Psychopharmacology (1995) 118 : 82–92

ORIGINAL INVESTIGATION

Janice L. Muir · Barry J. Everitt · Trevor W. Robbins

Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT_3 receptor antagonist, ondansetron

Received: 17 May 1994 / Final version: 28 July 1994

Abstract To investigate further the cholinergic specificity of the effects of basal forebrain lesion-induced disruption of attentional performance, the present study examined the efficacy of various pharmacological agents in improving performance of a five-choice serial reaction time task in rats that had received lesions of the cholinergic basal forebrain. Specifically, the effects of the novel 5-HT_3 receptor antagonist, ondansetron (0.3, 1, 10 ng/kg), and of nicotine (0.03, 0.06, 0.1, 0.3 mg/kg) and the anticholinesterase, physostigmine (0.05, 0.1 mg/kg), on attentional function were examined in animals which had received AMPA-induced lesions of the nucleus basalis magnocellularis (nbM). The behavioural impairments observed immediately following the lesion were a reduction were choice accuracy and an increase in correct response latency. Although these impairments showed recovery over the course of the following weeks, the deficit in choice accuracy could be reinstated by reducing the duration of the visual stimulus and thus increasing the attentional load placed on the animals. This reduction in choice accuracy could be dose dependently improved by systemic administration of either physostigmine or nicotine, suggesting that this impairment in attentional function may be attributed to disruption of cholinergic function. The pharmacological specificity of these improvements was supported by the inability of *d*-amphetamine to improve task performance (0.2, 0.4, 0.8 mg/kg). Ondansetron was also unable to improve accuracy of performance in lesioned animals, but was effective in reducing the anticipatory or premature responding observed in both control and lesioned animals, even when elevated (in the case of controls) by treatment with systemic *d*-amphetamine. The results of the present study therefore suggest that cholinergic dysfunction can lead to attentional impairments which can be ameliorated by cholinergic treatments such as physostigmine and nicotine, but that ondansetron, despite its proposed ability to release cortical acetylcholine, was unable to restore choice accuracy at the doses employed. The results further suggest a double dissociation of effects on accuracy and the disinhibition of responding.

Key words Basal forebrain · AMPA · Attention
Physostigmine · Nicotine · Ondansetron
Amphetamine · Acetylcholine

Barry J. Everitt · Trevor W. Robbins
Department of Experimental Psychology and MRC Centre for Brain Repair, University of Cambridge, Downing Street, Cambridge, CB2 3EB, UK

Janice L. Muir (✉)
School of Psychology, University of Wales College of Cardiff, P.O. Box 901 Cardiff, CFI 3YG, Wales UK

Introduction

It has been suggested that the decline in memory, as well as other cognitive deficits associated with Alzheimer's disease, is attributable, at least in part, to degeneration of the cholinergic magnocellular neurons of the nucleus basalis of Meynert (nbM) and their cortical projections (Bartus et al. 1982; Coyle et al. 1983). A variety of techniques have therefore been utilized in experimental animals in order to examine the behavioural effects of cholinergic dysfunction, including pharmacological manipulation of the cholinergic system and excitotoxic lesions of the cholinergic neurons of the basal forebrain (BF). This latter approach has revealed a vast range of impairments, both cognitive and non-cognitive in nature, primarily following ibotenic acid lesions of the BF. Therefore, it is not surprising that during recent years the functional significance of the cortical cholinergic system for learning and memory has been the subject of considerable investigation and controversy (Dunnett et al. 1991; Fibiger 1991).

The non-selectivity of most excitotoxins for cholinergic neurons has led to the reinterpretation of the results of many studies, with the subsequent realisation that many of the learning and memory impairments originally attributed to the cholinergic corticopetal system were instead the result of disruption of corticostriatal outputs passing through the dorsal and ventral globus pallidus. Nevertheless, refinement of the excitotoxic lesioning technique over recent years has yielded substantial information regarding the functions of the cholinergic corticopetal system. Experiments using quisqualic acid (Robbins et al. 1989a,b; Muir et al. 1992a), for example, have revealed that the most convincing deficit observed as a result of this lesion is an impairment in the visual discrimination of brief visual targets presented within a spatial array. It has been suggested that these impairments represent disruption of attentional function, as manipulations to the basic paradigm which increase the attentional load on the animal either by reducing the duration of the visual stimulus (Muir et al. 1994) or by interpolating distracting bursts of white noise into the task (Muir et al. 1992a), re-instate behavioural impairments in animals which have shown behavioural recovery on the baseline schedule of the task. Indeed, a role for the basal forebrain-cortical cholinergic system in attentional function is further supported by the results obtained from complementary pharmacological studies, where the behavioural deficits induced by ICV hemicholinium (HC-3) or the impairments observed following infusion of the GABA agonist muscimol into the BF could be reversed with systemic physostigmine treatment (Muir et al. 1992a,b).

More recently, to clarify further the role of the cortical cholinergic system in attentional function, lesions of the BF have been made using α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), the prototypical agonist at the AMPA sub-type of non-NMDA glutamate receptor. The results of this study (Muir et al. 1994) revealed that AMPA-induced lesions of the BF not only produced greater reductions in cortical choline acetyltransferase (ChAT) activity than those observed previously following either quisqualate- or ibotenate-induced BF lesions (Robbins et al. 1989a,b; Muir et al. 1992a), together with extensive preservation of non-cholinergic pallidal neurons, but also produced substantially larger behavioural deficits on the attentional task. Most importantly, with respect to inferring cholinergic specificity of these behavioural effects, performance of these animals could be significantly improved in a dose dependent manner by systemic administration of the anticholinesterase, physostigmine (Muir et al. 1994).

Additional support for a role of acetylcholine in attentional function is provided by recent clinical findings in which the sub-optimal performance of patients with Alzheimer's disease on a form of the same five-choice attentional task used in the animal studies was improved following administration of the anticholinesterase, tetrahydroaminoacridine (THA; Sahakian et al. 1993). Furthermore, studies examining the potential importance of nicotinic systems in cognitive function reveal a consistent effect of nicotine on human cognitive ability, particularly in terms of improved attentional processing (Wesnes and Warburton 1984; Sahakian et al. 1989; Jones et al. 1992; Warburton 1992). In contrast, the effect of nicotine on memory function is variable and unclear (e.g. Peters and McGee 1982; Dunne et al. 1986). Similarly, studies using experimental animals have reported variable effects of nicotine treatment on learning and memory (e.g. Battig 1970; Dunnett and Martel 1990; Levin and Rose 1990, 1991). To date, the effect of nicotine on attentional function has not been adequately assessed in animals, although Hodges et al. (1991), examining the effects of cholinergic manipulations on radial maze performance in the rat, have suggested that cholinergic drugs such as nicotine act on "attentional stimulus detection mechanisms" that participate in both long- and short-term aspects of memory. Therefore, one aim of the present study was to investigate the ability of nicotine treatment to improve attentional dysfunction in animals with AMPA-induced lesions of the basal forebrain using the five-choice attentional paradigm which we have used previously (Robbins et al. 1989b; Muir et al. 1992a,b) to assess cholinergic function.

