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The role of nicotinic and muscarinic acetylcholine receptors in attention

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Abstract *Rationale:* This study tried to determine the relative roles of muscarinic and nicotinic cholinergic receptors in attentional processing. *Methods:* The effects of cholinoceptor agonists and antagonists, and of an anticholinesterase, were studied on performance of rats in a five-choice serial reaction time task. *Results:* Scopolamine (0.1 mg/kg) and mecamylamine (5.0 mg/kg) produced deficits in accuracy and reaction time, respectively. This may suggest a differential role for the two types of cholinoceptors in information processing. Combinations of sub-threshold doses of scopolamine (0.01–0.03 mg/kg) and mecamylamine (0.5–1.6 mg/kg), which alone did not affect accuracy or reaction time, did not produce significant deficits in attention. However, the pattern of effects after combined treatment suggested that the differential deficits seen with these drugs alone remained. The anticholinesterase physostigmine (0.1 mg/kg) and the non-selective muscarinic agonist oxotremorine (0.03 mg/kg) induced severe behavioural disruption at doses that appeared to be relatively well tolerated in previous studies; this precluded the derivation of accuracy and response time data at these doses. At lower doses, neither physostigmine (0.05 mg/kg) nor oxotremorine (0.003 mg/kg) significantly affected any performance measure; this may reflect the ability of both drugs to indirectly or directly activate presynaptic muscarinic receptors that inhibit acetylcholine release, respectively. *Conclusions:* Both muscarinic and nicotinic cholinoceptors may be important in attention but they may serve different roles in information processing; this hypothesis could be tested using tasks that place different emphasis on different stages of information processing.

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Introduction

The cholinergic system is known to be important in cognition (Drachman and Leavitt 1974; Bartus et al. 1982). However, since the endogenous neurotransmitter acetylcholine (ACh) acts on both muscarinic and nicotinic cholinergic receptors, the relative roles of these two receptor systems in cognitive processes is unclear. This is important because it may have implications for potential cholinergic therapy in clinical disorders in which cognition is impaired. A plethora of experimental drug investigation suggests that both cholinergic receptor subtypes are important for learning, memory and attention (reviews by Levin 1992; Williams et al. 1994; Stolerman et al. 1995). However, various lines of evidence (see below) suggest that the two receptor subtypes may subserve differential roles in cognitive processes.

In general anatomical terms, the density of muscarinic and nicotinic receptors differs in the brain. Thus, there is a high density of muscarinic receptors in the target sites of Ch1–Ch4 projecting cholinergic nuclei (i.e. forebrain nuclei) but a low density of nicotinic receptors. Conversely, there is a high density of nicotinic receptors but low muscarinic receptor density in the projection areas of brainstem Ch5 and Ch6 cholinergic nuclei (Clarke et al. 1984; Monferini 1992). It is likely that this opposite rostral/caudal gradient for the two receptor subtypes has functional significance, as suggested by Perry and Perry (1985). Electrophysiological data show that acetylcholine in the thalamus acting on muscarinic and nicotinic receptors inhibits and excites GABA neurons, respectively (McCormick 1989). Recently, Xiang et al. (1998) have demonstrated a similar phenomenon within neocortical networks and suggested that this leads to finer control of information processing. Can such differences lead to behavioural differences in the effects of nicotinic and

muscarinic drugs and do these two receptors affect different aspects of cognition?

It has been proposed that the cholinergic system may be involved in attentional processes as well as in learning and memory indirectly. For example, neurotoxin-induced lesions of the nucleus basalis of Meynert in the rat selectively impair attention rather than learning or memory (Robbins et al. 1989; Muir et al. 1994, 1996). Moreover, the immunotoxin 192 IgG saporin, which depletes choline acetyltransferase by 95%, impairs attention; although this depends upon the cholinergic forebrain projection system lesioned (Torres et al. 1994; Wenk et al. 1994; Leanza et al. 1996). It also evident from the literature that the effect on learning and memory of some manipulations of the cholinergic system may be interpreted as indirect effects resulting from changes in attention (Spencer et al. 1985; Deacon 1991; Hodges et al. 1991a, 1991b; Pontercorvo et al. 1991; Stanhope et al. 1995).

