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Subtype-selective nicotinic agonists enhance olfactory working memory in normal rats: A novel use of the odour span task

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ABSTRACT

Nicotinic agonists have been shown to enhance performance in cognitive tasks based on attention and memory. The aim of this study was to use a test of olfactory working memory; the odour span task (OST) in rodents, to investigate the effects of subtype-specific nicotinic agonists on working memory in normal rats. Rats were trained in a non-matching to sample (NMTS) rule and then the full OST, which involved identifying a novel odour from an increasing number of presented odours. Male hooded Lister rats were treated with nicotine, selective nicotinic agonists or vehicle (saline). In order to validate the task, muscarinic and nicotinic receptor antagonists were also examined. Nicotine at both 0.05 and 0.1 mg/kg significantly increased mean span length in the OST. The selective α4β2 nicotinic receptor agonist metanicotine (0.1 mg/kg s.c.) and the selective α7 nicotinic receptor agonist (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide) (compound A, 10 mg/kg i.p.) also improved performance. In contrast, mecamylamine and scopolamine significantly decreased mean span length. These findings suggest a role for the activation of both α4β2 and α7 subtypes of neuronal nicotinic receptor in mediating enhancements of olfactory working memory capacity in normal, non-compromised rats. These nicotinic receptor subtypes may therefore prove to be useful targets for the development of novel treatments for neuropsychiatric disorders that involve cognitive dysfunction.

Nicotine, the primary psychoactive agent in tobacco smoke is well known for its cognitive-enhancing effects. Studies with tobacco smokers have demonstrated that cognitive deficits induced by smoking abstinence can be restored by nicotine in various memory and attentional tasks [3]. Non-smokers also show improvements with nicotine but results have been more varied [15,18]. Findings from preclinical studies have been more definitive; beneficial effects of nicotine on cognitive performance, in particular on sustained attention, have been reported in rodents, even in uncompromised subjects [17,34].

Nicotine elicits the release of a multitude of neurotransmitters crucial to cognition, which include acetylcholine, dopamine, glutamate, serotonin and gamma-aminobutyric acid [11,26,48]. The nicotinic acetylcholine receptor (nAChR) is the primary target responsible for mediating these diverse actions of nicotine on behaviour [49]. The α4β2 subtype of this pentameric receptor is the most widely expressed in the CNS and it has attracted considerable interest in relation to dependence and cognition [16,22,40]. α4β2 nAChRs are anatomically localised predominantly within the thalamus, hippocampus and amygdala as well as the dopaminergic and glutamatergic terminal regions [9,14,37,38,41]. Levels of this nAChR subtype are reduced in Alzheimer's disease, and this decline may be relevant to the cognitive deficits that characterise the condition [31]. Blockade of α4β2 nAChRs with dihydro-β-erythroidine administered locally into the ventral hippocampus impairs working memory measured on the radial arm maze, thus further implicating the α4β2 subtype in cognitive processing [20,45,47]. Lippiello et al. provided further support for the involvement of α4β2 nAChRs; metanicotine (RJR2403) improved working memory on the radial arm maze in rats with ibotenic acid forebrain lesions and also enhanced passive avoidance retention in rats with scopolamine-induced amnesia [28].

The α7 nAChRs have also been implicated in cognition [20,25,37]. Young and colleagues demonstrated deficits in olfactory working memory in α7 knockout mice compared to wild-type controls [51]. These findings suggest a crucial role for α7 nAChRs in normal cognition, which was confirmed by the ability of presynaptic α7 nAChR's in the olfactory bulb and prefrontal cortex to control glutamate release [47].

Selective α4β2 and α7nAChR agonists in normal and compromised rats also improve spatial working memory [7,20,23,28]. Levin and colleagues (2009) observed impaired performance on the