In contrast to directly manipulating the system with cholinomimetic drugs, a second aim of the current study was to examine the behavioural effects of *indirectly* manipulating the cholinergic system in these AMPA lesioned animals by administration of the 5-HT_3 receptor antagonist, ondansetron. There is considerable evidence to suggest that acetylcholine release is under the inhibitory influence of 5-hydroxytryptamine (5-HT) (Robinson 1983; Watling et al. 1988) that is mediated via the 5-HT_3 receptor (Barnes et al. 1989). Early results using ondansetron indeed suggest enhancement of cognitive performance in animals that have received lesions of the BF (Barnes et al. 1990; Domeney et al. 1991). However, it has also been reported that ondansetron fails to reverse scopolamine-induced or age-related EEG changes (Reikkinen et al. 1991), and therefore the effects of ondansetron in cholinergically compromised animals remain unclear.

Finally, within the present study, the ability of nicotine and ondansetron to improve attentional function in rats with AMPA-induced lesions of the basal forebrain was compared to the effects obtained following administration of the anticholinesterase, physostigmine, which we have recently shown to reverse BF lesion-induced impairments in performance of this task (Muir et al. 1994). In addition, the effect of amphetamine on task performance was also assessed in order to control for the possible general "arousing"/activating effects of drug treatment, and to test the pharmacological specificity of any enhancement.

Materials and general methods

Subjects

Male Lister hooded rats (Olac, Bicester, UK) were housed in pairs in a temperature controlled (21°C) room, under natural daylight conditions, with water available ad libitum. Rats were food deprived and maintained at 90% of their free-feeding weight (MRC Diet 41B laboratory chow) throughout the experiment.

Surgical procedures

Animals received lesions of the BF following training to criteria performance on the five-choice task (described below). Animals were anaesthetized using Equithesin administered IP (0.3 ml/100 g) and placed in a Kopf stereotaxic instrument. A total of nine rats received bilateral injections of 0.015 M AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, Cambridge Research Biochemicals, UK) and seven sham-operated controls received infusions of 0.1 M phosphate buffer (pH 7.2). A volume of 0.5 µl AMPA or the same volume of buffer alone, was infused bilaterally over 90 s via a 30-gauge cannula attached to a 5-µl precision sampling syringe (SGE, Baton Rouge, USA) at each of two placements: (i) AP +0.2 mm from bregma, L ±3.4 mm from the midline and DV −7.0 mm below the dura; and (ii) AP + 1.0 mm from bregma, L ± 2.6 mm from the midline and DV −7.3 mm below the dura (incisor bar set at 5.0 mm above the interaural line). Following each infusion the injection cannula was left in place for a further 2 min. After completion of surgery, those rats receiving AMPA lesions exhibited minor seizures and were therefore treated with diazepam (0.1 ml/300 g, IP). One lesioned animal died 24 h following surgery.

Drug preparation and treatment

The behavioural effects of peripheral administration of ondansetron (kindly donated by Glaxo Group Research), nicotine hydrogen tartrate (Sigma), physostigmine salicylate salt (Sigma) and *d*-amphetamine sulfate (Sigma) were investigated in these animals over the period of several months, with a 2-week period separating commencement of each new drug treatment. During this 2-week period, the animals were tested once each week on the baseline schedule of the task (stimulus duration of 0.50 s) and immediately prior to commencement of each new drug treatment, animals received a single test session with the stimulus duration reduced to 0.15 s in order to assess that behavioural impairments were still apparent in the lesioned group under this stimulus condition. Ondansetron (0.3 ng, 1 ng and 10 ng/kg, IP), nicotine (0.01, 0.03, 0.1 and 0.3 mg/kg, SC) and amphetamine (0.2, 0.4 and 0.8 mg/kg, IP) were administered 10 min prior to behavioural testing, while physostigmine (0.05 and 0.1 mg/kg, IP) was administered 20 min prior to the start of a test session. The drugs were administered in the order of ondansetron, nicotine, physostigmine and amphetamine. Finally, the sham control animals received administration of amphetamine in conjunction with ondansetron. Each drug and its vehicle was administered according to a Latin Square design, with 1 rest day followed by a baseline day separating each test day.

Choline acetyltransferase (ChAT) activity in the cerebral cortex

At the conclusion of behavioural testing, animals were decapitated and the brains rapidly removed and placed onto an ice-cooled plate. Samples of medial frontal cortex, anterior dorsolateral frontal neocortex, cingulate and parietal cortices as well as hippocampus were dissected and stored at −70° C for subsequent assay of ChAT activity using the method of Fonnum (1975).

Medial frontal cortex was taken as the area extending 3 mm caudal to the frontal pole (i.e. caudal surface corresponding to +2.0 mm from bregma) and 1 mm laterally from the midline. This medial frontal cortex sample comprised areas Cg1, Cg3 and Fr2 according to the classification of Zilles (1985). The anterior dorsolateral cortex was taken as the lateral area of cortex from this initial slice, extending laterally to the rhinal fissure, and included Zilles' areas Fr1, Fr2, Fr3 and Par1.

The first sample of post-genual cingulate cortex (cingulate 1) included the medial cortex extending 3–5 mm from the frontal pole (caudal surface coinciding with bregma) and 1 mm laterally from the midline. This sample contained areas Cg1, Cg2 and Fr2. Posterior dorsolateral frontal cortex was taken from this lateral extent to the point immediately above the rhinal fissure and comprised of areas Fr1, Fr3, FL and Par1. The second sample of post-genual cingulate cortex (cingulate 2) encompassed the medial cortex from bregma and extended 2 mm posterior to bregma. This area therefore included Cg1, Cg2, Fr2 and a small section of RSG. Parietal cortex (Fr1, HL, FL, Par1 and Par2) was taken from the lateral extent of this cingulate sample to the point immediately above the rhinal fissure. Finally, a section of hippocampus was carefully dissected.

Histology

Following removal of the cortex for the measurement of ChAT activity, brains were fixed by immersion in 10% formol saline. Following fixation and storage in 30% sucrose, the brains were sectioned on a freezing microtome at 60 µm thickness. Every fourth section through the region of the lesion was mounted on a glass slide for staining with cresyl violet. These sections were used to verify lesion placement and to assess the extent of lesion-induced neuronal loss.

General behavioural procedures

Apparatus

The test apparatus for these experiments consisted of five 25 × 25 cm^2 aluminium chambers built in the Department of Experimental Psychology, University of Cambridge. The rear wall of each chamber was concavely curved and contained 9 apertures, each 2.5 cm square, 4 cm deep and set 2 cm above floor level. Illumination of each hole was provided by a standard 3-W bulb located at the rear of the hole. In addition, each hole had an infra-red photocell beam monitoring the entrance and each hole could be blocked by a metal cover when not required (for details see Carli et al. 1983).

The five chambers were individually housed within wooden sound-attenuating cabinets, ventilated by low-level noise fans, which also served to mask extraneous background noise. Each chamber was illuminated by a 3-W house-light mounted in the centre of the roof alongside a small general purpose loud speaker. White noise could be delivered through the speaker by a purpose built white noise generator.

Animals were placed in the chamber through a Perspex door located in the front wall. Directly below this door, animals obtained access to the food magazine by pushing a hinged Perspex panel monitored by a microswitch. Food pellets (45 mg, dustless, Bioserv, New Jersey, USA) were dispensed automatically into the magazine. The distance from the magazine panel to each of the holes in the rear wall was 25 cm. The apparatus and on-line data collection was controlled by means of two Acorn A5000 systems with software written in Arachnid (Paul Fray, UK).