Therefore, we have looked at the effects of cholinergic drugs in a five-choice serial reaction time task (five-choice SRTT) which primarily assesses attention in rats. This task requires rats to respond to discrete visual stimuli presented randomly in one of five spatial locations (Carli et al. 1983). Importantly, lesioning nucleus basalis projections to the cortex impairs performance on this task and this can be reversed by the cholinesterase inhibitor physostigmine and transplantation of cholinergic-rich cortical grafts (Muir et al. 1992; see review by Dunnett et al. 1991). However, little is known about the underlying cholinergic receptor basis for the effects of lesions, transplantation or physostigmine. Muir et al. (1995) showed that nicotine (0.06–0.1 mg/kg) also reversed lesion-induced deficits in accuracy on this task, but no studies have assessed the effects of muscarinic agonists. This is surprising, as the muscarinic antagonist scopolamine impairs the performance of rats in other attentional tasks (Bushnell et al. 1997). Furthermore, muscarinic agonists can enhance learning and memory in various tasks (Haroutunian et al. 1985; Rupniak et al. 1989).

The aims of the present study were to: (i) ascertain the relative roles of the nicotinic and muscarinic cholinergic receptors on attention by using the antagonists scopolamine and mecamylamine; (ii) determine whether in combination these antagonists had synergistic or additive effects; (iii) ascertain the effects of a muscarinic agonist (oxotremorine) and a cholinesterase inhibitor (physostigmine). Although scopolamine and mecamylamine have been tested in the five-choice SRTT, their effects on accuracy were equivocal and only reproducible in middle-aged rats or when a distracter was interpolated in the ITI (Jäkälä et al. 1992; Jones and Higgins 1995; Jones et al. 1995). Combinations of these two drugs have not previously been tested in an attentional task. Likewise, oxotremorine has never been tested in this task. Finally, although Muir et al. (1994, 1995) demonstrated that physostigmine had no effect on accuracy in sham-lesioned rats in the five-choice SRTT, this may have been due to a ceiling effect under standard conditions.

We report here on tests with both physostigmine and oxotremorine to ascertain whether these drugs can counteract the impairment of performance when the signal length is reduced from 1.0 to 0.25 s (Mirza and Stolerman, 1998). By contrast, it was anticipated that mecamylamine and scopolamine would impair attention. However, these rats had had extensive training on this task, and this leads to resistance to behavioural or pharmacological manipulations (Sarter 1990; Spear et al. 1990). Therefore, the signal length was reduced to 0.5 s for tests with antagonists; this small reduction in signal length had no effect on accuracy (Mirza and Stolerman 1998).

Materials and methods

Subjects

Male Lister hooded rats (Harlan UK) weighing 300–350 g were used. Rats were housed individually and placed on a food-restricted diet to maintain them at 80% of their free-feeding weight. Rooms were at controlled temperature (20–22˚C) and an alternating light-dark cycle was in effect (light from 7 a.m. to 7 p.m.). Water was available ad libitum. The treatment of animals complied with British Law and the Code of Practice of the Institute of Psychiatry. These animals had been tested previously with nicotine (Mirza and Stolerman 1998) and there was a 3-week period before the current experiments began.

Apparatus

Sound-insulated and ventilated enclosures were used to house an aluminium chamber measuring 26×26×26 cm (Paul Fray Ltd, Cambridge, UK). One wall of the chamber had five 2.5 cm square holes, 5 cm deep and 5 cm above floor level, equidistant from a food tray at the front of the chamber. Each hole had a light beam across its entrance and a 2.8 W bulb at its rear. The food tray, situated on the opposite wall of the chamber, had a flap at its entrance. A houselight was situated in the roof of the chamber. The apparatus was controlled by an Acorn computer in an adjoining room.

Procedure

The methods were based on those of Mirza and Stolerman (1998), who described the procedures for training. After acquisition, a session began with the illumination of the house light and the delivery of a food pellet. Once the rat pushed the tray flap to collect this food pellet there was an inter-trial interval (ITI) of 5 s, after which there was a 1-s flash of light in one of the apertures (selected at random). If a rat responded (i.e. nose-poked) in the lit hole whilst the light remained illuminated, or within a fixed period of time after it had gone out (limited hold, 5 s), a food pellet was delivered, a correct response was registered and the next trial was initiated when the rat pushed the tray flap to collect the food pellet. If a rat responded in a hole other than the one in which the light had flashed, a commission error was registered. If the rat failed to respond in the allocated time, an omission error was registered. Either a commission or omission error resulted in a punishment contingency in which the house light was extinguished (time-out, 5 s). If a rat responded in a hole during the time-out, the time-out was restarted. After an error, the next trial was initiated by opening the tray flap once the house light had come back on. Responses during the ITI were registered as anticipatory responses, but had no consequences. Training sessions consisted of 100 trials or 30 min, whichever was the shorter, and data were recorded for successive periods of 6 min.

