a competitive antagonist at the homomeric α7 nAChR (Macallan et al. 1988; Decker et al. 1995; Davies et al. 1999) but also blocks α6* receptors (Salminen et al. 2005). Both compounds have been tested in the 5-choice serial reaction time task (5-CSRTT), a rodent model of attention (Blondel et al. 2000; Grottick and Higgins 2000), and caused at most subtle impairment by themselves. In single-dose interaction studies, DHβE, but not MLA, antagonized the effects of nicotine. The effects of nicotine, however, consisted of reductions in response latency and increases in premature responding. Response indices more closely indicative of stimulus detection and attention, such as response accuracy and omission errors, were not affected by nicotine in these experiments. Thus, the question of nAChR subtype involvement in the attention-enhancing effects of nicotine remained unanswered.

The present study tested the effects of DHβE and MLA administered alone and against the effects of nicotine (0.1 mg/kg) under a slightly modified version of the 5-CSRTT that showed attention-enhancing effects of nicotine reliably (e.g., Hahn et al. 2002a, b; Hahn and Stolerman 2002). We chose lower doses of the antagonists than previously tested. The largest test dose of DHβE was chosen to be the lowest dose to fully antagonize effects of nicotine in previous studies (Stolerman et al. 1997; Blondel et al. 2000; Grottick and Higgins 2000; Struthers et al. 2009). The dose range of MLA was chosen such that the largest dose tested produced complete blockade of α7 nAChR responses in vitro (Alkondon et al. 1992; Turek et al. 1995) and approached doses previously tested in animal models of attention (Blondel et al. 2000; Grottick and Higgins 2000; Grottick et al. 2000; Shoaib and Bizarro 2005). We aimed for a dose-dependent reduction of the effects of nicotine with no or minimal effects on performance in the absence of nicotine.

## Methods

### Subjects

Twelve male hooded Lister rats (Harlan Olac, Bicester, UK) were housed individually in a temperature- (20±1°C) and humidity- (50±10%) controlled environment, on a 12 h light–dark cycle with lights on at 7:00 A.M. Rats had free access to water and were maintained on a food-restricted diet to maintain them at 85% of their free-feeding weights. The treatment of animals complied with local and national laws and ethical guidelines and followed the "Principles of laboratory animal care". Experiments were carried out according to the Animals (Scientific Procedures) Act 1986, under license from the UK home office.

### Apparatus

Aluminium operant chambers measuring 26 $cm^3$ (Paul Fray Ltd., Cambridge, UK) were housed in sound-insulated and ventilated enclosures. The curved rear wall of each chamber contained five 2.5-$cm^2$ holes, 5 cm above floor level. At the entrance of each hole a photocell monitored interruptions of a beam of infrared light, and at the rear, there was a green light-emitting diode. A food tray, the entrance to which was covered by a hinged flap, was located in the opposite wall, equidistant from each aperture. Illumination was provided by a house light situated in the roof. The apparatus and data collection were controlled by software running under RISC OS on an Acorn computer.

### Behavioural procedure

The training procedure was described by Mirza and Stolerman (1998). In the final form of the task, light stimuli of 1-s duration were presented randomly in one of the holes after an intertrial interval (ITI) of 5 s. If the subject nose-poked into the hole while it was illuminated or within 5 s after the light had terminated (limited hold), a 45-mg food pellet was delivered into the food tray, and a correct response was registered. A response into any other hole was recorded as an incorrect response and resulted in a time-out of 2-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 by a correct response 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 min. Tests started when stable performance of <20% omissions and >70% correct responses was acquired.

In an effort to maximize scientific gain per animal, the present experiments were performed in rats that had been subjects in a previous study (Hahn and Stolerman 2002). The present subgroup of rats had been the control group in the previous study, which had not received nicotine daily but had been exposed to a total of 14 low to moderate doses of nicotine over the course of 10 weeks. Prior to the start of the experiments reported here, rats had been drug-free and

undergone continued task training for 3 weeks. At the time of the current experiments, the rats were approximately 1 year old.