Behavioural procedure

Rats were trained, prior to lesion surgery, to discriminate a brief visual stimulus presented randomly in one of five spatial locations, as described previously (Robbins et al. 1989b, 1993). The training procedure began with two 15-min sessions with the response apertures covered with metal caps. During these sessions, the magazine panel was partially open and food pellets were placed in the tray. In the next two 30-min sessions, the metal caps were removed from five of the apertures (from left: 1,3,5,7,9) and several food pellets placed within each aperture as well as within the food tray. During the fifth session the test schedule was implemented.

At the beginning of each test session, the house light was illuminated and free delivery of a single food pellet to the magazine was made. The trial was initiated by the rat opening the panel to collect this pellet. After a fixed 5-s inter-trial interval (ITI), the light at the rear of one of the apertures was illuminated for a short period (0.5 s). Responses in this aperture during illumination and for 5 s afterwards (the limited hold period) were rewarded with the delivery of a food pellet and a correct response was recorded. Additional responses in the apertures were recorded as perseverative responses and resulted in a 5-s period of darkness (time-out). Further responding in the apertures during the time-out restarted this period. Responses in a non-illuminated hole during the signal period (incorrect response) and failures to respond within the limited hold period (omission) were similarly punished with a period of darkness. Once again, responses made in an aperture during this period restarted the time-out.

A response in the food panel after the delivery of a food pellet, or after the time-out period, initiated the next trial. Additional responses in the panel during the ITI or time-out periods were recorded but had no further consequences. Responses in the apertures during the ITI were recorded as anticipatory responses and resulted in a time-out period of darkness, additional responses during this time restarting the time-out period.

During any one session, the light stimulus was presented an equal number of times in each of the five holes in a random order. A daily session consisted of 100 trials or was terminated after 30 min of testing. The end of a test session was signalled by extinguishing all the lights. For the first session of training, the stimulus duration and limited hold periods were both set at 1 min, and the ITI and time-out periods set at 3 s. These variables were altered on subsequent trials according to the individual animal's performance, until the target set of task parameters could be instituted. The target parameters were: stimulus duration, 0.5 s; limited hold period, 5 s; ITI and time-out period, 5 s. The animals were considered to have reached criterion when these target parameters were attained on five consecutive sessions with >80% correct responses and <20% omissions within the 30-min session time. Approximately 30 sessions were required for the animals to attain this criterion.

Performance of the task was assessed using the following behavioural measures:

(i) *Accuracy.* The accuracy of performance was measured as the proportion of responses that were correct (number of correct responses/total number of responses), expressed as a percentage.

(ii) *Speed.* Two measures of speed of responding were used. The first was the latency to respond correctly, defined as the time between the onset of the visual stimulus and the point at which the animal's nose breaks the infra-red beam of the lit hole. The second measure was magazine latency: the time between performance of a correct response and the opening of the magazine panel to collect the food pellet.

(iii) *Anticipatory responses.* The number of responses in the apertures during the ITI. This measure assesses the ability of the animal to withold responding within the 5-s ITI prior to presentation of the stimulus.

(iv) *Perseverative responses.* Additional responses in the apertures following the initial response in an aperture.

(v) *Errors of omission.* The proportion of trials on which no response was made during the limited hold period (number of missed trials/total number of trials), expressed as a percentage.

Three weeks following surgery, the 15 animals used in this experiment were tested across ten sessions on the standard schedule of the task. At the completion of these baseline test sessions, pharmacological reversal of the behavioural impairments obtained on the task was attempted by peripheral administration of ondansetron, nicotine, physostigmine and finally amphetamine (see Drug treatments).

Statistical methods

Data for each variable were subjected to analysis of variance (ANOVA) using the GENSTAT (Rothamsted, UK) statistical package. Further post-hoc comparisons were made using the Newman-Keuls test.

Results

Neurochemical results

As shown in Table 1, infusions of AMPA into the basal forebrain resulted in significant reductions in ChAT activity in all cortical regions assayed, with the exception of the hippocampus where ChAT activity was unaffected by the lesion. The reduction in cortical ChAT activity were similar to those observed previously following AMPA lesions (Muir et al. 1994) and ranged from approximately 39% in medial areas of cortex (MF, C1 and C2) to 70% in more lateral cortical areas (ADL1, ADL2 and parietal).

Histology

The lesion profile of these animals was, as expected, very similar to that reported in previous studies

Table 1 Effects of AMPA-induced lesions of the basal forebrain on regional ChAT activity in the cortex (mean ± SE)

Region	µmol Ach formed/g tissue/h		% reduction
	control (n = 7)	lesion (n = 8)	
MF	2.434 ± 0.07	1.551 ± 0.13	37%**
C1	2.636 ± 0.17	1.511 ± 0.11	43%**
C2	2.225 ± 0.08	1.371 ± 0.13	39%**
ADL1	2.033 ± 0.09	0.646 ± 0.04	68%**
ADL2	1.626 ± 0.21	0.700 ± 0.22	66%**
Parietal	1.894 ± 0.12	0.687 ± 0.09	70%**
Hippocampus	2.566 ± 0.09	2.645 ± 0.13	n.s.

**$P < 0.001$ Student's t-test

(Page et al. 1991; Page and Everitt 1993; Muir et al. 1994), with infusions of AMPA effectively destroying the Ch4 cholinergic cell group without significant neuronal loss from the dorsal globus pallidus. Furthermore, the magnocellular cholinergic neurons of the vertical and horizontal limb nuclei of the diagonal band of Broca were also spared and the ventral pallidum was little damaged.

Behavioural results

Three weeks post-lesion surgery

As shown in Fig. 1, AMPA lesions of the basal forebrain (BF) resulted in a significant reduction in choice accuracy [$F(1,13) = 6.93$, $P < 0.05$] and a significant increase in correct response latency [$F(1,13) = 11.18$, $P < 0.01$] which remained constant across the 10 test sessions. In addition, perseverative responses were significantly increased following the lesion [$F(1,13) = 8.21$, $P < 0.05$] (means: CON = 28.6; BF = 61.8) and similarly anticipatory responses were significantly elevated in the lesion group across test sessions [$F(1,13) = 7.70$, $P < 0.05$] (CON = 16.4; BF = 51.4). There was no effect of the lesion on either errors of omission or on the latency of the animals to collect earned food reward.

However, following this 10-day assessment of performance, it became apparent that the lesioned animals were beginning to show behavioural recovery, as observed previously following discrete lesions of the BF cholinergic system (Muir et al. 1994). Animals were therefore given several additional sessions on the task in order to obtain a stable baseline upon which to initiate drug treatment. At the conclusion of these additional test sessions, the sham control and lesion animals did not significantly differ in their performance of the task as measured by choice accuracy and correct response latency, although the lesion group continued to show an increase in anticipatory (CON = 18; BF = 40) and in perseverative (CON = 22; BF = 52) responding.

