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European Journal of Pharmacology 393 (2000) 147–154

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Nicotine in an animal model of attention

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Accepted 21 January 2000

Abstract

Studies in smokers have suggested that at least part of the improved psychomotor performance produced by nicotine is the result of an effect on attention. Many animal experiments have assessed the effects of nicotine and its antagonists on diverse types of learning and memory but relatively few have looked at it in tasks designed to assess attention. In a five-choice serial reaction time task (5-CSRTT), rats with restricted access to food were presented with an array of five holes; illumination of a randomly selected hole signalled that a nose-poke into it would be reinforced by food presentation. Initially, signal length and the inter-trial interval (ITI) were varied and the procedure was demonstrated to satisfy some criteria for a vigilance task. The effects of nicotine on deficits in performance induced by varying signal length and ITI were assessed. Under appropriate conditions, small doses of nicotine increased the percentage of correct responses (accuracy), decreased omission errors and reaction time, and increased anticipatory responses. Subsequently, the effects of varying the ITI were examined more extensively in a slightly modified task. Here, nicotine produced small but robust, highly significant dose-related increases in accuracy, as well as decreases in omission errors and reaction times. Nicotine also increased accuracy when light stimuli were presented in an unpredictable manner. The nicotine antagonist mecamylamine produced a modest deficit in reaction time only. It is concluded that appropriate doses of nicotine can produce robust improvements in performance of normal rats in an attentional task. The effect cannot be attributed easily to changes in sensory or motor capability, learning or memory and may provide the measures needed to investigate the neuropharmacological and neuroanatomical bases of the elusive attentional effect of nicotine.

Keywords: Nicotine; Mecamylamine; Cognition; Attention

1. Introduction

The expressed reasons for human smoking have included reports that it aids concentration, leading to suggestions that such possible benefits may constitute a major motive for the use of tobacco (Warburton, 1990). For several decades, the validity of such reports has been supported by findings from laboratory studies in both animal and human subjects suggesting that nicotine can improve aspects of psychomotor performance and cognition. Some studies reported that nicotine could robustly increase rates of operant responding for food or other reinforcers (Morrison, 1967; Risner et al., 1985; Goldberg et al., 1989). Other studies reported variously that underlying processes such as attention, learning and memory were all improved by nicotine, but findings of one report were rarely reproduced by another which was perhaps not surprising due to the enormous variations in methodology (Garg and Holland, 1968; Battig, 1970; Nelsen and Goldstein, 1972). These early studies are summarised elsewhere (Hunter et al., 1977; Stolerman, 1990). This paper describes how continuing persistent and increasingly systematic studies have, over the years, supported the essence of these inconsistent and variable initial results and have progressed towards establishment of methods that yield relatively well-defined and reproducible effects.

A large proportion of the studies in animal subjects have used tasks designed to assess different forms of learning and memory. However, from human research, notably with smokers, it is apparent that nicotine's cognitive benefits are predominantly and most consistently seen in tasks which tax information processing ability and sustained attention (Warburton, 1990; Parrott and Craig, 1992). Therefore, the focus on learning and memory in

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0014-2999/00/$ - see front matter
PII: S0014-2999(99)00886-9

many studies with animals is a little difficult to understand. Only under rather specific conditions has it been found that nicotine improves memory in humans (Stolerman et al., 1995).

Studies of nicotine in smokers are to varying extents confounded by baseline shifts associated with the nicotine withdrawal syndrome. Tobacco withdrawal is thought to be associated with an expressed difficulty in concentrating upon a task and by actual impairments in task performance. If the baseline condition for assessing the effect of nicotine is subnormal due to withdrawal, then the effect of nicotine will appear larger than it really is. This has led to the suggestion that in the worst case the cognitive enhancing effects of nicotine are nothing more than the result of relief from withdrawal-induced deficits (Hatsukami et al., 1991; Parrott and Roberts, 1991). However, some studies have attempted to identify a 'normal' baseline where smokers are not in withdrawal, and have still demonstrated some enhancement of performance. Thus, studies that have attempted to control for the confounding effects of withdrawal have still demonstrated beneficial effects of nicotine (West and Hack, 1991). A small number of studies have also found that nicotine can improve attention in non-smokers using rapid visual information processing tasks (Wesnes and Warburton, 1984; Foulds et al., 1996). These findings are paralleled by the many observations of improvements in laboratory animal performance upon exposure to the acute effects of nicotine (Stolerman, 1990; Stolerman et al., 1995). Therefore, it seems that performance enhancement need not be attributed exclusively to either the direct effects of nicotine or to the effects of nicotine withdrawal; the two phenomena appear to co-exist, such that improvements in performance are most likely greater in nicotine-dependent individuals than in non-smokers.

