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Effects of cholinergic and non-cholinergic drugs on visual discrimination and delayed visual discrimination performance in rats

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Abstract. The effects of several centrally active drugs were investigated using two visual discrimination tasks: a two-lever food-rewarded conditional brightness discrimination, and a similar conditional brightness discrimination where a delay was introduced between the disappearance of the stimulus and the opportunity to respond on the levers for food. The substances tested (amphetamine, scopolamine, methylscopolamine, physostigmine, diazepam and β-carboline benzodiazepine receptor antagonist, ZK 93426), all produced differing profiles of action on the performance parameters recorded. In the simple conditional visual discrimination, amphetamine increased omissions without significant effects on accuracy or response latency. Physostigmine enhanced response latencies and failures to respond without significant effects on accuracy. ZK 93426 had no consistent effects on accuracy although at higher doses, some increase in response latency was seen in the delayed responding version of the visual discrimination task. Diazepam had negative effects on all parameters in both discrimination procedures. Scopolamine disrupted responding, but not accuracy in the simple discrimination, whereas accuracy was reduced in a dose, but not delay dependent manner in the delayed discrimination. A similar effect to that observed with scopolamine was observed following methylscopolamine in the delayed discrimination procedure. In the simple visual discrimination small increases in accuracy were recorded, accompanied by increased response latencies.

Key words: Visual discrimination – Delayed responding – Rats – Memory – Scopolamine – Methylscopolamine – Amphetamine – Physostigmine – Diazepam – ZK 93426

As interest grows in the cognitive effects of drugs, and with it possible treatment strategies for cognitive disorders, increasing attention has been given to the effects of benzodiazepines and cholinergic agents. The reasons for this are readily apparent: disruptions of memory have been repeatedly demonstrated in clinical research/human studies utilising various benzodiazepines (Dorow et al. 1987; Borbely et al. 1988) or anti-cholinergics, typically scopolamine (e.g. Flicker et al. 1990). On the other hand, given the current level of concern over cognitive dysfunction in old age, amnestic substances may be useful in characterising animal models of cognition.

Cognitive deficits in Alzheimer's disease have been linked to the loss of cholinergic function in the cortex and hippocampus (Coyle et al. 1983), a link which has led to increasing attempts to characterise the effects of altered central cholinergic function. Generally the results have been disappointing. Although there are several reports indicating positive effects of physostigmine (Warburton and Brown 1972; Dunnett 1985; Rupniak et al. 1990) and negative effects of scopolamine on cognition in animals (Warburton and Brown 1971; Bartus and Johnson 1976), there are almost as many indicating no effect, or effects only under particular conditions (for a review see Hagan and Morris 1989). Thus, despite the widepread acceptance of the cholinergic hypothesis of cognitive function and scopolamine as a prototypical amnestic agent, unequivocal data supporting such effects are absent. Moreover, complex behavioural procedures have tended to demonstrate changes in discriminative ability following cholinergics rather than amnestic effects (Milar 1981; Ksir and Slifer 1982; van Haaren and van Hest 1989). Indeed, increasing the intensity of the stimulus can prevent or counteract the disruptive effects of scopolamine on performance (Evans 1975; Ksir 1975).

Until recently delayed responding procedures were comparatively rare in operant research using rodents. Paradigms such as delayed matching to sample are well established in both monkey and human research (Bartus and Johnson 1976; Flicker 1990) but have proven difficult, if not impossible to establish in rodents (Dunnett 1985, but see Spencer et al. 1985). Delayed conditional discrimination offers several advantages over simple discrimination procedures in that delay dependent and de-

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lay independent effects can be assessed simultaneously with the ability to discriminate the stimulus. An overall parallel, i.e. delay independent shift in performance, suggests a non-specific effect on stimulus sensitivity as opposed to effects on forgetting. Following Dunnett's initial paper on a delayed matching-to-position procedure in rats (Dunnett 1985) several analogous delayed auditory and visual discrimination procedures have been reported. Recently a series of publications have demonstrated the usefulness of such procedures in assessing age (Dunnett et al. 1988), sex (van Hest et al. 1990) and various drug effects on performance (Kirk et al. 1988; Tan et al. 1989, 1990; Sahgal et al. 1990).