Consequently, the stimulus duration was reduced to 0.15 s for all animals in order to reinstate performance deficits in the lesion group and thus obtain a stable baseline upon which to initiate drug treatment. As observed in a previous study (Muir et al. 1994), this manipulation to the basic paradigm produced a significant stimulus duration × group interaction as measured by choice accuracy [$F(1,13) = 4.36$, $P < 0.05$]. Newman Keuls post-hoc comparisons revealed that a significant reduction in choice accuracy was obtained for both sham control and for BF lesioned animals when the stimulus duration was reduced to 0.15 s. However, this reduction in accuracy was significantly greater in the lesion group than in sham animals, even though performance of the two groups did not differ significantly under baseline (0.50 s) conditions (see Fig. 1). Indeed, this difference remained stable over the course of the experiment. In order to assess whether the lesion group were still impaired in performing the

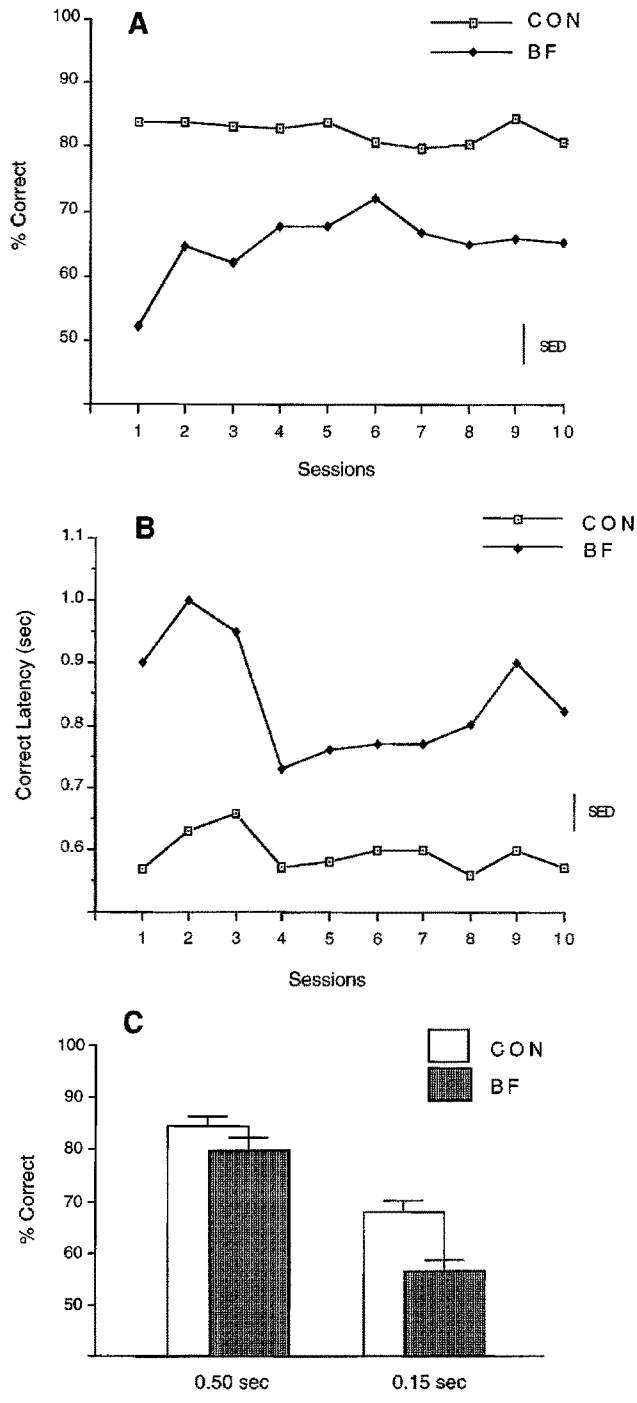

Fig. 1 Performance of sham controls (*CON*) and AMPA-lesioned animals (*BF*) on the baseline schedule of the task 3 weeks post-lesion surgery: choice accuracy (**A**), correct response latency (**B**). Effect of reducing the duration of the visual stimulus on choice accuracy following behavioural recovery (**C**) (1 SED refers to 1 standard error of the differences between the means and is derived from the interaction of lesion group and sessions in the analysis of variance). **A** and **B**: *squares* CON, *diamonds* BF. **C**: *clear columns* CON, *filled columns* BF

task, animals received a test session with the stimulus duration reduced to 0.15 s immediately prior to the commencement of testing with a new drug. In each case, the impairment in choice accuracy was apparent and the next drug and its vehicle could be administered according to a Latin square design.

Effects of ondansetron

Administration of the 5-HT_3 antagonist, ondansetron, did not significantly improve the deficit in accuracy of task performance observed in the lesion group [$F(3,39) = 1.44$, $P > 0.05$] (see Fig. 2A), the performance of the lesioned animals remaining relatively constant regardless of the dose of ondansetron administered. Although there was a tendency for the control group to show a deficit (see Fig. 2A), this was not significant. In terms of other measures, the increase in perseverative responding observed in lesioned animals (CON = 37.1; BF = 64.4) was also unaffected by ondansetron treatment [$F(3,39) = 0.49$, $P > 0.05$].

However, as shown in Fig. 2B, anticipatory responding was dose-dependently reduced by ondansetron treatment in all animals [$F(3,39) = 4.42$, $P < 0.01$]. The drug × group interaction failed to reach significance and this was most likely attributable to the small reduction in anticipatory responding observed in the sham control group as well as the more convincing reduction observed in BF lesioned animals following ondansetron treatment. Separate analyses carried out on the control and lesion groups revealed that while ondansetron did not significantly reduce anticipatory responding in sham controls [$F(3,18) = 1.66$, $P > 0.05$], a significant dose dependent reduction in anticipatory responding in lesioned animals was obtained [$F(3,21) = 3.28$, $P < 0.05$]. These changes in anticipatory responding occurred in the absence of changes in motor functions or possible motivational impairments, as there was no effect of this drug on either correct response latency [$F(3,39) = 0.66$, $P > 0.05$]; latency to collect earned food reward [$F(3,39) = 0.59$, $P > 0.05$] or errors of omission [$F(3,39) = 0.36$, $P > 0.05$] (see Table 2).

Furthermore, when anticipatory responding was enhanced in sham control animals by adminstration of 0.8 mg/kg amphetamine, ondansetron was found dose-dependently to reduce this responding [$F(2,12) = 5.32$, $P < 0.05$], (AMPHET = 45.9; AMPHET + 0.3 ng ONDANS = 32.9; AMPHET + 1 ng ONDANS = 12.1 responses).

Effects of nicotine

In contrast to the results obtained with ondansetron, systemic administration of nicotine resulted in a significant dose-dependent improvement in choice accuracy in the lesion group [$F(4,52) = 2.69$, $P < 0.05$] (see Fig. 3). Post hoc comparisons revealed that administration of 0.06 mg/kg and 0.1 mg/kg nicotine produced a significant increase in percent correct responding in the lesion group compared to performance under saline conditions. This effect was dose- dependent as there was no significant effect of the smaller 0.03 mg/kg dose on task performance. Furthermore, post hoc comparisons revealed that the highest dose of nicotine (0.3 mg/kg), which also failed to significantly improve accuracy of performance in the lesion group, significantly disrupted performance of the task by sham control animals. Indeed, following this high dose of nicotine, the control group did not significantly differ in their accuracy of performance compared to the BF lesion group under saline conditions.