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radial arm maze by transgenic KO mice lacking either the β2 or α7 nAChRs [21]. In a similar working memory paradigm, Young and colleagues (2006) demonstrated that nicotine could restore deficits in an olfactory working memory task using odours instead of spatial cues. In this study, transgenic mice over-expressing human-caspase 3 demonstrated significant deficits in odour span, a measure of memory capacity, which was fully restored by acute nicotine administration [52]. In the context of *in vivo* behavioural tasks, working memory is defined as 'a short term memory for an object, stimulus, or location that is used within a testing session, but not typically between sessions' [12]. The odour span task (OST) used by Young and colleagues in the aforementioned transgenic mice studies represents a novel variation of the classic non-matching-to-sample (NMTS) task used frequently to assess spatial working memory. Originally developed by Dudchenko and colleagues (2000), the OST has been used to identify anatomically relevant regions involved in memory formation [13]. In this task, rats are trained to dig in bowls of scented woodchip for food rewards. Once retrieved, a different scented bowl is added and this novel bowl must be chosen in order to gain the reward. Bowls are continually added in this way to assess the number of scents that can be remembered by an animal in a given trial, i.e. its working memory capacity. Turchi and Sarter demonstrated a critical role of basal forebrain cholinergic innervation in rodent olfactory working memory capacity using the OST [46]. However, to date the OST has not been utilised to examine cognitive-enhancing effects of psychoactive substances in non-compromised subjects.

The present experiments report on the application of the OST to determine whether nicotine enhances performance in normal rats and to further investigate which receptor subtypes are involved using selective α4β2 and α7 nAChR agonists. To further characterise the OST, the effect of both nAChR and muscarinic receptor antagonists were examined using mecamylamine and scopolamine, respectively. These results provide a better understanding of the nAChR subtypes relevant to the cognitive-enhancing effects of nicotine, which may constitute novel targets to exploit in treating neuropsychiatric disorders involving cognitive impairment [25].24 male hooded Lister rats (Harlan, UK) each weighing 240–270 g at the beginning of training were housed in groups of four under standard conditions (a temperature regulated room with a 12 h light/dark cycle, lights on at 07:00 h). Rats were food restricted at 11 weeks of age for the duration of the study with weight monitored daily and food adjusted to allow for natural growth. Under this schedule no animals showed a weight of less than 85% *ad libitum* body weight. Animals were permitted free access to water in the home cage and all testing was conducted in the light phase of the 12 h light/dark cycle. The experiment was carried out in accordance with the UK Animals (Scientific Procedures) Act, 1986. All training and testing took place on a wooden platform covered in black plastic film (93 cm × 93 cm square with 5 cm raised border). This was elevated 83 cm from the floor by placing on a table. The bowl locations were evenly spaced around the platform. Once training began, the position of the platform and table was kept the same throughout. The scented woodchip used for the task was presented in opaque ceramic dishes. Similar bowls were also used for feeding in the home cage. The 24 odours used in the task were rosemary, mint, onion powder, oregano, cinnamon, thyme, mixed spice, chinese-5-spice, paprika, fenugreek, nutmeg, garlic powder, caraway seed, celery salt, tea leaves, ginger (ASDA own brand), cocoa powder, cumin, coffee powder, coriander, parsley, sage, dill, lemon tea (Lift®). All were Tesco own brand or Schwarz® except as indicated. 3 g of each odour was mixed with 100 g of woodchip and 9 crushed Nestlé® Cheerios.

Rats were handled daily during the week prior to the start of training. Rats were trained to dig in unscented woodchip for a food reward (half a Nestlé® Cheerio). Once reliably digging in the woodchip for the Cheerio, scented bowls were introduced. Upon retrieving the Cheerio, the first bowl was relocated and a second differently scented bowl was added. The rat had to sample both odours and only dig in the bowl containing the novel odour which was the only bowl baited. Each rat took part in up to 10 trials per session, time limited to 15 min. The animal was however, allowed to complete a trail if mid-span on the 15th minute. Odours used were chosen randomly each day. All animals were exposed to all 24 scents within the first 4 days of training. A random number list was used to indicate where each bowl would be placed on the platform for each span. A 'span' was recorded for each rat, determined as the number of bowls chosen correctly before sampling a previously selected bowl minus one, as the first bowl generates no memory load. The odours and training methods were based on those described by Dudchenko and colleagues and also Young et al. (Dudchenko, 2000 #9; Young, 2006 #3). A choice was recorded when the rat actively dug in a bowl. Other parameters measured included time to first sample, used as an indicator of motivation for the task.

