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Nicotine improves performance in an attentional set shifting task in rats

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ABSTRACT

A large number of studies in both humans and experimental animals have demonstrated nicotine-induced improvements in various aspects of cognitive function, including attention and memory. The prefrontal cortex (PFC) is thought to be critically involved in the modulation of executive function and these attentional processes are enhanced by nicotine acting at nicotinic acetylcholine receptors. The involvement of nicotinic processes on cognitive flexibility in particular has not been specifically investigated. The effects of nicotine on attentional flexibility were therefore evaluated using the rodent attentional set shifting task in rats. Nicotine injected both acutely and following repeated pre-exposure significantly improved both intradimensional and extradimensional set shifting performance in the task. Further investigation of the acute effects of nicotine demonstrated this improvement in attentional flexibility to be dose-dependent. These results implicate the nicotinic receptor system in the mediation of processes underlying cognitive flexibility and suggest that nicotine improves attentional flexibility in rats, both within and between perceptual dimensions of a compound stimulus. Nicotine-induced alterations in prefrontal circuitry may underlie these effects on cognitive flexibility.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Nicotine is widely accepted as the primary psychoactive agent in tobacco smoke and has been shown to improve cognitive performance across multiple domains (Levin et al., 2006). Interest in the development of nicotinic agonists as cognitive enhancers has gained momentum, since nicotinic receptors (nAChRs) have been implicated in neuropsychiatric diseases characterised by cognitive impairments including Alzheimer's, schizophrenia, attention-deficit hyperactive disorder and mild cognitive impairment (Newhouse et al., 2004, 2012).

Neuronal nAChRs are considered to be involved since they are widely distributed throughout the rat (Clarke et al., 1985; Tribollet et al., 2004) and human brain (Gotti et al., 1997). More specifically, there is evidence that the major nAChR subtypes in rats are highly expressed in brain regions subserving cognitive functions such as the prefrontal cortex (PFC) (Gil et al., 1997; Vidal and Changeux, 1993), a brain region known to play a critical role in the modulation of executive function (Dalley et al., 2004a; Chudasama and Robbins, 2006); the hippocampus and other subcortical limbic structures (Changeux et al., 1998; Gotti et al., 2006, 2007). Furthermore, in the PFC, dopamine and glutamate have been shown to be modulated by nicotine and subtype selective agonists (Livingstone et al., 2009) which further support the role for nAChRs in cognitive function (Vidal, 1996; Mansvelder et al., 2006).

In the preclinical literature, nicotine and other subtype nAChRs agonists have been demonstrated to improve sustained and divided aspects of attention (Stolerman et al., 2000; Hahn et al., 2002) using the five choice serial reaction time task (5CSRTT; developed by Carli et al., 1983). However, another important aspect of executive function based on prefrontal cortical function which has not been systematically studied with respect to nicotinic receptor involvement is attentional flexibility.

Attentional control involves the ability to change behaviour effectively in response to alterations in the significance of environmental stimuli, a process that requires flexibility of attentional set for different dimensional properties of stimuli. Attentional flexibility is commonly measured clinically using the Wisconsin Card Sorting Test (WCST; Milner, 1963). Birrell and Brown (2000) devised an analogous model to the Wisconsin Card Sorting Test (WCST) to be executed in rodents, the Attentional Set Shifting Task (ASST). The ASST is an adaptation of the WCST, utilising the dimensions of odour, medium and texture of the bowl (Birrell and Brown, 2000). The task requires the rodent to learn to associate

Abbreviations: CD, compound discrimination; 5CSRTT, five choice serial reaction time task; ED, extradimensional; ID, intradimensional; nAChR, nicotinic acetylcholine receptor; PFC, prefrontal cortex; REV, reversal; SD, simple discrimination; WCST, Wisconsin Card Sorting Test.