The improvement in task performance observed following nicotine treatment was specific to choice accuracy as there was no effect of nicotine in reducing the significant increase in the level of perseverative responding observed in lesioned animals [$F(1,14) = 9.54$, $P < 0.01$] (CON = 40.3; BF = 70.4). The significant elevation in anticipatory responding in the

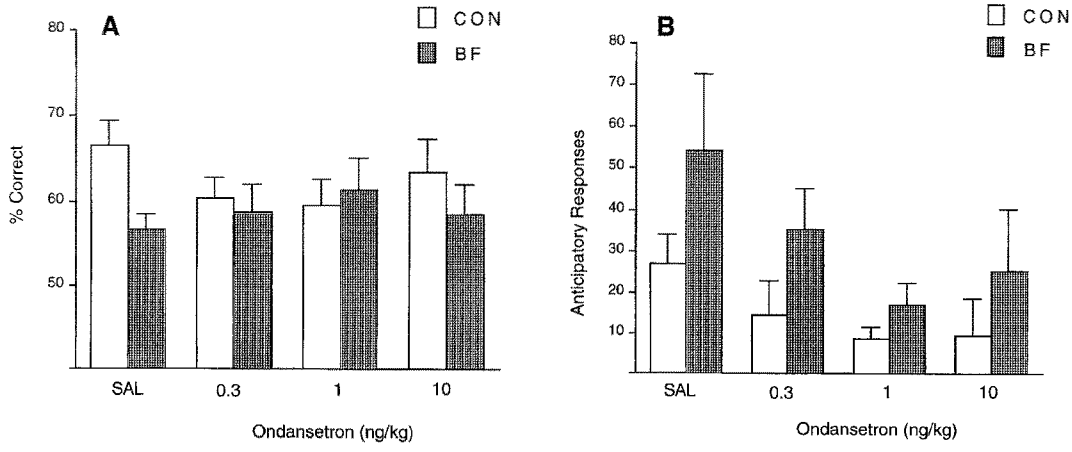

Fig. 2 Effect of administration of the 5-HT_3 receptor antagonist, ondansetron, on performance of sham control and AMPA-lesioned animals: choice accuracy (**A**), anticipatory responding (**B**) (mean ± SEM). *Clear columns* CON, *filled columns* BF

Table 2 Summary of performance of the five-choice task following systemic administration of ondansetron and nicotine in sham control (*CON*) animals and those with AMPA-induced lesions of the basal forebrain (*BF*). Means ± SE

	CON					BF				
Ondansetron (ng/kg)	*SAL*	*0.3*	*1*	*10*		*SAL*	*0.3*	*1*	*10*	
Correct latency (sec)	0.63 ± 0.06	0.71 ± 0.1	0.72 ± 0.07	0.74 ± 0.04		0.71 ± 0.04	0.63 ± 0.07	0.70 ± 0.07	0.76 ± 0.08	
Perseveration	35.3 ± 6.3	38.9 ± 6.3	37.7 ± 5.5	36.6 ± 7.4		69.9 ± 8.3	66.0 ± 6.3	65.4 ±10.4	56.4 ± 6.4	
Omissions	20.1 ± 3.9	17.2 ± 5.2	20.5 ± 4.9	22.9 ± 4.5		14.7 ± 4.4	11.3 ± 2.8	11.5 ± 2.3	12.0 ± 3.5	
Nicotine (mg/kg)	*SAL*	*0.3*	*0.06*	*0.1*	*0.3*	*SAL*	*0.03*	*0.06*	*0.1*	*0.3*
Correct latency (sec)	0.63 ± 0.03	0.72 ± 0.04	0.66 ± 0.03	0.63 ± 0.03	0.61 ± 0.06	0.57 ± 0.02	0.60 ± 0.04	0.63 ± 0.03	0.64 ± 0.03	0.59 ± 0.04
Anticipatory responding	26.9 ± 9.2	12.0 ± 2.8	15.0 ± 4.2	12.0 ± 4.1	26.4 ± 9.4	35.0 ± 10	29.1 ± 13	30.3 ± 10	34.9 ± 11	31.6 ±5.5
Perseveration	31.3 ± 6.3	31.6 ± 2.8	49.6 ± 10	42.0 ± 7.5	43.0 ± 7.9	76.1 ± 9.9	74.8 ± 17.4	67.9 ± 15	65.0 ± 8.2	68.4 ±10.7
Omissions	19.1 ± 3.9	18.3 ± 4.6	12.7 ± 1.4	9.6 ± 2	14.6 ± 4.6	13.3 ± 3.8	7.7 ± 2.2	6.3 ± 3.3	7.4 ± 2.3	6.9 ±2.5

lesion group which was observed earlier in the course of these experiments was no longer apparent [$F(1,14) = 3.23$, $P > 0.05$] (see Table 2).

Effects of physostigmine

Administration of physostigmine resulted in a significant dose-dependent improvement in choice accuracy of performance in the lesion group [$F(2,26) = 3.79$, $P < 0.05$] (see Fig. 4). Post hoc comparisons revealed that administration of 0.05 mg/kg physostigmine produced a significant increase in percent correct responding in the lesion group compared to performance under saline. Indeed, performance of the lesion group under this dose of physostigmine was not significantly different from performance of sham controls. Furthermore, the improvement in task performance was specific to this dose as there was no significant improvement in performance following the administration of the higher dose of physostigmine (0.1 mg/kg).

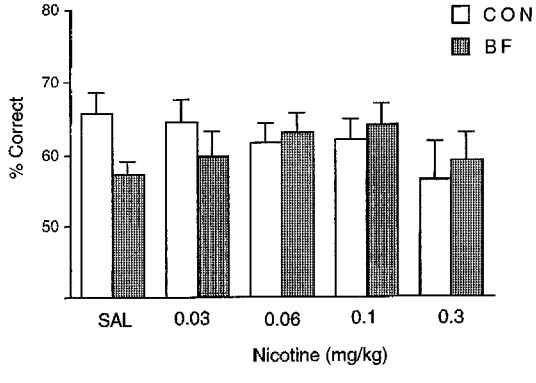

Fig. 3 Effect of administration of nicotine on choice accuracy performance in the five-choice serial reaction time task (mean ± SEM). *Clear columns* CON, *filled columns* BF

A significant effect of the lesion on latency to respond correctly to the visual stimulus was also observed at this time [$F(1,13) = 17.47$, $P < 0.001$], although this was predominantly due to the higher dose of physostigmine significantly increasing the response latencies of the lesioned animals (CON = 0.67 s; BF = 0.93 s), which were not significantly increased following the 0.05 mg/kg dose in lesion animals relative to their latencies under saline conditions (see Table 3). There was no significant effect of the lesion or physostigmine treatment on errors of omission.

As shown in Table 3, the significant increase in perseverative responding observed in the BF lesion group was maintained [$F(1,13) = 6.58$, $P < 0.05$] (CON = 37.3; BF = 62.7), but was not significantly affected by physostigmine treatment at any of the doses administered [$F(2,26) = 0.58$, $P > 0.05$]. There was no significant effect of the lesion on anticipatory responding [$F(1,13) = 0.59$, $P > 0.05$].

Effects of amphetamine

As shown in Fig. 5, amphetamine was not effective in improving the accuracy of performance in the BF lesion group [$F(3,39) = 1.62$, $P > 0.05$]. Indeed, at the highest dose of amphetamine administered (0.8 mg/kg) there was a trend for performance to be even less accurate in the BF lesion group than under saline conditions, an effect which was even more apparent in the sham control animals (see Fig. 5). Investigation of the latency of the animals to respond correctly to the visual target at this high dose revealed that, although not significant, the disruption in performance in the sham animals may have been at least partly attributable to their more rapid responding (see Table 3).