In order to explore further the effects of putative amnestic and promnestic substances, a series of experiments were undertaken investigating the activity of these agents on a food rewarded conditional visual discrimination task, and on a conditional visual discrimination procedure with a series of delays introduced between the disappearance of the stimulus and the opportunity to respond.

Materials and methods

A similar training and housing regimen was used for all experiments. Any differences in the procedures used are noted in the relevant passage, e.g. drug doses, statistics.

Subjects

The subjects were 32 male Wistar rats (2 groups of 16; Tierzucht und haltung, Schering AG) weighing approximately 250 g at the start of training. Rats were individually housed with water freely available but fed a restricted diet of lab chow (15–20 g per day).

Equipment

Sixteen Coulbourn operant chambers (Coulbourn Instruments Inc, Lehigh Valley, PA, USA), fitted with two levers, a pellet dispenser, house and centrally positioned cue lights, were connected to, and controlled by an IBM XT and MedLab Interface (Medlab Associates Inc, East Fairfield, VT, USA). For eight boxes the levers were retractable and for eight boxes they were fixed permanently in the test chamber. Programs were written and data collected using the OPN programming system (Spencer and Emmett-Oglesby 1985).

Procedure

Visual discrimination. Rats were initially trained to press either lever for food on an FR 1 schedule of reinforcement. Following shaping, the animals were trained to press one lever when the central cue light was brightly illuminated and the other lever when the cue light was dimly lit. After a period of initial testing, in which only correct responses were allowed and the order and time of appearance of bright and dim cue lights was predictable, training began with the final test parameters. In this procedure a trial began with the illumination of the central (bright or dim) cue light, following which the rat had 5 s in which to respond. A correct response (e.g. for the bright stimulus the right lever, for the dim the left) resulted in the delivery of a 45 mg food pellet, the illumination of the tray and the switching off of the cue light. There followed a variable interval timeout of 5 s mean duration before a new trial began. An incorrect response or no response in 5 s resulted in the termination of the trial, cue light extinguished, no food delivered and a variable interval timeout of mean duration 20 s. Each rat received 100 trials per day, 5 days per week; bright and dim stimuli appeared with equal probability but in a different random order on each test day. The difference in intensity between the bright and dim stimulus was adjusted individually for each rat by means of a 10 Kohm variable resistor until performance was stable at approximately 80% correct responses per session over at least ten sessions. Training to stability took between 10 and 16 weeks depending on the individual animal.

Delayed visual discrimination. The initial training procedure was identical up to stability. After the rats had satisfactorily acquired the initial discrimination the parameters were changed. The two levers were withdrawn from the box and the cue light was illuminated for 5 s, at the end of which time the cue light was turned off and the levers introduced into the chamber for 5 s; this represented the 0 delay condition. Over several weeks the rats were introduced to several delays at first 0, 2, 4 and 8 s but later 0, 5, 15 and 45 s. Each delay was presented 64 times (32 bright and 32 dim trials) in a different random order each day to give a total of 256 trials per session. Rats were trained until performance was stable at approximately 75–80% correct in the 0 delay condition over ten sessions. Training to stability took a further 16–20 weeks. Only 12 of the

Table 1. Summary of doses, pretreatment times and rats tested in each of the two visual discrimination procedures. Each series of drug tests began with the appropriate vehicle control. For more details see text under Materials and methods

	Dose mg/kg	Pretreatment time (min)	Number responding at all doses
Visual discrimination			
Scopolamine	0.02, 0.078, 0.313, 0.46, 0.625	30	7/16
Methylscopolamine	0.078, 0.313, 0.625	30	16/16
Physostigmine	0.025, 0.05	15	15/16
Amphetamine	0.078, 0.313, 1.25, 1.75	30	5/16
Diazepam	0.313, 1.25, 5, 7.5, 10, 15	30	13/16
ZK 93 426	0.313, 1.25, 5	30	16/16
Delayed visual discrimination			
Scopolamine	0.078, 0.313, 0.46, 0.625	30	10/10
Methylscopolamine	0.078, 0.313, 0.46	30	8/10
Diazepam	0.313, 1.25, 5, 10	30	11/11
ZK 93 426	1.25, 5, 10	30	12/12

original 16 rats acquired the task to a satisfactory standard during this time.