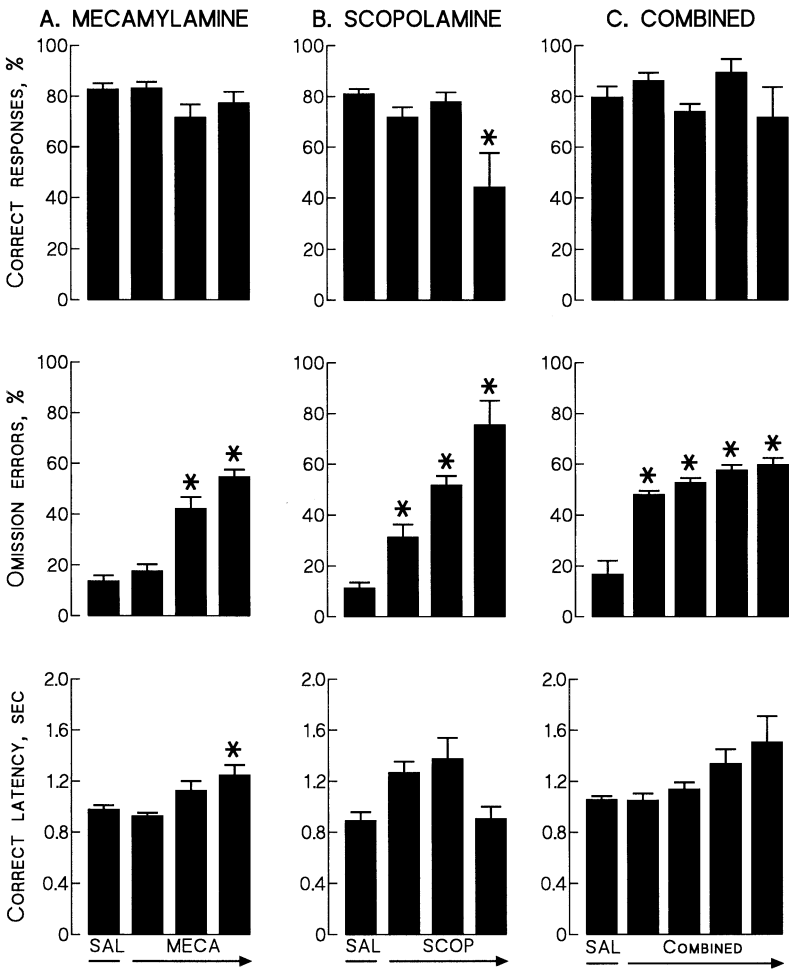

Fig. 1A–C Effects of the drugs shown on the performance of rats in a five-choice SRTT. **A** Shows results for mecamylamine (*n*=8) in doses of 0.5 mg/kg (●), 1.6 mg/kg (▲) and 5.0 mg/kg (■). **B** Shows results for scopolamine (*n*=6) in doses of 0.01 mg/kg (●), 0.03 mg/kg (▲) and 0.1 mg/kg (■). **C** Shows results for mecamylamine/scopolamine combinations (*n*=7) in doses of 0.5/0.01 mg/kg (●), 0.5/0.03 mg/kg (▲) and 1.6/0.01 mg/kg (■), 1.6/0.03 mg/kg (▼). Control (vehicle) results are also shown. *Arrows* under the graphs indicate increasing doses of the drugs, as stated above. Results are expressed as means±SEM. **P*<0.05 compared with saline control (Tukey HSD)