The significant increase in perseverative responding in the BF lesion group was still apparent at this time

Table 3 Summary of performance of the five-choice task following systemic administration of physostigmine and amphetamine in sham control (*CON*) animals and those with AMPA-induced lesions of the basal forebrain (*BF*). Means ± SE

	CON				BF			
Physostigmine (mg/kg)	*SAL*	*0.05*	*0.1*		*SAL*	*0.05*	*0.1*	
Correct latency (sec)	0.60 ± 0.05	0.60 ± 0.05	0.67 ± 0.08		0.70 ± 0.06	0.70 ± 0.06	0.93 ± 0.09	
Anticipatory responding	10.1 ± 2.0	15.4 ± 3.4	10.6 ± 1.0		14.1 ± 5.6	14.9 ± 4.1	16.4 ± 8.4	
Perseveration	38.0 ± 5.7	38.7 ± 10.1	35.3 ± 7.0		72.4 ± 18.4	57.7 ± 9.1	58.1 ± 16.7	
Omissions	11.8 ± 2.3	12.9 ± 3.6	16.7 ± 1.6		14.4 ± 3.1	18.3 ± 4.2	19.1 ± 6.0	
Amphetamine (mg/kg)	*SAL*	*0.2*	*0.4*	*0.8*	*SAL*	*0.2*	*0.4*	*0.8*
Correct latency (sec)	0.60 ± 0.05	0.49 ± 0.03	0.45 ± 0.02	0.51 ± 0.04	0.60 ± 0.06	0.57 ± 0.03	0.54 ± 0.05	0.74 ± 0.1
Anticipatory responding	25.3 ± 9.9	41.1 ± 17.1	71.1 ± 17.4	89.3 ± 21.9	38.1 ± 11.7	79.9 ± 18.9	82.9 ± 25.9	112.0 ± 35.5
Perseveration	50.7 ± 5.8	45 ± 3.7	51.7 ± 5.1	59.3 ± 12.7	88.0 ± 13.6	82.2 ± 10.8	89.0 ± 19.6	57.4 ± 12.9
Omissions	11.6 ± 2.1	12.2 ± 2.2	14.0 ± 3.4	12.4 ± 4.2	12.5 ± 4.5	13.6 ± 4.4	14.4 ± 3.0	14.1 ± 3.2

[$F(1,13) = 12.05$, $P < 0.01$] (CON: 51.7; BF = 79.2), but was not significantly altered by amphetamine administration. As shown in Table 3, while there was no significant effect of the lesion on anticipatory responding [$F(1,13) = 1.41$, $P > 0.05$], as expected all animals showed a dose-dependent increase in premature responding following amphetamine administration [$F(3,39) = 11.16$, $P < 0.001$].

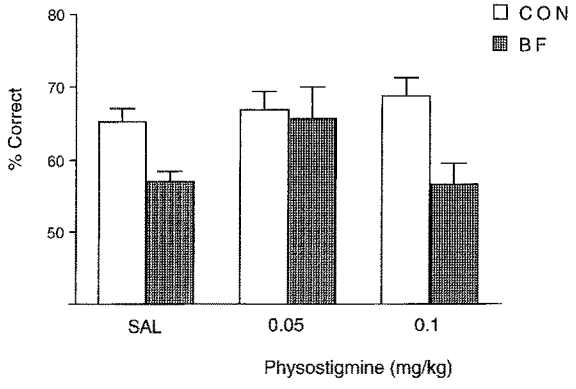

Fig. 4 The effect of the anticholinesterase, physostigmine, on performance of sham controls and AMPA-lesioned animals as measured by choice accuracy (mean ± SEM). *Clear columns* CON, *filled columns* BF

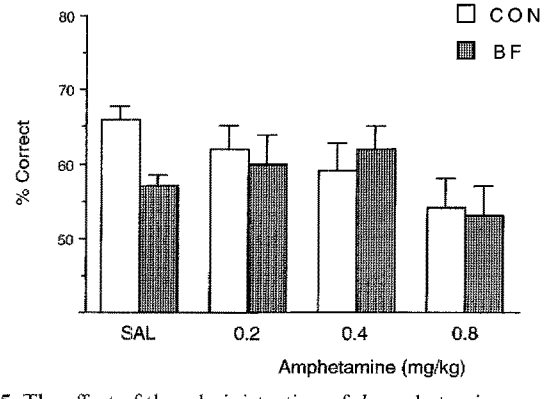

Fig. 5 The effect of the administration of *d*-amphetamine on choice accuracy performance of the five-choice attentional paradigm (mean ± SEM). *Clear columns* CON, *filled columns* BF

Discussion

The present paper has demonstrated dose-dependent reversal of impairments in performance of a five-choice attentional task following lesions of the cholinergic nbM by administration of physostigmine and nicotine but not by the 5-HT_3 antagonist, ondansetron, or by amphetamine. The performance deficits observed in these lesioned animals replicate our recent findings (Muir et al. 1994) of a disruption in attentional function, as measured by choice accuracy and correct response latency. Furthermore, as observed previously (Muir et al. 1994), while these behavioural impairments clearly show recovery over time, the deficit in choice accuracy can be reinstated by reducing the duration of the visual stimulus and thus increasing the attentional load placed on the animals.

Detailed analysis of the location of the errors made on the task revealed that approximately 50% of the errors were made by both sham and lesioned animals in the aperture adjacent to the correct location. Therefore, rather than producing a different pattern of errors compared to sham controls, the lesion simply increased the number of errors made in the vicinity of the correct location. This reduction in accuracy of task performance which was improved dose-dependently by systemic administration of either physostigmine or

nicotine suggests that this impairment in attentional function may indeed be attributed to disruption of cholinergic function. The significant improvement in performance observed following administration of 0.05 mg/kg physostigmine replicates our recent report (Muir et al. 1994) of the amelioration of deficits in choice accuracy on this task in animals with AMPA-induced lesions of the BF by administration of precisely the same dose of physostigmine as administered in the present study. Furthermore, this dose of physostigmine has also been shown successfully to reverse the impairment in task accuracy induced by either ICV administration of hemicholinium (HC-3) (Muir et al. 1992a) or by infusion of the GABA agonist muscimol into the nbM (Muir et al. 1992b).

Qualitatively similar behavioural improvements of attentional function were obtained following acute nicotine administration. While the ability of nicotine to improve attentional performance has been the subject of little consideration in the animal literature, studies in humans have revealed a consistent effect of nicotine, particularly in terms of improved attentional processing (Wesnes and Warburton 1984; Sahakian et al. 1989; Jones et al. 1992; Warburton 1992). However, given that the actions of nicotine are so varied, the precise mechanism which underlies the effects of nicotine in improving attentional performance is unknown. Nicotine is effective, for example, in stimulating the release of many neurotransmitters in various brain regions. In addition to its ability to facilitate the release of acetylcholine via presynaptic receptors (Rowell et al. 1987; Beani et al. 1989), nicotine has potent effects on the dopaminergic, noradrenergic and serotoninergic systems (Wonacott et al. 1989).

It seems unlikely, however, that the improvement in task performance observed in the present study following administration of nicotine is due to the effects of this drug on these other transmitter systems, as extensive analysis of their role in performance of this task has revealed that they each affect quite different components of task performance. For example, ceruleo-cortical noradrenaline loss does not affect perfomance on the baseline task, but accuracy is severely impaired if distracting bursts of white noise are interpolated into the task, or if stimuli are presented unpredictably (Carli et al. 1983). By contrast, increased mesolimbic dopamine release does not affect accuracy, but instead increases the overall speed and probability of responding (Cole and Robbins 1989), while serotonin depletion increases inappropriate premature anticipatory responses (Harrison et al. 1993). The distinctive effect of the AMPA-induced lesions of the basal forebrain on baseline choice accuracy preformance observed in the present study, and the ability of nicotine to improve this measure of task performance, suggest that the most likely mechanism underlying the effect of nicotine in this task is cholinergic, either via presynaptic enhancement of the release of acetylcholine or by the action of nicotine on remaining populations of postsynaptic cholinergic receptors.