The following behavioural measures are reported

*Percentage of correct responses (accuracy)* 100×[correct responses/(correct+incorrect responses)]. Accuracy was not calculated when less than ten 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 trials with omission errors. It is not influenced by the overall rate or speed of responding. Thus, accuracy is interpreted as the main index of stimulus detection and attentional performance.

*Percentage of omission errors* 100×(omission errors/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 five responses had been emitted. Response latency reflects the speed of visual information processing and of initiating and executing the motor response.

*Anticipatory response rate* (number of responses in ITIs/number of trials)/ITI-length (s). This yields the number of responses emitted per second, averaged across trials. Unpunished anticipatory responses as in the present version of the task have no direct influence on reward payoff. The measure reflects general rate-increasing or rate-decreasing drug effects on non-contingent responding.

Experimental design

Test sessions were conducted on Tuesdays and Fridays with training sessions on all other weekdays. In test sessions, the ITI was set to 15 s, as opposed to 5 s in training sessions, because performance-enhancing effects of nicotine were previously found to occur reliably with this parameter (Mirza and Stolerman 1998; Hahn et al. 2002a, b; Hahn and Stolerman 2002). Furthermore, the stimulus duration was set to 0.4 s in test sessions as opposed to 1 s in training sessions to degrade performance and avoid ceiling effects. All rats had been exposed to almost identical testing parameters (15 s ITI, 0.5 s stimulus duration) 18 times as part of experiments reported by Hahn and Stolerman (2002). Thus, rats had had ample opportunity to adapt to these testing conditions. Drug effects on learning are very unlikely to account for any of the interactions reported here, not only because of this extensive pre-exposure, but also because the randomised test design would prevent any carry-over learning effects from differentially affecting specific drug testing conditions.

All 12 rats participated in two experiments, separated by 2 weeks during which rats were only trained and no drugs were given. In one experiment, the effects of DHβE (0.0, 0.3, 1, and 3 mg/kg) were tested in combination with nicotine (0.1 mg/kg) or saline. In the second experiment, the effects of MLA (0.0, 0.4, 1.3, and 4 mg/kg) were tested in combination with nicotine (0.1 mg/kg) or saline. Thus, each experiment consisted of eight test sessions, over which each dose of the antagonist was tested in the presence and absence of nicotine, in a sequence that was randomised for each individual subject. DHβE was injected 10 min and MLA 15 min before test sessions. Nicotine or vehicle was injected 10 min before test sessions. Six rats first participated in the DHβE experiment, followed by the MLA experiment, and the other six rats were tested in the reverse order. Two rats were excluded from analysis of the DHβE experiment because their performance had become unstable, resulting in $n=10$ for this experiment.

Drugs

(−)-Nicotine bitartrate (BDH, Poole, UK) was dissolved in isotonic saline, and the pH was adjusted to 7 with NaOH solution. Dihydro-β-erythroidine hydrobromide and methyllycaconitine citrate (both from Sigma-Aldrich, Poole, Dorset, UK) were dissolved in saline. Nicotine and DHβE were administered subcutaneously (s.c.) and MLA intraperitoneally (i.p.), all at a volume of 1 ml/kg. Subcutaneous injections were given into the flank. All doses are expressed as those of the base.

Data analysis

Percentage data were arc-sine transformed for statistical analyses, latency data were log transformed and anticipatory response data were subject to square root transformation. In the figures, results are presented as raw values. Each measure was analysed separately by two-factor ANOVA for repeated measures with either nicotine (0.0 and 0.1 mg/kg) and DHβE (0.0, 0.3, 1, and 3 mg/kg), or nicotine and MLA (0.0, 0.4, 1.3, and 4 mg/kg) as within-subject factors. Two-factor ANOVA were followed by one-factor ANOVA and paired $t$ tests where indicated. For analysis of the DHβE experiment, data were averaged over the entire 30-min test session because behavioural and pharmacokinetic data indicate that effects of DHβE last throughout this time window (Shoaib et al. 2000; Grottick et al. 2003; Wang et al. 2006). For the MLA experiment, data were averaged over the first 20 min of test sessions because plasma levels of MLA drop sharply after this time

point (Turek et al. 1995), and accordingly, no effects of MLA were seen in the last 10 min of the session.