Experiment 1: effects of mecamylamine, scopolamine and combinations

The rats were divided into three groups (*n*=6–8) balanced according to percentage correct, percentage omission and correct response latency measures. The performance of vehicle-treated rats in each of the three studies described below indicates that the groups were closely matched on these parameters (see Fig. 1). Using a within-subjects design, group 1 (*n*=8) was injected with mecamylamine (0.0, 0.5, 1.6 and 5.0 mg/kg, experiment 1A), whereas group 2 (experiment 1B, *n*=6) was treated with scopolamine (0.0, 0.01, 0.03 and 0.1 mg/kg). The third group (experiment 1C, *n*=7) was injected with either 0.5 or 1.6 mg/kg mecamylamine, each in combination with either 0.01 or 0.03 mg/kg scopolamine; again a within-subjects design was used and the control condition comprised two injections of vehicle. Doses of drugs were based on those of Jones et al. (1995). Drugs were injected on Tuesdays and Fridays, with different doses given in a randomised order, and with baseline training sessions on intervening days. All injections were subcutaneous, 30 min before sessions. As outlined in the Introduction these tests were carried out with the signal length reduced from 1 to 0.5 s.

Experiment 2: effects of physostigmine and oxotremorine

The effects of physostigmine and oxotremorine on performance were tested in a single group of rats (*n*=7). The signal length was decreased to 0.25 s on test days in an attempt to impair performance and thus increase sensitivity to facilitatory effects of the drugs (see Introduction). Rats were injected with either physostigmine (0.05 or 0.1 mg/kg), oxotremorine (0.003 or 0.03 mg/kg) or vehicle 20 min before a test session; these doses were based on previous studies (Clissold and Heise 1990; Sahgal et al. 1990). Only one drug test was carried out each week to minimise carry-over effects.

Data analysis

The measures taken included the number of trials completed, the percentage of correct responses (100×correct responses/correct responses plus commission errors), the percentage of omission errors (100×total omission errors/total number of trials), anticipatory responses in the apertures during the ITI, perseverative responses in the apertures during the time-out period, and latency to make a correct response (calculated as the time between the onset of the stimulus and a nose-poke in the lit hole). Percentage data were arc-sine transformed, anticipatory and perseverative response data were subject to square root transformation and response latencies were transformed logarithmically. Analyses for each measure was done separately using two-factor ANOVA followed by one-factor ANOVA and Tukey's HSD test for multiple comparisons where appropriate (Statistica, Tulsa, Oklahoma, USA).

Drugs

Mecamylamine HCl, scopolamine HCl, physostigmine sulphate and oxotremorine sesquifumarate (Sigma, Poole, Dorset, UK) were dissolved in 0.9% saline and injected subcutaneously into the flank of the rat at a volume of 1 ml/kg.

Results

There were no significant drug dose×time interactions in any of the following studies and, therefore, these data are not shown.

Experiment 1A: mecamylamine

From Fig. 1A, it is apparent that mecamylamine had no effect on the percentage of correct responses [$F(3,21)=0.92$] but it did induce a significant, dose-dependent increase in the percentage of omission errors [$F(3,21)=20.4$, $P<0.001$]; results for both the 1.6 and 5.0 mg/kg doses differed from control (Fig. 1A). Interestingly, mecamylamine also increased correct response latency [$F(3,21)=2.91$, $P<0.05$, Fig. 1A, bottom row]. Table 1 shows that mecamylamine dose-dependently reduced the number of trials completed [$F(3,21)=29.4$, $P<0.001$] and decreased anticipatory responses [$F(3,21)=3.26$, $P<0.05$], although there was no effect on perseverative responses [$F(3,21)=1.4$]. Behavioural observations revealed that mecamylamine (1.6 and 5.0 mg/kg) induced ptosis within 15 min; also after 5.0 mg/kg, rats showed signs of sedation such as a flaccid posture and loss of body tone.

Experiment 1B: scopolamine

At the highest dose of scopolamine (0.1 mg/kg) there was a profound deficit in correct responses and an increase in omission errors; this was borne out by significant effects of dose [$F(3,15)=5.72$, $P<0.01$ and $F(3,15)=19.1$, $P<0.01$, Fig. 1B]. Further analysis revealed that after all three doses of scopolamine, rats made more omission errors as compared with vehicle. Scopolamine had no overall effect on correct response latency [$F(3,15)=2.75$, Fig. 1B, bottom row). Table 1 shows a significant, dose-dependent decrease in trials completed [$F(3,15)=34.4$, $P<0.01$] and anticipatory responses [$F(3,15)=4.8$, $P<0.01$] after scopolamine, but no effect on perseverative responses [$F(3,15)=0.1$]. Behavioural observations showed that after the highest dose (0.1 mg/kg) of scopolamine rats were more active and difficult to handle.