Drug testing. All drugs were suspended in a 1 ml/kg volume of 10% Cremophor EL (BASF, Ludwigshafen, FRG), and injected IP Tuesday and Friday in order of ascending dose. Each dose was given once and each series began with vehicle control. There was a slight drift upwards in the baseline over the course of the experiments (approximately 20 weeks after stability for the conditional discrimination, and 16 weeks for the delayed discrimination). No obvious trend was discernible within each drug series tested (average duration 3 weeks). Drugs were obtained from the following sources: ZK 93426 was synthesised at Schering by Dr. R. Schmiechen; scopolamine hydrobromide, Sigma Chemie GmbH, Deisenhofen, FRG; methylscopolamine hydrobromide, amphetamine sulphate and physostigmine salicylate, Merck, Darmstadt, FRG; and diazepam from Stada Arzneimittel, Bad Vilbel, FRG. The doses used in both procedures along with the pretest injection times are shown in Table 1. The higher doses of scopolamine (0.46 mg/kg and above) and diazepam (above 5 mg/kg) were tested with an interval of 1 week between drug doses.

Data analysis

Several parameters were collected and the data analysed using, in the case of the simple visual discrimination, a one factor repeated measures analysis of variance (ANOVA), and, for the delayed visual discrimination data, a two-factor repeated measures ANOVA (one factor drug and the second factor delay); analyses were carried out using the SAS statistical package. Following a significant result, multiple comparisons were carried out by means of the Tukey test. Several different performance parameters were noted, including percent correct responding (calculated as total correct responses divided by total trials on which a response occured); latency to respond following onset of the stimulus and number of trials in which the subject failed to respond.

The parameters are all calculated on the basis of the number of trials on which a response occurred. It follows that when subjects respond on only a small number of trials results may become highly biased. Therefore a criterion was adopted: data were used in the statistical analysis only when the subject had responded on at least 20% of trials for each drug session. Typically, higher doses of drugs disrupted responding in some subjects but not others.

Results

Visual discrimination

The overall ANOVA F statistics are shown for all substances discussed in Table 2. Pairwise comparisons between treatments were made using the Tukey multicomparisons test (multiple test level $\alpha = 0.05$). Figures 1 and 2 illustrate the results; only differences to control are marked by an asterisk.

Scopolamine induced significant dose related increases in latency to respond and missed trials. Effects on accuracy were less consistent. A slight decline in the number of correct responses was observed in almost all animals at higher doses. As with amphetamine, scopolamine caused many rats to fail to respond at all doses (9 from 16); in contrast to amphetamine, the trend towards failure to respond was more clearly observable from lower to higher doses.

Methylscopolamine also exerted significant effects on latency to respond and missed trials similar to those effects seen with scopolamine. However, unlike scopolamine, methylscopolamine did not cause any animal to stop responding completely at the doses tested. Methylscopolamine induced small, consistent and significant increases accuracy in comparison to vehicle (0.313 and 0.625 mg/kg).

Physostigmine (0.05 mg/kg) induced a significant increase in number of missed trials in comparison to control; one animal failed to respond at the higher dose tested. At the lowest dose tested rats responded significantly quicker than under vehicle treatment. No significant effects against control were observed in any of the other performance parameters.

ZK 93426 had no significant effects on accuracy or response latency. There was a small increase in missed trials; post hoc testing revealed significant differences between doses but not between doses and vehicle.