Animals completed approximately 18 training sessions until each animal reached the experimental criteria for stability; attaining a span level of at least five over two consecutive days and fluctuating within a maximum of three spans over four consecutive days. Not all animals required these sessions and once they reached criteria, were only tested every other session to prevent ceiling effects. To prevent boredom with the task and to allow training of 24 animals, during the session 4–11 where the animals were on the platform and taking the full 15 min to complete the task, the group was split and trained every other session. At random points during the training sessions, the reward for a correct choice was dropped into the bowl *after* a correct choice was made. Animals still chose correctly in each case, indicating the response was to olfactory cues provided and not scent of the reward. Occasionally bowls and scented woodchip were replaced during the trial, ensuring animals were not scent-marking to identify the novel bowl.

Animals were pseudo-randomly allocated to three treatment groups ($n = 8$ per group) following performance-matching to ensure equal pre-test mean span performance. A single acute dose of nicotine 0.05 or 0.1 mg/kg, or vehicle (0.9% NaCl), was administered subcutaneously (s.c.) 10 min before testing. These doses previously improved performance in other behavioural tasks [17]. The OST was carried out in the same format as training. However, the maximum number of scents was increased to 15 and the task was terminated once an animal made an error. All animals were drug naïve prior to the first dose of nicotine. All injections were administered by a third party to ensure the experimenter was kept blinded throughout the study.

Following this, the effect of two subtype-specific nAChR agonists on odour span performance was assessed. One week was allowed for washout of nicotine along with three training sessions to determine baseline levels of performance and allow each group to be performance matched [5,10]. Numbers of rats were equally distributed to the treatment groups ($n = 8$ per group) in terms of their previous experimental group. Metanicotine (Tocris, UK; 0.1 mg/kg s.c.), compound A ((R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide)) synthesised by GSK, Harlow UK; (10 mg/kg i.p.) or their vehicle (0.9% NaCl s.c. or i.p.) were administered 20 min before beginning the task. The doses were selected based on previous findings indicating improved radial arm maze performance [28,29] reversal of rodent auditory gating deficits [8,28] and dopamine release profiles in rat PFC [29].

The final study assessed the effect of nAChR and muscarinic receptor antagonists mecamylamine and scopolamine. Following a 1-week washout period, animals were retrained for a further three sessions. As before they were performance matched and then reallocated to one on three treatment groups. Mecamylamine