## Results

### DHβE

Nicotine enhanced response accuracy and reduced omission errors, as supported by a significant main effect on accuracy [$F(1,9)=8.52$, $P<0.02$] and omission errors [$F(1,9)=30.4$, $P<0.001$] (Fig. 1). A small dose-related reduction in accuracy by DHβE was not supported by a significant main effect of DHβE [$F(3,27)<1$]. However, DHβE increased omission errors in a dose-related manner [main effect of DHβE: $F(3,27)=5.56$, $P<0.005$]. DHβE did not alter the effects of nicotine, and accordingly, there was no DHβE × nicotine interaction [$P>0.9$ for both measures]. No effects of nicotine or DHβE were observed on the latency of correct responses or anticipatory responding.

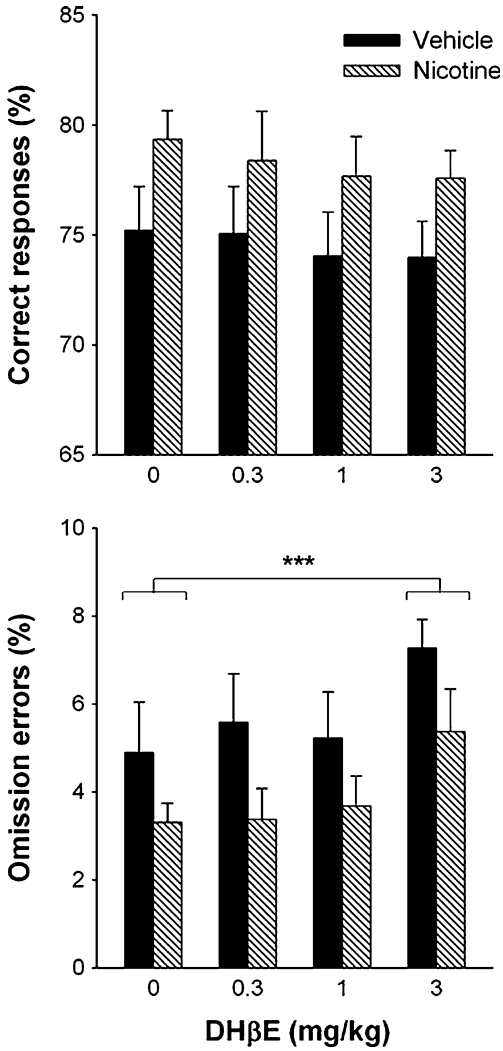


**Fig. 1** The effects of systemic doses of DHβE on performance after vehicle (*black bars*) and 0.1 mg/kg of nicotine (*hatched bars*). *Bars* represent the mean performance (±SEM) of ten rats in 30-min test sessions. ***$P<0.001$ in paired *t* test comparing performance after DHβE to performance after vehicle, averaged over nicotine and vehicle

### MLA

Nicotine enhanced response accuracy in the absence of MLA but not in the presence of MLA (Fig. 2). This was supported by a significant MLA × nicotine interaction [$F(3,33)=3.97$, $P<0.02$]. However, the effects of MLA in