Experiment 1C: combinations of mecamylamine and scopolamine

The combinations of mecamylamine and scopolamine marginally affected correct responses [$F(4,24)=2.65$, $P=0.057$, Fig. 1C, top row]. Furthermore, inspection of Fig. 1C (top row) shows that there was no dose-related trend in accuracy after administration of the combinations. By contrast, there was a highly significant increase in omission errors [$F(4,24)=23.4$, $P<0.01$, Fig. 1C, middle row]; this was significant after all dose combinations as compared with vehicle, but there was very little difference between the different dose-combinations. There was also an effect of the dose combinations on correct response latency [$F(4,24)=2.8$, $P<0.05$, Fig. 1C, bottom row]; however, further analysis did not reveal the basis for this significant effect, although Fig. 1C shows that the 1.6/0.01 and 1.6/0.03 mg/kg dose-combinations of mecamylamine and scopolamine appeared to increase latency slightly. Table 1 shows that the drug combinations decreased the total number of trials completed [$F(4,24)=45$, $P<0.01$], anticipatory responses [$F(4,24)=2.74$, $P<0.05$], and perseverative responses [$F(4,24)=10.6$, $P<0.01$]. Further analysis showed that all dose combinations reduced the number of trials completed compared with vehicle ($P<0.05$); there was also a decrease in perseverative responses after all dose combinations except for those with the lowest doses of each drug.

Table 1 Effect of mecamylamine, scopolamine and combinations of the two drugs on the number of trials completed, anticipatory and perseverative responses made by rats on the five-choice serial reaction time task under conditions where the stimulus duration has been decreased to 0.5 s. Results are given as mean±SEM

Dose of drug (mg/kg)	Total number of trials completed	Anticipatory responses	Perseverative responses
1. Mecamylamine (n=8)			
0.0	89.1±3.6	16.6±6.5	11.0±2.5
0.5	89.1±5.1	18.8±4.3	13.8±1.8
1.6	59.0±5.3*	8.1±2.4*	26.4±7.0
5.0	39.6±3.2*	7.1±3.3*	8.8±2.7
2. Scopolamine (n=6)			
0.0	100.0±3.7	35.3±11.3	10.2±2.8
0.01	92.3±6.7	17.3±7.9*	13.5±3.3
0.03	58.7±6.3*	8.3±2.8*	8.3±3.2
0.1	18.3±2.3*	2.7±1.7*	12.0±7.3
3. Combined (n=7)			
0.0/0.0	84.1±5.9	7.1±2.5	18.7±2.7
0.5/0.01	60.6±3.5*	6.3±3.6	15.1±3.9
0.5/0.03	34.4±4.6*	4.6±2.2	3.1±0.7*
1.6/0.01	17.9±4.0*	6.3±0.6	1.4±0.9*
1.6/0.03	14.4±2.3*	0.4±0.1	2.9±0.8*

*$P<0.05$ in comparison with control by Tukey's HSD test

Table 2 Effect of physostigmine and oxotremorine on the performance of rats on the five-choice serial reaction time task under conditions where the stimulus duration has been decreased to 0.25 s. Results are given as mean±SEM

Drug and dose (mg/kg)	Total number of trials completed	Percentage correct detections	Percentage omission errors	Anticipatory responses	Perseverative responses	Correct response latency (s)
1. Saline	90.1±5.3	58.5±3.3	26.3±6.3	22.7±4.0	34.7±11.9	1.03±0.10
2. Physostigmine (*n*=7)						
0.05	83.1±5.2	61.5±3.0	30.9±5.9	13.1±3.7	39.1±11.3	1.28±0.12
0.10	27.7±9.9*	–	–	–	–	–
3. Oxotremorine (*n* =7)						
0.01	86.9±2.8	52.9±2.2	25.9±3.3	27.6±14.2	31.0±5.9	1.18±0.10
0.03	9.4±1.8*	–	–	–	–	–

*P<0.05 in comparison with control by Tukey's HSD test

The basis for the reduction in anticipatory responses could not be determined by post hoc analyses.

Experiment 2: physostigmine and oxotremorine

As described above, the stimulus duration was decreased to 0.25 s (baseline=1 s) when physostigmine, oxotremorine or vehicle was administered. Table 2 shows that this parametric manipulation did induce a deficit in performance, since after saline the accuracy of correct responding was only 58.5±3.3%.