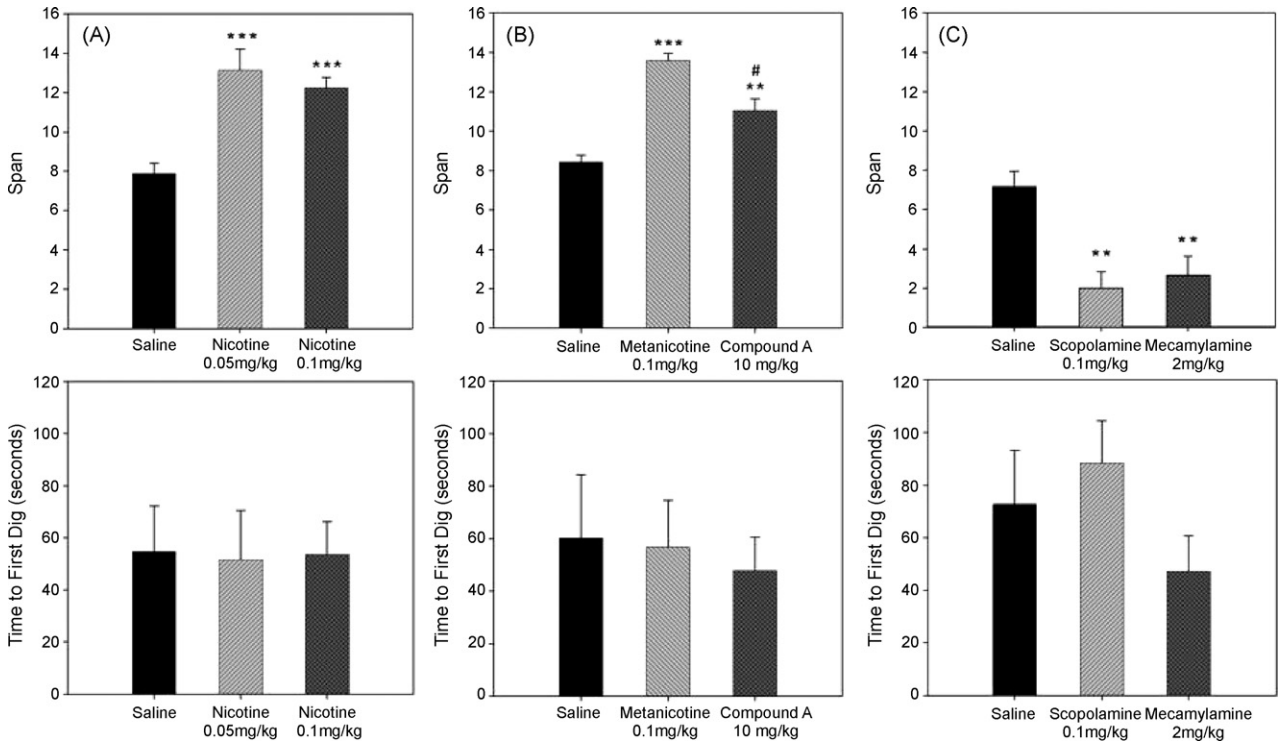

Fig. 1. (A) Animals (mean ± s.e.m.) treated with nicotine (0.05 and 0.1 mg/kg) exhibited significantly increased span length (***$p < 0.001$ when compared to control animals). (B) The effect of metanicotine (0.1 mg/kg), and compound A (10 mg/kg) on span length in the OST. Animals (mean ± s.e.m.) treated with the selective nAChR agonists exhibited an increase in span length (***$p < 0.001$ and **$p = 0.01$ when compared to control animal. #$p = 0.002$ when compared to metanicotine). (C) The effect of scopolamine (0.1 mg/kg SC) and mecamylamine (2 mg/kg SC) on span length in the OST. Animals (mean ± s.e.m.) treated with either antagonist exhibited reduced span length compared to vehicle (**$p = 0.001$ when compared to control animal). No significant difference was observed between the three groups when assessing the time taken to sample the first bowl in any case (A: $p = 0.968$; B: $p = 0.887$; C: $p = 0.272$).

(Sigma, Dorset, UK: 2 mg/kg s.c.), scopolamine (Sigma, Dorset, UK: 0.1 mg/kg i.p.) or their vehicle (0.9% NaCl s.c. or i.p.) were administered 30 min before beginning the task. Doses were based on those used in other cognitive tasks which produced deficits in performance [35].

Prior to testing, mean group span over 4 runs prior to tests was 8.2 ± 0.1. There was no significant difference in the mean span between the three experimental groups before testing ($F(2,19) = 1.23$, $p = 0.314$). A one-way ANOVA with nicotine treatment as the between subjects factor demonstrated significant differences in span length between the three groups ($F(2,19) = 21.80$, $p < 0.001$). Post hoc analysis revealed that both doses of nicotine (0.05 and 0.1 mg/kg) increased span length compared to the vehicle-treated group ($p < 0.001$; Fig. 1). No significant difference in time to first sample, used as a measure of motivation for the task, was observed between the three groups ($F(2,19) = 0.32$, $p = 0.968$).Following three further training sessions, baseline span averaged 8.0 ± 0.2. A one-way ANOVA confirmed no significant difference in mean span between the three groups prior to testing ($F(2,21) = 0.056$, $p = 0.95$). Tests with the nicotinic agonists produced significant differences in span length ($F(2,21) = 34.6$, $p < 0.001$) revealed using a one-way ANOVA with drug treatment as the between subject factor. Bonferonni post hoc tests revealed a significant increase in span length following administration of both metanicotine ($p < 0.001$) and compound A ($p < 0.001$). The dose of metanicotine administered produced a larger increase in span length than the dose given of compound A ($p < 0.002$; Fig. 1). Again, these improvements were in the absence of significant differences in time to the first sample ($F(2,21) = 0.12$, $p = 0.887$).Pre-treatment with mecamylamine and scopolamine significantly impaired OST performance (Fig. 1), as determined by one-way ANOVA with drug treatment as the between subjects factor ($F(2,17) = 47.4$, $p < 0.001$). Bonferonni post hoc analysis confirmed significant decreases in span length produced by either mecamylamine ($p < 0.01$) or scopolamine ($p < 0.01$) treatment. No significant difference was observed in time to first sample ($F(2,16) = 1.431$, $p = 0.272$).