In view of the deficits in attention in aging and age-related diseases, it is surprising that few animal paradigms for assessing attentional function have been developed (Lawrence and Sahakian, 1995). Moreover, attentional deficits may occur in the early stages of Alzheimer's disease and neurotransmitter systems that are affected in this disease, such as the cholinergic and noradrenergic systems, are known to be involved in attentional processes (Light, 1991; Robbins and Everitt, 1995). Thus, given the effects of nicotine in humans described above and the evidence that nicotine can improve attention in patients with Alzheimer's disease and attention-deficit hyperactivity disorder (Jones et al., 1992; Connors et al., 1996), there is a need for valid animal tasks assessing attention. Furthermore, when using animals the confounding effect of withdrawal-induced deficits is not a problem. Although an early study by Nelsen and Goldstein (1972) demonstrated that chronic treatment with 0.4 mg/kg nicotine for 3 weeks improved the performance of rats on a simple reaction time task, this has not been replicated and the validity of this task has been questioned (Turchi et al., 1995). More recently, Muir et al. (1995) showed that forebrain cholinergic lesion-induced deficits in a five-choice serial reaction time task (5-CSRTT) were reversed by nicotine (0.06–0.1 mg/kg) in rats. By contrast, Turchi et al. (1995) demonstrated no effect of nicotine (0.09–0.8 mg/kg) in non-lesioned animals in a vigilance task, where rats were trained to discriminate between signal and non-signal events. However, they did show that the nicotinic antagonist mecamylamine (1.0 mg/kg) impaired performance implying that nicotinic receptors were important in attention. Moreover, mecamylamine (3 mg/kg) can impair the performance of middle-aged rats on the 5-CSRTT (Jones and Higgins, 1995).

The 5-CSRTT used by Muir et al. (1995) was based on paradigms used to study the effects of arousal and environmental factors on human performance (Hockey, 1984). In the adaptation of this task for animals, a rat is required to respond to brief illumination of stimulus lights that occur unpredictably in one of five spatial locations; responding in the correct location is reinforced by presentation of food (Carli et al., 1983). To perform the task a subject must maintain sustained attention over the entire test session. However, due to the spatial nature of this task it is likely to have aspects of divided attention and visual search (Carli et al., 1983; Gutnikov et al., 1994). Parasuraman (1979,1985) has established criteria for the construct validity of vigilance tasks, which include sensitivity to (i) the frequency with which the events to be detected are presented, (ii) the strength (intensity) of the events, and (iii) the overall load on the cognitive ability of the organism. In addition, to capture the essence of the concept of vigilance, there should be a decrease in the detectability of events over time (i.e., the vigilance decrement).

In the present experiments, the 5-CSRTT was used to investigate the effects of nicotine in normal adult rats. Initially, various task parameters were manipulated to ascertain whether the task presented to the rats complied with some of the established criteria for a vigilance task in humans. The effects of nicotine were tested under conditions that differed from those present during the intervening daily training sessions; these changes in conditions, involving manipulations of stimulus duration and frequency (inter-trial interval, ITI), were intended to impair performance and, thus, render it more likely that a facilitatory effect of nicotine could be detected. It is important to note that this task appears to have predictive validity since manipulations of the cholinergic and GABA-ergic systems produce changes in performance in this task similar to those seen in humans performing attentional tasks (Robbins et al., 1989; Jäkälä et al., 1992; Muir et al., 1992a,b). If so, then the prediction should be that as with non-smoking humans, and smokers not suffering from withdrawal, nicotine should improve performance in drug-naive rats. Conversely, if some tonic level of nicotinic–cholinergic neurotransmission is important for normal cognitive function, then administration of nicotinic antagonists should

impair performance. Mirza and Stolerman (1998, 2000) have presented a more detailed account of some of these experiments.