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a food reward with a specific dimension which is later changed during the task (extradimensional shift EDS). Birrell and Brown observed the rodents took more trials to complete the extra-dimensional shift (switching to a previously irrelevant stimulus, whilst ignoring the previously relevant stimulus) component of the task than the intradimensional shift (switching within the same relevant dimension) component when rodents had bilateral lesions of the prefrontal cortex (Birrell and Brown, 2000). Thus, the ASST assesses a rodent's ability to shift attention to allow investigation of the mechanisms underlying both attentional set formation and maintenance in addition to attentional flexibility and reversal learning. It is formally equivalent to the human and primate versions of the task (Brown and Bowman, 2002; Dias et al., 1996a, 1996b; Owen et al., 1991), but uses more species appropriate stimuli.

In view of nicotine's cognitive-enhancing effects on sustained attention in non-compromised rodents (Hahn et al., 2002), the present studies evaluated a similar dosing regimen of nicotine in the ASST. More specifically, given the relatively short half-life for metabolism of nicotine in rats, tests were applied just prior to the extra-dimensional shift. To gauge the specificity of any improvements, similar tests were conducted on the intra-dimensional shift. These studies would also provide the potential utility of assessing attentional flexibility as a domain sensitive to cognitive enhancement by psychoactive substances.

2. Materials and methods

Two separate studies were carried out to investigate the effects of nicotine in the attentional set shifting test in rats. The first was carried out with the aim of assessing whether the depressant effects of nicotine would prevent the rats from digging in the bowls and thus nicotine pretreatment for 5 days was employed as described for tests on 5 choice serial time task (Hahn et al., 2002). Furthermore, this level of nicotine exposure was also able to ascertain tolerance developed to the acute effects of nicotine on affective and attentional flexibility, by examining the influence of acute vs sub-chronic nicotine treatment on both intradimensional (ID) and extra-dimensional (ED) set shifting performance. Subsequently, the pharmacological effects of nicotine in the task were further characterised in a second study exploring the dose related effects of acute nicotine on ED set shifting ability.

2.1. Animals

Male hooded Lister rats (Harlan, UK) weighing 260–360 g at the time of testing ($n = 12$ per group), were pair-housed in a temperature controlled room (21 ± 1 °C) on a 12 h light–dark cycle (lights on at 0800; all behavioural testing was carried out in the light phase). Rats were maintained on a diet of 16–20 g food per day with *ad libitum* water for a minimum of one week before the start of behavioural testing. Continuous weight monitoring along with reference to a standard growth curve for this rat strain ensured that under this feeding schedule, all rats gained weight while maintaining at least 85% of their free-feeding body weight. All experiments were carried out in accordance with the UK Animals (Scientific Procedures) Act, 1986 and associated guidelines.

2.2. Behavioural apparatus

The apparatus and testing procedure used was a modified version of that described by Birrell and Brown (2000) as reported by Egerton et al. (2005a). The test apparatus consisted of an adapted plastic home cage ($40 \times 73 \times 19$ cm). One third of the box was divided into two sections (by Plexiglas panels) into which two ceramic digging bowls (diameter 7 cm, depth 4 cm) could be placed. The bowls were filled with different digging media which were scented with different herbs and spices. The food reward (half a honey nut cheerio; Nestle, UK) was buried beneath the digging media in the bowl. A removable Perspex divider separated these sections from the rest of the box so access to both bowls could be controlled during testing. A smaller Perspex divider was used when required to block access to either of the bowls individually, for example when an error was recorded (see below).

2.3. Habituation phase

The habituation and testing procedure was adapted from that originally described by Birrell and Brown (2000). 24 h before testing the rats performed a habituation procedure. This consisted of initial training to dig in bowls of unscented wood chips for the cereal reward and then performance of a simple medium and odour discrimination. These simple discriminations (SDs) were carried out in the same order for all rats, in each case only one of the two exemplar choices was rewarded. Therefore in the medium SD, food reward was paired with polystyrene chips but not shredded paper and in the odour SD, reward was paired with mint but not oregano. The rats were trained to criterion performance levels of six consecutive correct trials on each of the SDs and these exemplars were not used again in testing.

2.4. Behavioural testing

The rats performed a series of discriminations in the order outlined in Table 2. These discriminations were always presented to the rat to be performed in the same order.