The effects observed in this study following systemic administration of *d*-amphetamine did not resemble those of nicotine but instead, in support of the findings of Cole and Robbins (1989), increased speed of responding and increased inappropriate anticipatory responses in both control and BF lesioned animals. Furthermore, unlike physostigmine and nicotine, ondansetron did not improve the accuracy of task performance in lesioned animals. A report indicating that 5-HT_3 receptor antagonists facilitate acetylcholine release in cortical tissue (Barnes et al. 1989) raised the possibility that these compounds may be effective in treating cholinergic dysfunction. However, the range of cognitive tasks which have been investigated using this indirect approach to manipulating the cholinergic system is somewhat limited. It must also be considered, however, that the lack of effect of ondansetron on choice accuracy in the present study may be due to the stimulus-independent manner in which this compound releases acetylcholine, which is not optimal for task performance, although the failure of ondansetron significantly to disrupt task performance in sham control animals suggests that this may not be the case.

In the present study, the main effect of ondansetron was to reduce the degree of anticipatory responding in both control and BF lesioned animals, particularly the significant increase in such responding that was observed in the lesioned group immediately after surgery. The neural locus of this action of ondansetron is unclear. One of the better documented effects of 5-HT_3 receptor antagonists is their anxiolytic potential which is shown by their disinhibition of suppressed behaviour (Costall et al. 1991; Upton et al. 1991; but see also File and Johnston 1989). However, given that in the present study the effect of ondansetron was to *reduce* inappropriate responding, it seems unlikely that this result can be explained in terms of this putative effect of 5-HT_3 receptor antagonism.

Alternatively, ondansetron may be acting to inhibit dopamine release in the nucleus accumbens, the 5-HT_3 receptor sub-type having been reported to have a facilitatory effect on dopamine release (Blandina et al. 1988). The increase in anticipatory responding in the present study is similar to that observed on this task following systemic or intra-accumbens administration of amphetamine (Cole and Robbins 1987). Furthermore, the basal forebrain, including the ventral pallidum, receives important GABAergic projections from the nucleus accumbens, a restricted proportion of which may interact with cholinergic cells of the nbM (for a review see Sarter et al. 1990). In the present study, reducing dopamine activity within the nucleus accumbens by ondansetron administration might thus enhance GABAergic transmission within the basal forebrain, which would modulate not only the ascending cholinergic neurons but also non-cholinergic

neuronal systems projecting to the mesencephalic locomotor region and thalamus (Alheid and Heimer 1988). Therefore, for a short time following the lesion, it is hypothesised that BF lesioned animals may exhibit a form of behavioural activation, caused by damage to non-cholinergic neurons, which is reflected in their increased premature responding. Thus the subsequent administration of ondansetron to these animals and the reduction in impulsivity may reflect a reduction of nucleus accumbens dopamine activity by 5-HT_3 antagonism. This hypothesis is supported from the present findings that when anticipatory responding was increased in control animals by systemic administration of amphetamine, this premature responding could be dose dependently reduced by ondansetron.

It is important to note, however, that the effect of this lesion-induced increase in anticipatory responding was not long-lasting. During the 2-week wash-out period prior to the commencement of nicotine treatment the effect had disappeared. This supports our previous finding of a short-lasting effect of AMPA lesions on this measure (Muir et al. 1994). In contrast, the significant increase in perseverative responding persisted in all lesioned animals throughout the course of the experiment which also supports our earlier report (Muir et al. 1994). Taken together, these findings suggest that the mechanisms underlying anticipatory responding and perseverative responding can be dissociated and may be attributable to different substrates that are possibly non-cholinergic and cholinergic respectively.

Furthermore, our recent results suggest that the neural substrate underlying the improvement in task performance following either physostigmine or nicotine treatment includes the frontal cortex. Thus quinolinic acid lesions of cortical areas that are cholinergically denervated by AMPA-induced BF lesions reveal that the medial prefrontal cortex is important for task performance, lesions of this area of cortex producing behavioural impairments remarkably similar to those observed following AMPA lesions of the BF (Muir, Everitt and Robbins, unpublished observations). Nicotinic receptors are indeed present in several areas of the rat brain which are critical for cognitive function, including frontal cortex (Clarke et al. 1985) and iontophoretic studies have shown that AMPA lesions of the nbM increase the percentage of frontal cortical neurons showing responses to nicotine (Abdulla et al. 1993). This up-regulation of nicotinic receptor binding within the frontal cortex is of particular interest, given the effects of medial prefrontal cortex lesions on this task. It is reasonable to suggest, therefore, that the ability of systemic nicotine to improve task performance in the present study is attributable to its action within the frontal cortex.

Acknowledgements The work presented here was supported by a Programme Grant from the Wellcome Trust.

References

Alheid GF, Heimer L (1988) New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid and corticopedal components of the substantia innominata. Neuroscience 27:1–39

Abdulla FA, Calaminici MR, Mitchell SN, Sinden JD, Stephenson JD (1993) Chronic nicotine treatment and unilateral lesion of nucleus basalis (nb) with α-amino-3-OH-4-isoxole propionic acid (AMPA) alter rat frontal cortex pyramidal cell sensitivity to nicotine. Br J Pharmacol 109:32P

Barnes JM, Barnes NM, Costall B, Naylor RJ, Tyers MB (1989) 5-HT_3 receptors mediate inhibition of acetylcholine release in cortical tissue. Nature 338:762–763

Barnes JM, Costall B, Coughlan J, Domeney AM, Gerrard PA, Kelly ME, Naylor RJ, Onaivi ES, Tomkins DM, Tyers MB (1990) The effects of ondansetron, a 5-HT3 receptor antagonist, on cognition in rodents and primates. Pharmacol Biochem Behav 35:955–962

Bartus RT, Dean RL, Beer B, Lippa AS (1982) The cholinergic hypothesis of geriatric memory dysfunction. Science 217:408–417

Battig K (1970) The effect of pre- and post-trial application of nicotine on the 12 problems of Hebb-Williams test in the rat. Psychopharmacologia 18:68–76

Beani L, Bianchi C, Ferraro L, Nilsson L, Nordberg A, Romaanelli L, Spalluto P, Sundwall A, Tanganelli S (1989) Effect of nicotine on the release of acetylcholine and amino acids in the brain. Prog Brain Res 79:149–155

Blandina P, Goldfarb J, Green JP (1988) Activation of a 5-HT_3 receptor releases dopamine from rat striatal slice. Eur J Pharmacol 155:349–350

Carli M, Robbins TW, Evenden JL, Everitt BJ (1983) Effects of lesions to ascending noradrenergic neurons on performance on a 5-choice serial reaction time task in rats: implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav Brain Res 9:361–380

Clarke PBS, Schwartz RD, Paul SM, Pert CB, Pert A (1985) Nicotinic binding in rat brain: autoradiographic comparison of [^{3}H]acetylcholine, [^{3}H]nicotine and [^{3}H]-α-bungarotoxin. J Neurosci 5:1307–1315

Cole BJ, Robbins TW (1987) Amphetamine impairs the discriminative performance of rats with dorsal noradrenergic bundle lesions on a 5-choice serial reaction time task: new evidence for central dopaminergic-noradrenergic interactions. Psychopharmacology 91:458–466