2. Materials and methods

2.1. Subjects

Male hooded rats initially weighing 250–300 g were used throughout. They had access to amounts of food that restricted their weights to 80% of those of freely feeding animals of the same sex, strain and age, and they were housed individually in rooms with controlled temperature (20–22°C) and a daily light–dark cycle. Water was available freely at all times.

2.2. Apparatus

Sound-insulated and ventilated enclosures were used to house an aluminium chamber measuring $26 \times 26 \times 26$ cm (Paul Fray, Cambridge). The back wall of the chamber had five, 2.5 cm^2 holes placed 5 cm above floor level, equidistant from a food tray and pellet dispenser at the front of the chamber. Each hole had a photocell beam across its entrance and could be illuminated by a lamp at its rear. There was a flap for recording entries into the food tray. A houselight was situated in the roof of the chamber, and experiments were controlled by a computer in an adjoining room.

2.3. Training procedures

During initial shaping sessions, rats were trained to collect food pellets delivered without any response requirement, and then to nose-poke into the holes to obtain food. From the fifth session, training on the 5-CSRTT began. These procedures were adapted from those of Carli et al. (1983).

After a pre-determined delay (ITI), a randomly chosen hole was illuminated. If a rat responded (i.e., nose-poked) in the illuminated hole while the light was on or within a fixed period of time after it had gone out (limited hold), a food pellet was delivered and a correct response was registered. If a rat responded in a hole other than the one which had been illuminated, a commission error was registered. If, by the end of the limited hold, the rat failed to respond an omission error was registered. Either a commission or omission error resulted in a time-out during which the house light was extinguished; if a rat responded in a hole during the time-out, the timer was restarted. The next inter-trial (ITI) began when the rat opened the door to the food tray, either after making a correct response or after the end of the time-out in other cases. Anticipatory responses during an ITI were registered but had no consequence.

Each training session consisted of 100 trials or 30 min, whichever was the shorter. During training, the stimulus duration and limited hold were progressively shortened, and the ITI was progressively increased. The final parameters were 1 s for the stimulus duration and 5 s for the limited hold and time-out. In one experiment, the ITI varied from 5 to 30 s for different groups as explained below. Subjects were trained to a performance level of $> 80\%$ correct responses and $< 20\%$ omission errors.

2.4. Test sessions

Once performance reached criterion, experiments were performed to determine the effect of manipulating task parameters on performance and to assess the effects of nicotine and related substances. Performance was maintained at criterion level for a least 2 weeks before testing began. Tests with parameters varied as detailed below were performed twice a week with training sessions at standard parameters on intervening days. Similarly, dose–response tests with drugs were performed twice weekly; the saline vehicle and different doses of drugs were tested in each rat in random order, with training sessions on the intervening days.

2.5. Data analysis

Accuracy was assessed from the number of correct responses calculated as a percentage of the total number of responses (i.e., correct and incorrect responses). Omission errors were calculated as a percentage of the total number of stimuli presented. Responses in the apertures during the ITI constituted anticipatory responses. The correct response latency (reaction time) was defined as the mean interval between the onset of stimuli and nose-pokes into the correct aperture. Data were analysed using single- or multi-factor ANOVA, followed by Tukey HSD or Dunnett t tests for multiple comparisons where appropriate. A maximum value of $p = 0.05$ was allowed for effects to be considered as significant.

2.6. Drugs

Nicotine bitartrate, mecamylamine HCl, or scopolamine HCl (Sigma, Poole, Dorset, UK) was dissolved in 0.9% saline and injected subcutaneously into the flank of the rat at a volume of 1 ml/kg. All doses were calculated as those of the bases.

3. Results

3.1. Parametric manipulations of conditions

Three groups of rats ($n = 7–8$ each) were used to test the effects of signal lengths varying from 0.25–1.0 s, with

the ITI held constant at 5.0 s as in training (Mirza and Stolerman, 1998). Decreasing the stimulus duration reduced the percentage of correct responses and increased omission errors. The decrease in accuracy was accompanied by an increase in the reaction time for correct responses. Decreasing stimulus duration had no effect on the number of anticipatory responses.