The effects of physostigmine and oxotremorine were analysed separately. Table 2 shows that the largest doses tested of oxotremorine (0.03 mg/kg) and physostigmine (0.1 mg/kg) significantly suppressed the number of trials [F(2,12)=155.2, P<0.001 and F(2,12)=26.3, P<0.001, respectively]. Since rats failed to respond in the majority of the trials that were initiated (omission errors), the derivation of the percentage of correct responses and correct response latency was precluded. Thus, data for the largest dose of each drug were excluded from analysis.

Physostigmine had no effect on percentage of correct responses or omission errors [F(1,6)<1 in each case], and whilst there was a tendency for an increase in the latency of correct responses, this was not significant [F(1,6)=1.9]. Physostigmine had no effect on the number of anticipatory [F(1,6)=1.5] or perseverative responses [F(1,6)=0.5]. The findings with oxotremorine were also negative. Thus, there was no significant effect on the percentage of correct responses, omission errors, correct response latency, anticipatory responses or perseverative responses [F(1,6)<1 in all cases, see Table 2].

Discussion

This study found that (i) the muscarinic antagonist scopolamine impaired accuracy and the nicotinic antagonist mecamylamine impaired reaction time; (ii) combinations of certain doses of these antagonists had no effect on either accuracy or reaction time; (iii) neither physostigmine nor oxotremorine affected performance.

The deficit in accuracy after scopolamine (0.1 mg/kg) in young rats in the 5-choice SRTT has not previously been reported. Scopolamine either had no effect or only impaired accuracy when middle aged rats (≥15 months) were used or when a white noise distracter was interpolated in the ITI (Jäkälä et al. 1992; Jones and Higgins 1995; Jones et al. 1995). However, in this study, scopolamine 0.1 mg/kg decreased trials completed and anticipatory responses, whilst increasing omission errors, suggestive of behavioural disruption; however, there was no effect on perseverative responses or correct latency. Thus, the profile of our data differs from previous studies (Jones and Higgins, 1995; Jones et al. 1995). Also, at lower doses scopolamine increased omission errors and/or decreased trials initiated (findings indicative of decreased motivation) but without affecting accuracy. Similarly, Carli and Samanin (1992) demonstrated that anorectic drugs such as 5-HT_{2C} agonists increase omission errors and reaction times without affecting accuracy in the five-choice SRTT. However, scopolamine does impair accuracy, and therefore motivational or sensorimotor (see also below) effects do not adequately explain its profile.

The increase in omission errors after methyl scopolamine, which does not cross the blood-brain barrier readily, is only about half of that induced by scopolamine HBr, and this form of the drug has no other effects (Mirza and Bright, unpublished data). Therefore, the increase in omission errors after scopolamine in this study may be partly peripherally and partly centrally mediated (Jäkälä et al. 1992). It is possible that an increase in omission errors reflects lapses in attention (Nutt and Smith 1996).

The nicotinic antagonist mecamylamine had no effect on accuracy, although it increased omission errors and the latency of correct responses. Since reaction time in well-learned tasks may be the better measure of decision-making quality, there may be a real mecamylamine-induced deficit in attention (McGaughy and Sarter 1995; Mirza and Stolerman 1998). In other attentional tasks, mecamylamine impairs both reaction time and accuracy (Turchi et al. 1995; Bushnell et al. 1997). The discrepancy between these and the present findings may be a func-

tion of the greater visual-spatial nature of the five-choice SRTT compared to two-lever tasks. However, our data concur with clinical findings that mecamylamine impairs reaction time without affecting accuracy (Newhouse et al. 1992).

In non-human species mecamylamine may affect motivation for food and this may alter reaction times. Indeed, mecamylamine decreased trials initiated and anticipatory responses, with increased omission errors suggesting decreased motivation for food leading to behavioural suppression. The nicotinic receptor agonist nicotine has an anorectic effect under specific conditions in humans and rats (Grunberg 1986). Such findings suggest that a nicotinic receptor antagonist like mecamylamine is unlikely to decrease feeding. However, the profile of mecamylamine in this study is similar to that seen with anorectic 5-HT_{2C} agonists in the five-choice SRTT and this issue warrants further investigation (Carli and Samanin 1992).