Cole BJ, Robbins TW (1989) Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi on performance of a 5-choice serial reaction time task; implications for theories of selective attention and arousal. Behav Brain Res 33:165–179

Costall B, Naylor RJ, (1991) Anxiolytic effects of 5-HT_3 antagonists in animals. In: Rodgers, RJ, Cooper SJ (eds) 5-HT_{1A} agonists, 5-HT_3 antagonists and benzodiazepines: their comparative behavioural pharmacology. Wiley, Chichester, pp 133–157

Coyle JT, Price DL, DeLong MR (1983) Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 219:1184–1190

Domeney AM, Costall B, Gerrard PA, Jones DNC, Naylor RJ, Tyers MB (1991) The effect of ondansetron on cognitive performance in the marmoset. Pharmacol Biochem Behav 38:169–175

Dunne MP, MacDonald D, Hartley LR (1986) The effects of nicotine upon memory and problem solving performance. Physiol Behav 37:849– 854

Dunnett SB, Martel FL (1990) Proactive interference effects on short- term memory in rats: 1. Basic parameters and drug effects. Behav Neurosci 104:655–665

Dunnett SB, Everitt BJ, Robbins TW (1991) The basal forebrain-cortical cholinergic system: interpreting the functional consequences of excitotoxic lesions. Trends Neurosci 14:494–501

Fibiger HC (1991) Cholinergic mechanisms in learning and memory and dementia: a review of recent evidence. Trends Neurosci 14:220–223

File SE, Johnston AL (1989) Lack of effects of 5-HT_3 receptor antagonists in the social interaction and elevated plus-maze test of anxiety in the rat. Psychopharmacology 99:248–251

Fonnum F (1975) A rapid radiochemical method for the determination of choline acetyltransferase. J Neurochem 24:407–409

Harrison AA, Muir JL, Robbins TW, Everitt BJ, Wilkinson LS (1993) Enhanced impulsivity and distractibility in tests of visual attention in rats with forebrain serotonin depletion. Soc Neurosci Abstr 19:244.8

Hodges H, Allen Y, Sinden J, Lantons PL, Gray JA (1991) Effects of cholinergic-rich neural grafts on radial maze performance after excitotoxic lesions of the forebrain cholinergic projection system- II. Cholinergic drugs as probes to investigate lesion-induced deficits and transplant-induced functional recovery. Neuroscience 45:609–623

Jones GMM, Sahakian BJ, Levy R, Warburton DM, Gray JA (1992) Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. Psychopharmacology 108:485–494

Levin ED, Rose JE (1990) Anticholinergic sensitivity following chronic nicotine administration as measured by radial-arm maze performance in rats. behav Pharmacol 1:511–520

Levin ED, Rose JE (1991) Nicotinic and muscarinic interactions and choice accuracy in the radial-arm maze. Brain Res Bull 27:125–128

Muir JL, Dunnett SB, Robbins TW, Everitt BJ (1992a) Attentional functions of the forebrain cholinergic systems: effects of intraventricular hemicholinium, physostigmine, basal forebrain lesions and intracortical grafts on a multiple-choice serial reaction time task. Exp Brain Res 89:611–622

Muir JL, Robbins TW, Everitt BJ (1992b) Disruptive effects of muscimol infused into the basal forebrain on conditional discrimination and visual attention: differential interactions with cholinergic mechanisms. Psychopharmacology 107: 541–550

Muir JL, Everitt BJ, Robbins TW (1994) AMPA-induced lesions of the basal forebrain: a significant role for the cortical cholinergic system in attentional function. J Neurosci 14:2313–2326

Page KJ, Everitt BJ (1993) Transynaptic induction of c-fos in basal forebrain diencepahalic and midbrain neurons following AMPA- induced activation of the dorsal and ventral striatum. Exp Brain Res 93:399–411

Page KJ, Everitt BJ, Robbins TW, Marston HM, Wilkinson LS (1991) Dissociable effects on spatial water maze and passive avoidance acquisition and retention following AMPA- and ibotenic acid-induced excitotoxic lesions of the basal forebrain in rats: differential dependence on cholinergic neuronal loss. Neuroscience 43:457–472

Peters R, McGee R (1982) Cigarette smoking and state-dependent learning. Psychopharmacology 76: 232–235

Riekkinen P, Sirvio J, Riekkinen P (1991) Non-reversal of scopolamine- or age-related EEG changes by ondansetron, methysergide or alaproclate. Psychopharmacology 103:567–570

Robbins TW, Everitt BJ, Ryan CN, Marston HM, Jones GH, Page KJ (1989a) Comparative effects of quisqualic and ibotenic acid-induced lesions of the substantia innominata and globus pallidus on the acquisition of a conditional visual discrimination: differential effects on cholinergic mechanisms. Neuroscience 28:337–352

Robbins TW, Everitt BJ, Marston HM, Wilkinson J, Jones GH, Page KJ (1989b) Comparative effects of ibotenic acid- and quisqualic acid- induced lesions of the substantia innominata on attentional function in the rat: further implications for the role of the cholinergic neurons of the nucleus basalis in cognitive processes. Behavioural Brain Research 35:221–240

Robbins TW, Muir JL, Killcross AS, Pretsell D (1993) Methods for assessing attention and stimulus control in the rat. In: Sahgal A (ed) Behavioural neuroscience. A practical approach, Oxford University Press, Oxford, pp 13–47

Robinson SE (1983) Effect of specific serotonergic lesions on cholinergic neurons in the hippocampus, cortex and striatum. Life Sci 34:345–353

Rowell RP, Carr LA, Garner AC (1987) Stimulation of [^{3}H] dopamine release by nicotine in rat nucleus accumbens. J Neurochem 49: 1449–1454

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

Sahakian BJ, Owen AM, Morant NJ, Eagger SA, Boddington S, Crayton L, Crockford HA, Crooks M, Hill K, Levy R (1993) Further analysis of the cognitive effects of tetrahydroaminoacridine (THA) in Alzheimer's disease: assessment of attentional and mnemonic function using CANTAB. Psychopharmacology 110:395–401

Sarter M, Bruno JP, Dudchenko P (1990) Activating the damaged basal forebrain cholinergic system: tonic stimulation versus signal amplification. Psychopharmacology 101:1–17

Upton N, Blackburn TP (1991) Anxiolytic-like activity of the selective 5- HT_3 receptor antagonist, BRL46470A, in the rat elevated x-maze test. Br J Pharmacol 102 [Suppl]:253P

Warburton DM (1992) Nicotine as a cognitive enhancer. Prog Neurospychopharmacol Biol Psychiatry 16:181–219

Watling KJ, Aspley S, Swain CJ, Saunders J (1988) [^{3}H]Quaternised ICS205-930 labels 5-HT receptor binding sites in rat brain. Eur J Pharmacol 149:397–398

Wesnes K, Warburton DM (1984) Effects of scopolamine and nicotine on human rapid information processing performance. Psychopharmacology 82:147–150

Wonnacott S, Irons J, Rapier C, Thorne B, Lunt GG (1989) Presynaptic modulation of transmitter release by nicotinic receptors. In: Nordberg A, Fuxe K, Holmstedt B, Sundwall A (eds) Progress in brain research. Elsevier, Amsterdam, pp 157–163

Zilles K (1985) The cortex of the rat. Springer, Berlin