In the next experiment, the effects of varying the ITI from 1.0–20 s were examined with stimulus duration held at 1.0 s as in training (Mirza and Stolerman, 1998). The percentage of correct responses decreased with ITI of either 10 or 20 s, as compared with 5 s during training. Increasing the ITI also increased the correct response latencies and anticipatory responses. Decreasing the ITI also impaired the percentage of correct responses and increased omission errors, increased latencies for correct responses, and decreased the number of anticipatory responses.

3.2. Initial studies of nicotine under conditions that impaired baseline performance

The effects of nicotine (0.0, 0.05, 0.15 and 0.4 mg/kg sc 10 min before a session) were tested with a within-subjects design in three separate experiments where conditions were adjusted in a manner intended to impair performance, based on the results of the studies described above. In the first of these studies, the effect of nicotine was tested on the performance of rats under weak signal conditions (stimulus duration = 0.25 s, $n = 12$). In the second study, the effect of nicotine on performance with long ITI was assessed (ITI = 20 s, $n = 11$). For this experiment, the session length was increased to 40 min, thereby allowing rats to complete 100 trials despite the increase in ITI. Finally rats were tested with nicotine under short ITI conditions (ITI = 1 s, $n = 12$).

When the stimulus duration was decreased, there was a decline (vigilance decrement) in the percentage of correct responses over time; nevertheless, there was no effect of nicotine at any dose tested. There was also no overall effect of nicotine on the latency to make a correct response, but there was a nicotine-time interaction; nicotine (0.05 mg/kg) reduced latencies in the last quarter of the 30-min sessions. Nicotine had no effect on omission errors but it did increase anticipatory responding, especially in the final third of the sessions (Mirza and Stolerman, 1998).

When the ITI was increased above that used for training, nicotine (0.15 mg/kg) increased the percentage of correct responses. This improvement in accuracy was not accompanied by a change in the time to make a correct response. Nicotine also decreased the percentage of omission errors at all doses tested and dose-dependently increased the number of anticipatory responses. In the study where the ITI was decreased below that used for training, nicotine (0.15 mg/kg) slightly increased the percentage of correct responses but had no effect on other measures. These effects of nicotine generally attained a moderate level of statistical significance ($p < 0.05$).

3.3. Studies with nicotine where ITI was varied separately during training and testing

Initially, the effects of nicotine were examined using a factorial design to separate the effects of varying the ITI during training and testing. A number of minor changes to the training procedure were instituted at this stage. These changes included the use of free-running sessions in which one ITI began immediately after a correct response or, in the case of an incorrect response, at the end of time-out. Additionally, the time-out for incorrect responses was reduced from 5 to 2 s, there was no time-out after omission errors, and green light-emitting diodes were used to illuminate the five holes instead of filament bulbs. Three groups of rats were used, trained with ITI of 5, 15 and 30 s (stimulus duration = 1 s, $n = 9–11$). Each group was then tested with nicotine (0.0, 0.05, 0.1, 0.2 and 0.4 mg/kg sc 10 min before a session); each dose was tested three times in each rat, with ITIs of 5, 15 and 30 s (Hahn, Stolerman and Shoaib, unpublished data).

Results are considered first for the overall effects of nicotine in all rats across all test ITI values ($n = 31$), and then the influences of variation in ITI during training or testing are described. Overall, nicotine produced dose-related increases in the accuracy of correct responding which reached a maximum at a dose of 0.2 mg/kg and declined at 0.4 mg/kg. The percentage of omission errors and correct response latencies were reduced at doses of 0.05–0.2 mg/kg but not in a dose-related manner; the maximal effect was seen already at 0.05 mg/kg, the smallest dose tested. Similarly, nicotine (0.05–0.2 mg/kg) slightly increased the number of anticipatory responses. All these effects of nicotine were statistically highly significant ($p < 0.001$ by three-factor repeated measure ANOVA).

Training at different ITI had little effect on most measures of overall performance of the task, although response latencies were slightly greater ($p < 0.05$) with the longest ITI ($p < 0.001$). Animals training with long ITI also made overall fewer numbers of anticipatory responses ($p < 0.001$). This last effect was seen mainly in the tests with long ITI, where animals trained with long ITI made many fewer anticipatory responses than animals trained with short ITI (training ITI-test ITI interaction, $p < 0.001$). There was no interaction between the effect of nicotine and the training ITI for measures of correct responding, response latency and omission errors. However, a small 0.05 mg/kg dose of nicotine increased anticipatory responding, but only in the group of rats trained with the longest ITI (drug-group interaction, $p < 0.01$).