There was no general reduction in behavioural activity with both mecamylamine and scopolamine, and their different profiles cannot be explained in this way. Neither drug affected perseverative responses and whilst mecamylamine induced ptosis and sedation, scopolamine increases pupil diameter and induces hyperactivity (Jones and Higgins 1995). However, in the case of mecamylamine it is feasible that ptosis led to an increase in response time.

The data from the experiment involving combinations of scopolamine and mecamylamine do not verify the hypothesis that a functional interaction between muscarinic and nicotinic receptors is important for attentional processing. In most cases, the effects of the combinations of the two drugs could easily be ascribed to actions of one or the other of the drugs alone (e.g. omission errors: Fig. 1 middle row). The effect of the dose combinations on the accuracy of correct responses approached significance (P=0.057), and larger-scale studies with greater statistical power may demonstrate an effect. Interestingly, in combination, these two drugs profoundly decreased perseverative responses, although neither drug alone affected this measure. This decrease in perseverative responses with a concurrent decrease in trials and anticipatory responses, and an increase in omission errors, indicates global behavioural disruption not seen completely with either drug alone.

The anticholinesterase inhibitor physostigmine, at a dose of 0.1 mg/kg, profoundly decreased the number of trials completed and there was no evidence for cognitive enhancement. The doses of physostigmine were similar to those in studies where enhancements of cognitive functions were reported (Clissold and Heise 1990), but like many first-generation anticholinesterases, physostigmine has poor bioavailability, a short half-life and a narrow therapeutic window (Nordberg and Svensson 1998). Moreover, anticholinesterases increase concentrations of ACh in the synaptic cleft, and this ACh may activate both inhibitory muscarinic M_2 autoreceptors (which decrease ACh release), as well as postsynaptic cholinoceptors (Svensson et al. 1996). The balance between pre- and post-synaptic activation may determine the effects of such drugs in vivo. Interestingly, in rats with lesions of the cholinergic system, physostigmine reverses impairments in the five-choice SRTT (Muir et al. 1992, 1995; McGaughy and Sarter 1998).

Muscarinic agonists seem not to have been examined previously in the five-choice SRTT. The present results show that a small (0.01 mg/kg) dose of oxotremorine had no effect on any measure in this task, and that at the larger dose of 0.03 mg/kg rats completed insufficient trials for meaningful data to be generated. This was surprising, since the doses were based upon those used by Sahgal et al. (1990), who did not find non-specific effects of oxotremorine up to a dose of 0.1 mg/kg in a delayed response task. Cognitive enhancing effects of oxotremorine have been demonstrated at doses as low as 5–10 µg/kg in mice (Castellano and McGaugh 1991), whereas doses of 0.1–0.2 mg/kg have been reported to improve retention in passive avoidance (Haroutunian et al. 1985; Yamazaki et al. 1991). The behavioural disruption produced by 0.03 mg/kg oxotremorine precluded the use of larger doses of this drug in the five-choice SRTT. Since oxotremorine is a non-selective muscarinic agonist, it is likely to activate both inhibitory presynaptic M_2 and postsynaptic muscarinic receptors and as with physostigmine this may explain its lack of efficacy in this study (Bradbury et al. 1991).

This study showed that both scopolamine and mecamylamine impaired performance in the five-choice SRTT, but that the nature of the impairment differed. Although non-cognitive effects of the antagonists should be considered critically, notably in the case of mecamylamine, the differential impairments are not readily explainable as artefacts of such effects. In the five-choice SRTT rats must initially decide on a response and then make a choice response. After scopolamine, rats showed no deficit in reaction time but selected the wrong hole leading to impaired accuracy. This deficit in selection could be due to an effect of scopolamine on discrimination, memory or motivation. By contrast, after mecamylamine rats would select the correct hole but would take longer deciding on the selection. The difference between the two antagonists suggests that muscarinic and nicotinic receptors may be important at different stages of information processing; nicotinic receptors may have an important role in the early stages of stimulus evaluation, whereas muscarinic receptors may be important in later processing stages involving response selection.

At the doses tested, combinations of the two antagonists showed no significant synergistic or additive effects, although this possibility should be examined further. In contrast to some studies, physostigmine did not improve performance although this may not be surprising considering its pharmacokinetic and neurochemical profile. Oxotremorine also failed to affect attention, suggesting that this model may predict the limited therapeutic potential and the reported lack of clinical efficacy of such non-selective muscarinic agonists (Davis et al. 1987).

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