All three nAChR agonists tested in the OST were effective in enhancing memory capacity. Both doses of nicotine produced comparable improvements and these increases in span length were similar to improvements observed with the subtype-selective agonists metanicotine ($\alpha4\beta2$) and compound A ($\alpha7$). The nAChR antagonist mecamylamine diminished span length and a similar decrease was also observed with the muscarinic antagonist scopolamine. Improvements in memory capacity by nicotinic agonists were not confounded by other behavioural effects such as increased motivation; the 'time to first sample' variable remained unaffected following compound administration. During the course of the task, the odours were presented in various orders and multiple times. At no point did this appear to affect performance. However, animals were randomly allocated to groups and odours were also randomly allocated. Therefore, based on the significant difference seen between control and drug-treated animals, it is reasonable to assume this is due to drug treatment and not odour aversion or preference.

Scopolamine has been extensively used to model age-related deficits in cognition; impairing performance in various cognitive tasks in a range of species [2,4,6,19,39,42]. Compared to scopolamine, mecamylamine has not been fully characterised in working memory tasks. The $\beta2^*$ selective nAChR antagonist, dihydro-β-erythroidine, impairs performance in the radial arm maze task [1]. It is unlikely that the non-cognitive effects of these drugs contribute to results shown; animals treated with mecamylamine and scopolamine took the same time or longer to begin the task as in previous experiments which would be unexpected if animals were

in a hyperactive state for example. These findings support the role for cholinergic processes that involve both nAChRs and muscarinic receptors [33,43].

Previous reports with the OST have focussed primarily on distinguishing the neurobiological processes underlying impaired performance following lesions in rats or gene deletions in transgenic mice [13,46,51–53]. However, to date the OST has not been used to evaluate cognitive enhancers in normal subjects. The enhancements observed with the nicotinic agonists on the OST provide further support that the nAChR is a key target that can enhance various forms of cognition [17,25]. However, no selectivity has been shown for either the α7 or α4β2 nAChR subtypes as both significantly enhanced performance. It is possible that there are functional differences between the two which manifest as the same change in span length but future work should reveal more on this matter.

The magnitude of improvement produced by the nicotinic agonists in the OST cannot be fully compared as only single doses were tested alongside two doses of nicotine. Doses chosen were based on previous data from other cognitive tasks such as the 5-choice serial reaction time task [17] and the radial arm maze [27]. Metanicotine has previously been reported to have significant enhancing effects on cognition. Levin and Christopher used the radial arm maze to test the effect of metanicotine on working memory in rats; two experimental groups tested 1 and 6 h, respectively after drug administration, both showed significantly improved performance [24].

Improvements to working memory were produced by activating either α7 or α4β2 nAChR subtypes. Therefore, non-selective agonists, like nicotine, may have benefits, both as potential cognitive enhancers and also to restore impaired cognitive function associated with neurodegenerative diseases such as Alzheimer's disease. The ability of the α7 specific agonist compound A to increase span length in the OST highlights the integral role played by the α7 nAChR subtype in cognitive enhancement and working memory. α7 nAChR positive allosteric modulators have previously demonstrated similar improvements [36,44]. The dose of compound A was based on our previous report profiling the neurochemical effects of this agonist on dopamine release in the rat prefrontal cortex [29]. Both α7 and β2-containing nAChRs were shown to influence dopamine release in the prefrontal cortex, an event that may be related to the improvements observed with the nicotinic agonists in the OST. Nicotinic receptor binding sites are present on rat midbrain dopamine neurons [50] and α4β2 receptors located in the striatum mediate dopamine release [47]. Dopamine neurotransmitter systems have been implicated in memory enhancement [47]. Several studies have shown the deficits in memory caused by antagonism of nAChR's can be potentiated by dopamine receptor blockade [32]. However, α7 nAChR's are also known to stimulate glutamate release, an event integral in synaptic plasticity [30]. α7 receptors can also elicit release of DA in the PFC through glutamate release which has implications for neuropsychiatric disorders such as schizophrenia in which dysfunctional glutamatergic transmission is thought to be an underlying factor in the cognitive deficits associated with the disorder [29]. These findings support the role for both α4β2 and α7 nAChRs in working memory and their potential therapeutic role in neuropsychiatric illnesses.

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