Overall performance of the task was better when rats were tested with an ITI of 15 s than with ITI of either 5 or 30 s ($p < 0.001$ for the percentages of correct responses, omission errors, and latencies of correct responses). Antic-

ipatory responding increased progressively with ITI length ($p < 0.001$). However, for none of these measures was there a significant interaction of nicotine with the ITI used for testing. Thus, nicotine improved task performance regardless of the use of 5, 15 or 30 s ITI during the testing phase of the experiments.

3.4. Studies with nicotine where stimulus duration was varied during testing

In these studies, the impact of changes in the duration of the light stimuli was studied over a wider range of stimulus lengths than in the preliminary studies described above. One group of rats were used, trained with an ITI of 15 s and a stimulus duration of 1 s ($n = 11$). These rats were tested with nicotine (0.0, 0.05, 0.1 or 0.20 mg/kg sc 10 min before sessions); each dose was tested three times in each rat, with stimulus durations of 0.125, 0.25 and 1.0 s (Hahn, Stolerman and Shoaib, unpublished data).

Results are considered first for the overall effects of nicotine across all stimulus durations, and then any influences of variation in stimulus duration are described. Nicotine produced a dose-related increase ($p < 0.05$) in the accuracy of correct responding which reached a maximum at a dose of 0.1 mg/kg and declined slightly at 0.2 mg/kg. There were also dose-related reductions in the percentages of omission errors ($p < 0.001$) and correct response latencies ($p < 0.01$) at doses of 0.05–0.2 mg/kg and a dose-related increase in the number of anticipatory responses ($p < 0.001$).

Overall performance of the task, as assessed by correct responses, correct response latency and omission errors, was progressively degraded as stimulus duration decreased ($p < 0.001$ in each case). Anticipatory responding increased as stimulus duration decreased ($p < 0.001$). The effects of nicotine on the percentage of correct responses were most pronounced ($p < 0.001$) at the long 1.0 s stimulus duration used for training and there was a significant interaction of nicotine dose with stimulus duration ($p < 0.001$). However, the effects of nicotine on omission errors, correct response latencies and anticipatory responses did not interact with stimulus duration.

3.5. Study of nicotine when stimulus presentation was less predictable

Three groups of rats were used, trained with ITI of 5, 15 and 30 s (stimulus duration = 1 s, $n = 9–11$). Each group was then tested with saline and nicotine (0.1 mg/kg sc 10 min before a session) under conditions where the mean ITI was 5.0 s, but individual ITI varied unpredictably from 1.17 to 8.83 s. Performance in the undrugged state under these conditions was slightly poorer than under normal training conditions. Nicotine (0.1 mg/kg) increased the percentage of correct responses ($p < 0.01$) and reduced omission errors ($p < 0.05$), but was without significant effect on correct response latency or anticipatory responding (Hahn, Stolerman and Shoaib, unpublished data).

3.6. Studies with mecamylamine and scopolamine

Two groups of rats were used with similar baseline performances on measures of percentage correct responses, omission errors and correct response latency. Mecamylamine (0.0, 0.5, 1.6 and 5.0 mg/kg) was tested in one group 1 ($n = 8$) and scopolamine (0.0, 0.01, 0.03 and 0.1 mg/kg) in the other group ($n = 6$). Doses of drugs were based on those of Jones and Higgins (1995) and all injections were subcutaneous, 30 min before sessions. Mecamylamine had no effect on the percentage of correct responses at any dose tested but it did induce a significant, dose-dependent increase in the percentage of omission errors ($p < 0.001$). Mecamylamine also increased correct response latencies ($p < 0.05$) and decreased anticipatory responses ($p < 0.05$). 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.

At the highest dose tested of scopolamine (0.1 mg/kg), there was a profound deficit in correct responses and an increase in omission errors ($p < 0.01$ for both measures). Scopolamine had no overall effect on correct response latency but produced a significant, dose-dependent decrease in anticipatory responses ($p < 0.01$). Observations showed that after the highest dose (0.1 mg/kg) of scopolamine rats were more active and difficult to handle (Mirza and Stolerman, 2000).