Treatment groups were counterbalanced for initially relevant dimension (odour or medium) and the order of presentation of the stimuli for each discrimination. As the combination of exemplars was too numerous to permit full counterbalancing, the stimuli were always presented as pairs (Table 3). The order and left/right presentation of stimulus pairs was also determined pseudo-randomly. The combination of the exemplars was derived from previous experiments and published reports (Birrell and Brown, 2000; Egerton et al., 2005a).

All trials were initiated by lifting the large divider to allow the rat access to the two bowls. As in the habituation SDs, only one of the exemplars was rewarded. Similarly, the first four trials in every discrimination consisted of discovery trials; rats were allowed to dig in both bowls, with an error being recorded if the dig occurred in the unbaited bowl. During subsequent trials if the first dig was in the unbaited bowl, access to the other (correct) bowl was blocked and the trial terminated. Trials continued until the criterion level of six consecutive correct trials was reached, with testing then progressing to the next discrimination.

Initially rats performed a simple discrimination (SD) between two bowls that differed only along one of the two perceptual dimensions being used (in the example in Table 2 this is odour, with nutmeg being the rewarded and cloves the unrewarded exemplar both in the coarse sawdust medium). On reaching criterion, testing progressed to the compound discrimination (CD), where the correct and incorrect exemplars of the relevant dimension remain the same as in the SD (i.e. nutmeg vs cloves in the example), but a second (irrelevant) dimension is introduced (i.e. fine as well as coarse sawdust medium). The CD was followed by a reversal discrimination (REV1) in which the exemplars and dimensions are unchanged from the CD, but the previously correct exemplar is now incorrect and vice versa (i.e. in our example, odour is still relevant, but it's now cloves not nutmeg which is rewarded). The ID shift is then carried out. A complete change design was used, where new exemplars of the relevant and irrelevant dimensions are presented to the rat with the same dimension being relevant (i.e. in our example it is still odour that is the relevant dimension, however we now have cinnamon being rewarded but not cumin). The ID shift was then followed by another reversal discrimination (REV2), whereas in REV1 the exemplars remain the same as in the ID shift but the relevant and irrelevant exemplars within a dimension are reversed (so in our example, it is still odour that's the relevant dimension, but it is now cumin that is rewarded, not cinnamon). This is followed by the ED shift stage of the task. As in the ID shift, there is a total change design with the rat being presented with completely novel exemplars of both relevant and irrelevant dimensions. However in contrast to the ID shift, the previously relevant and irrelevant dimensions are now reversed, so that for a rat initially trained on odour, medium becomes the relevant stimulus in ED shift and vice versa. In our example (Table 2) the rat has to now attend to medium as the relevant dimension, with large pebbles being rewarded but not small pebbles – the odours of paprika and thyme are now irrelevant. The test session concludes with a final reversal discrimination (REV3) of the ED shift.

In study 1 two different sets of medium and odour pairs were employed for test 1 and test 2 (Table 3). The order of presentation of these in testing was counterbalanced within experimental groups such that equal numbers of rats were exposed to each of the exemplar pairs at each stage of the test.

2.5. Drug administration and experimental design

Rats were randomly allocated to one of the treatment groups in Table 1 ($n = 12$ per group).

In Study 1, the pretreatment injections (either 0.2 mg/kg nicotine or saline vehicle s.c.) were carried out on three consecutive days before testing. This pre-injection protocol with nicotine was employed to reduce nicotine's acute aversive

Table 1
Study Design.

Study	Experimental group	Pretreatment	Acute injection (test)
1	VEH/VEH	Saline vehicle	Saline vehicle
	VEH/NIC	Saline vehicle	0.1 mg/kg nicotine
	NIC/NIC	0.2 mg/kg nicotine	0.1 mg/kg nicotine
2	VEH	No pretreatment	Saline vehicle
	0.05 mg/kg NIC		0.05 mg/kg nicotine
	0.1 mg/kg NIC		0.1 mg/kg nicotine
	0.2 mg/kg NIC		0.2 mg/kg nicotine