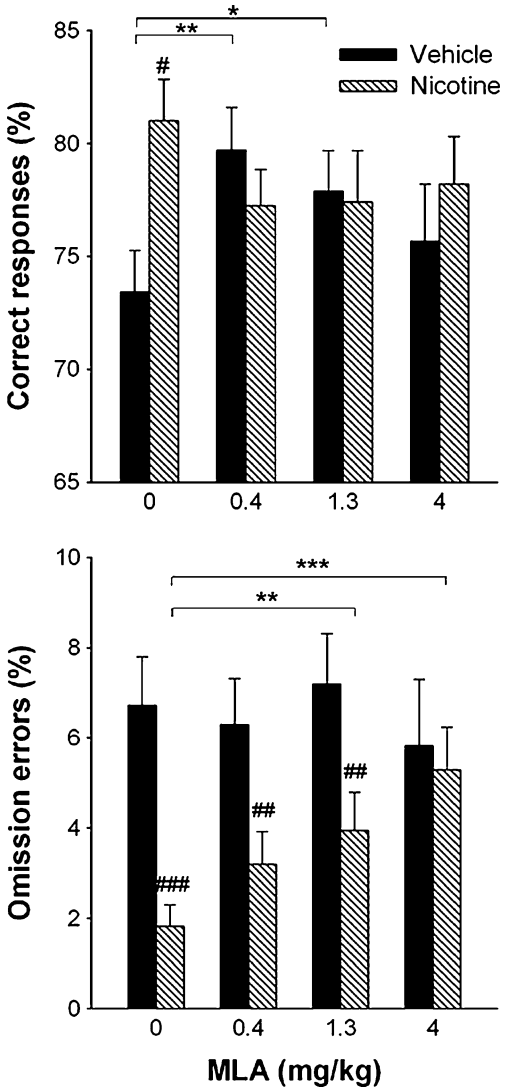


**Fig. 2** The effects of systemic doses of MLA on performance after vehicle (*black bars*) and 0.1 mg/kg of nicotine (*hatched bars*). *Bars* represent the mean performance (±SEM) of 12 rats in the first 20 min of test sessions. *$P<0.05$, **$P<0.01$, and ***$P<0.001$ in paired *t* test comparing % correct responses after MLA to vehicle in the absence of nicotine, or comparing % omission errors after MLA to vehicle in the presence of nicotine. $^{\#}P<0.05$, $^{\#\#}P<0.01$, and $^{\#\#\#}P<0.001$ in paired *t* test comparing performance after nicotine to performance after vehicle

the presence of nicotine were not significant in a single-factor ANOVA for repeated measures [$F(3,33)<1$]. Instead, MLA had significant effects in the absence of nicotine [$F(3,33)=3.92$, $P<0.02$]. At the lowest dose, MLA alone caused a robust increase in accuracy comparable to the effect of nicotine, and a weaker but significant increase was also apparent at the medium dose tested. The nicotine × MLA interaction was therefore primarily due to an effect of MLA alone, and not to MLA blocking the effects of nicotine.

Nicotine reduced omission errors, and MLA caused a dose-dependent reduction of this effect and completely blocked the effect of nicotine at the largest dose. This was supported by a significant MLA × nicotine interaction [$F(3,33)=5.65$, $P<0.005$]. In a single-factor ANOVA, there was a significant effect of MLA in the presence of nicotine [$F(3,33)=6.34$, $P<0.005$] but not in the absence of nicotine [$F(3,33)<1$].

No effects of nicotine or MLA were observed on the latency of correct responses or anticipatory responding except for a main effect of MLA on anticipatory responding [$F(3,33)=3.33$, $P<0.05$], which was due to a slight decrease in responding at the largest dose of MLA (0.22±0.09 responses/s) relative to vehicle (0.24±0.08 responses/s).

## Discussion

The present study yielded three main findings: (1) DHβE did not antagonize the attention-enhancing effects of nicotine, (2) MLA reversed the reduction in omission errors by nicotine, and (3) MLA alone improved response accuracy at low doses.

1. The nAChR antagonist DHβE at the doses tested did not antagonize either the increase in response accuracy or the reduction in omission errors produced by nicotine, while the largest dose of DHβE (3 mg/kg) slightly impaired performance. Effects of nicotine in the 5-CSRTT were blocked by DHβE (3 mg/kg) in previous studies (Blondel et al. 2000; Grottick and Higgins 2000). However, the effects of nicotine in these studies consisted of increases in response speed and anticipatory responding, likely reflecting non-specific behavioural activation rather than attention-enhancing effects. Speed-related effects of nicotine in the 5-CSRTT are mediated by different pharmacological and neuroanatomical mechanisms than effects on response accuracy and omission errors (Hahn et al. 2002b, 2003a, b; Hahn and Stolerman 2005; Robbins 2002). Thus, it is possible that nAChR subtypes blocked by DHβE (α4β2, α4β4, α3β2, α2β2) mediate psychomotor stimulant effects of nicotine but not effects on stimulus detection and attention. This argument is strengthened by the observation that DHβE blocked the locomotor stimulant effect of nicotine in rats (Stolerman et al. 1997), but a direct within-study comparison is not possible, because nicotine did not modulate response latency and anticipatory responding in the present work. The effects of nicotine on these two measures had been not always significant and tended to be less robust than effects on accuracy and omissions in previous experiments conducted in our laboratory as well.