4. Discussion

The major features of the findings presented here are, firstly, that nicotine increased the accuracy of responding in the 5-CSRTT and secondly, that in the newer experiments with the slightly modified procedure, the magnitude of the effect was related to the dose of nicotine in most studies. It is unclear which of the several small changes in the experimental procedure was responsible for this finding. It may simply be that the use of an increased number of subjects in the major experiment improved precision sufficiently for small effects to be resolved. Alternatively, one or more of the steps taken to modify the training procedure may have been responsible.

The nicotine antagonist mecamylamine produced deficits in reaction time only, and even that was at a rather large dose, whereas scopolamine impaired accuracy. The difference between the two antagonists may imply that muscarinic and nicotinic receptors may be important at different stages of information processing; nicotinic receptors may have a role in the early stages of stimulus evaluation, whereas muscarinic receptors may be important in later processing stages involving response selection.

This hypothesis could be tested using tasks that place different emphasis on different stages of information processing.

In the initial experiments with nicotine, its effect was interpreted as a possible vigilance enhancement. The task showed characteristics required of a vigilance task because manipulations of stimulus duration and ITI degraded performance, and the effect of nicotine was first detected with long ITI where sustained attention was required. However, in the current form of the procedure, tested in a larger number of rats and with more doses of nicotine, the value of the ITI did not seem to be particularly important and a vigilance decrement was not apparent. Therefore, the nature of the attentional enhancement produced by nicotine, and the optimal conditions for demonstrating it, require further investigation. The enhancement may reflect actions on one or more of the diverse aspects of attention reflected in the task (i.e., selective, sustained and divided attention) and it might also be mediated indirectly by an increased ability of the rat to position itself appropriately prior to stimulus onset. It must also not be overlooked that the maximum magnitude of attentional improvement was very small, no more than 5–6%. Small effects are characteristic for many drugs in cognitive tasks and large improvements in performance that has reached a high stable level after protracted training can hardly be expected. Working with such small effects means that rigorous experimental designs must be employed to ensure that the impact of all other variables is eliminated by strict randomisation or counterbalancing.

Perhaps one of the greatest concerns in studies of the attentional and cognitive effects of drugs has been variability of results between one experiment and another; the problem is magnified by the diversity of procedures, such that when findings from different laboratories appear inconsistent, it is difficult to know whether results are truly irreproducible or are procedure-dependent. Therefore, particular focus is given here in considering whether findings suggestive of attentional enhancement in the 5-CSRTT are robust and reproducible. Firstly, all laboratories that have reported on nicotine in this procedure have described improvements in task performance. These are the groups in Cambridge (Muir et al., 1995), London (Mirza and Stolerman, 1998) and France (Blondel et al. 1998, 1999), to which the new data discussed above may be added. However, there are some important variations in outcome. The older data showed effects at one dose only (Mirza and Stolerman, 1998). Only in the present studies and those of Mirza and Stolerman (1998) have improvements in accuracy been reported in addition to those for measures like response latencies that may be influenced by non-attentional factors. Therefore, it is particularly important to note the extent to which the present findings include evidence for the robustness of the effects. The reason for the absence of any effect on accuracy in the studies of Blondel et al. (1999) may be their use of short duration stimuli during testing performance, a manipulation shown by the present studies to weaken rather than enhance the effect of nicotine on accuracy.

With regard to dose-related increases in accuracy, these were seen in three groups of rats in the experiments involving variations in ITI, and then confirmed in the study examining the role of stimulus duration. A significant increase in accuracy was also seen in the single-dose study with variable (less predictable) ITI, and in the previous work of Mirza and Stolerman (1998). Therefore, this seems to be a relatively robust effect although the precise training and testing conditions to ensure its optimal reproduction have yet to be identified. Furthermore, it is not clear from the data available how many times the effect may be reproduced in a stable manner in the same animals. The behavioural effects of nicotine are characterised by complex patterns of tolerance and sensitisation (Stolerman, 1990), and there may also be influences of repeated drug exposure on at least some of the indices employed in the 5-CSRTT. The present experiments also show reductions in omission errors in the three separate studies on ITI duration, stimulus duration and stimulus predictability, although in no case was a dose-related effect demonstrated. The latency of correct responses was reduced and the numbers of anticipatory responses were increased in the separate studies on ITI duration and stimulus duration. Other studies also showed reductions in omission errors and increases in anticipatory responses (Mirza and Stolerman, 1998; Blondel et al., 1998, 1999).

One of the advantages of the 5-CSRTT is that it provides a number of inter-related indices of response. In this report, emphasis is placed upon the correct responses expressed as a percentage of the total number of responses; such a measure of response choice, as contrasted with response rate, might be expected to be relatively independent of the overall proclivity of subjects to respond at a faster or slower rate. Such changes in rate are of course ubiquitous in behavioural pharmacology. The three other measures for which data were presented above (omission errors, response latency, anticipatory responses) also showed changes after administration of nicotine in different experiments. However, these effects were not demonstrated to be consistently dose-related, perhaps because in some cases, even the smallest dose tested of nicotine produced a maximal effect. Tests at smaller doses are therefore required. Another reason for the lack of dose–response relationships may be the probability that these measures are sensitive not only to changes in attention, but also to overall response-rate increasing or decreasing effects of nicotine. The combined influence of attentional and rate effects of the drug could obscure a clean dose–response relationship for either effect alone. The doses of nicotine used in the study were similar to those which can increase locomotor activity and rates of positively reinforced lever pressing (reviewed by Stolerman, 1990). Thus, reductions in omission errors and in response latencies, if

not accompanied by increases in the accuracy of response choice, would not provide unequivocal evidence for an attentional effect of nicotine. Similarly, the increases in the numbers of anticipatory responses produced by nicotine may easily reflect a response bias consequent upon increased motor activity; anticipatory responses do not increase the numbers of food reinforcers obtained or result in such reinforcers being obtained earlier than would otherwise be the case. A drug-induced increase in anticipatory responding, reflecting an aspect where efficiency of responding is degraded rather than improved, may be the almost inevitable result of drug-induced increases in locomotor activity.

One of the critical issues facing investigations focused on rather abstract constructs such as attention is whether observed performance changes might be explicable in other ways. The possibilities include changes in learning, motivation, sensory capability, and motor performance. An action of nicotine on learning can hardly be a factor in the present experiments since rats are trained to a high level of stability before drug testing begins so there should be no new learning taking place under the influence of nicotine. An improvement in sensory function (i.e., ability to detect the light stimuli) seems an unlikely explanation; if nicotine was enhancing ability to see the stimuli, then its effects would be expected to be most marked under conditions where sensory ability was taxed most severely, as in the study with stimuli of short duration. In fact, as noted above, the effects of nicotine were weaker rather than stronger under such conditions. It also seems unlikely that nicotine would increase the strength of motivation for food since its effects on food intake in the rat, while dependent upon factors such as sex and type of food, are consistently depressant (Grunberg et al., 1985, 1986). However, investigations to examine the profile of changes in performance produced by varying levels of food deprivation (cf. Carli and Samanin, 1992) would add usefully to the knowledge base available for interpreting drug effects in this task. Simple increases in motor ability, reflecting increases in locomotor activity produced by nicotine, could explain the effects seen for speed-related measures such as omission errors, response latency and anticipatory responses. However, motor stimulation cannot explain why rats make increased numbers of nose-pokes selectively into the correct hole which varies randomly from trial to trial. Therefore, of the measures taken, it is only the percentage of correct responses that unequivocally indicates an attentional effect. Reductions in omission errors and response latencies, accompanied by increased anticipatory responding, are often associated with increased accuracy under different conditions in the undrugged animal but, in view of the complex pattern of drug-induced motor changes, they may be unreliable for pharmacological work.

Future studies, as well as characterising further the conditions under which nicotine-induced attentional changes may be assessed in the 5-CSRTT, will also focus on the many questions remaining unanswered about their neurobiological basis. Little is known at present about the nicotinic receptor subtypes at which the effect is presumed to originate, or about the neurotransmitter systems that may be involved through their interactions with the nicotinic–cholinergic mechanisms, or about the neuroanatomy of the effect.

Acknowledgements

The research described above was supported by the Medical Research Council.

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