   A later study in aged rats (Grottick et al. 2003), employing a 1-h version of the 5-CSRTT, reported that nicotine reduced the decrement in accuracy, omission errors and response latency with time on task, and DHβE reduced all of these effects. The added demands of this task version on maintaining alertness over time, i.e., vigilance, may have rendered it particularly sensitive towards the stimulant properties of nicotine, which were then reduced by DHβE. Alternatively, nAChRs bound by DHβE really are involved in the primary effects of nicotine on stimulus detection, but antagonism by DHβE could not be detected in the present experiment because the effects of nicotine may not have been sufficiently robust. In this case, however, at least a trend effect would be expected, which was not seen.
2. The α7 nAChR antagonist MLA dose-dependently reversed the reduction in omission errors by nicotine, suggesting α7 nAChR involvement in this effect of nicotine. This conclusion and others below, all derived from the work with MLA, have to be qualified by the previously mentioned ability of this substance to block α6* receptors (Salminen et al. 2005). While MLA did not modulate any effects of nicotine in the 5-CSRTT in previous studies (Blondel et al. 2000; Grottick and Higgins 2000), again, these effects had not included response indices such as accuracy and omission errors (Hahn et al. 2002a, b discussed possible reasons for this discrepancy). To interpret the effects of MLA on omission errors as reflecting a reversal of nicotine effects on stimulus detection or on rate-related performance aspects, it is necessary to view them in the context of effects on other response indices. MLA did not reverse the effects of nicotine on response accuracy, but a trend in this direction was observed, and the effect may have been partly concealed by the effect of MLA alone on this measure. MLA caused only a very subtle decrease in anticipatory responding at the largest dose; thus, its effects on omission errors very likely go beyond a mere modulation of general response rate or motivation (Bizarro and Stolerman 2003) and reflect more specific performance aspects such as response readiness to the task stimuli and possibly stimulus detection.

The α7 nAChR agonist AR-R 17779 was ineffective in the 5-CSRTT (Grottick and Higgins 2000), even when tested under the same conditions in which nicotine increased accuracy and decreased omission errors (Hahn et al. 2003a), but this drug may have poorer CNS penetration than first thought (Grottick et al. 2000). Other α7 agonists have not been tested in the 5-CSRTT, but studies in α7 knockout mice did suggest α7 nAChR involvement in performance of this task (Young et al. 2004, 2007, Hoyle et al. 2006). Furthermore, the partial α7 nAChR agonist and 5-HT3 antagonist R3487 (MEM3454) showed beneficial effects in a different rodent model of attention (Rezvani et al. 2009). Several α7 agonists have also shown pro-cognitive effects in other rodent models that were not primary measures of attention and mostly reflected mnemonic processes or sensory gating (Pichat et al. 2007; Sydserff et al. 2009; Roncarati et al. 2009; Rushforth et al. 2010). Evidence for attentional benefits from α7 nAChR activation today is largely based on neuropsychological measurements in people with schizophrenia (Olincy et al. 2006; Freedman et al. 2008). The present findings suggest that the 5-CSRTT may after all be a suitable rodent model for studying the attentional effects of α7 nAChR ligands.

3. MLA alone improved response accuracy at low doses, displaying an inverted U-shape dose–response function. This effect was unexpected given that attentional enhancement is usually reported with nicotinic agonists and impairment with antagonists (see Young et al. 2001 for a review of findings with the non-selective nAChR antagonist mecamylamine). Improved performance was not observed in previous studies employing larger doses of MLA (Blondel et al. 2000; Grottick and Higgins 2000); thus, the effect may indeed be specific to the lower dose range tested in the present experiment. For mecamylamine, there are several reports of cognitive enhancement with low doses. Small doses of mecamylamine were found to improve working memory in rats and monkeys (Terry et al. 1999) and learning in rodents (Levin and Caldwell 2006). The latter effect displayed a U-shaped dose–response relationship reminiscent of the dose–response function of MLA in the present study. In adults with attention-deficit/hyperactivity disorder, a small dose of mecamylamine improved recognition memory (Potter et al. 2009). The present findings with MLA suggest that performance-enhancing effects of low-dose nAChR antagonism are, at least in part, (a) attentional in nature and (b) may be mediated by the α7 nAChR subtype.

Effects of MLA alone were not seen on omission errors. This dissociation from its effect on accuracy may reflect the different importance of response choice versus response readiness for these two measures, or the different relative contribution of other behavioural components to each index. While our findings support the involvement of α7 nAChRs in both measures, the enhancing effects of small doses of MLA suggest that the optimal tone at these receptors is low for aspects of response choice and higher for aspects of response readiness to task stimuli. α7 nAChRs are located pre- and postsynaptically on both excitatory and inhibitory neurons, depending on the brain structure (Alkondon and Albuquerque 2004; Gotti et al. 2009). Thus, the effects of changes in α7 nAChR tone can be expected to modulate an intricate balance and to be complex in nature.

The speculative possibility that the attention-enhancing effects of nicotinic agonists may in fact be due to nAChR desensitisation suggests mimicry of these effects as a further possible mechanism that may underlie the effects of small doses of MLA. Beneficial effects of nicotinic agonists in attention tasks have been observed with compounds acting on non-α7 nAChRs (Grottick and Higgins 2000; Grottick et al. 2003; Hahn et al. 2003a; McGaughy et al. 1999), while improved response accuracy in the present study was seen with α7 antagonism but not with non-α7 antagonism by DHβE. Thus, the pharmacological mechanisms mediating agonist- and antagonist-induced improvement do not fully overlap. While this speaks against α7 desensitisation as the sole mechanism of nicotine-induced attentional enhancement, it does not rule out the possibility that α7 desensitisation has beneficial effects on attention that may contribute to the attention-enhancing potential of nicotine. At physiologically relevant doses of nicotine, nAChR desensitisation is less pronounced at α7 than non-α7 subtypes (reviewed by Picciotto et al. 2008). However, the optimal tone at α7 nAChRs for attentional performance is unknown, and we cannot rule out that even modest desensitisation may benefit performance. Another possibility is that small doses of MLA or mecamylamine may promote receptor re-sensitisation or act as mild agonists. Thus, low doses of these compounds would modestly enhance nicotinic neurotransmission by themselves, but would compete with the action of nicotine. To our knowledge, no data are available to date to support this hypothesis.

The recent finding that MLA sharpened nicotine-induced transient increases in medial prefrontal acetylcholine release and helped unmask attention-enhancing effects of nicotine on a measure of stimulus detection (Howe et al. 2010) points towards previously unexplored functions of cortical α7 nAChRs. There are obvious parallels between this and the present finding which was also on a measure of stimulus detection, although we observed effects of MLA alone that were not additive with nicotine. We can however

draw the general conclusion that the goal-driven detection of brief signals can, under certain circumstances, benefit from α7 nAChR antagonism.

In conclusion, the present study provides preclinical support for α7 nAChR involvement in the effects of nicotine on attention. The mechanism appears to depend on the precise performance aspects measured, with different optimal receptor tones for aspects of stimulus detection and for response readiness to task stimuli. The present study also draws into question the generality of the involvement of nAChRs bound by DHβE (α4β2, α4β4, α3β2, α2β2) in nicotine-induced performance enhancement, suggesting mediation of the stimulant effects but not effects on stimulus detection or attention. Overall, the present results suggest that nAChR subtypes are differentially involved in specific aspects of attention or stages of the information-processing stream. This implies that a fine-tuned adjustment, matching the specific deficits seen in different disorders, may be achievable with subtype-selective nicotinic compounds.

**Acknowledgments** This work was supported by an MRC Programme Grant. None of the authors report any financial relationship with the organization that sponsored this research. All experiments comply with the current laws of the United Kingdom.

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