Diazepam exerted significant effects on all parameters measured. Accuracy was reduced, in comparison to vehicle, as measured by % correct responding, at 10 and 15 mg/kg. Both latency to respond and number of trials missed increased approximately in line with increasing dose, although only the highest dose in each case was significantly different from vehicle. Three animals failed to respond at all doses and were dropped from the statistical analysis. All these subjects showed similar effects to those observed in the remaining rats.

Table 2. Summary of one factor repeated measures ANOVA F-values on the various parameters assessed in the simple visual discrimination procedure

		% Correct	Latency	Misses
Scopolamine	F (5,30)	2.146	12.601***	21.911***
Methylscopolamine	F (3,45)	4.749**	32.615***	36.162***
Physostigmine	F (2,30)	1.066	5.98**	4.706*
Amphetamine	F (4,16)	0.639	2.738	3.566*
Diazepam	F (6,72)	138.408***	28.552***	6.422***
ZK 93 426	F (3,45)	0.661	1.129	5.526**

*$P<0.05$
** $P<0.01$
*** $P<0.001$

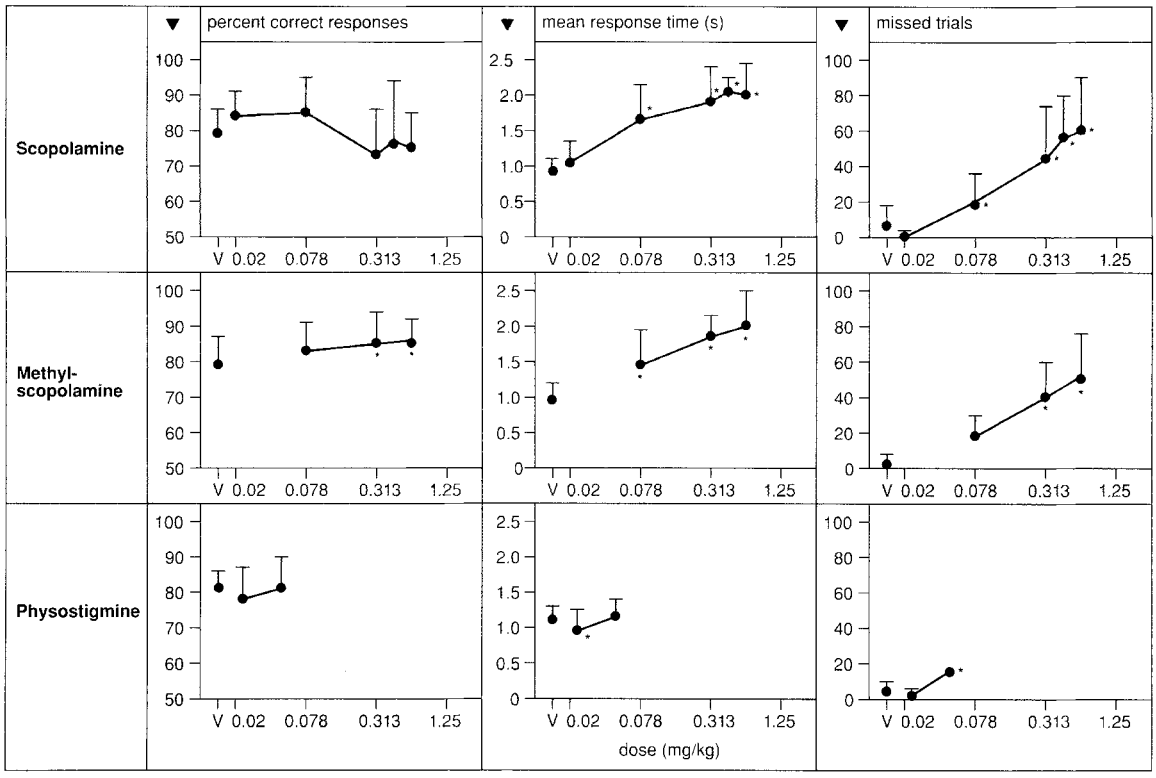

Fig. 1. The effects (means and standard deviation) of the cholinergic agents scopolamine, methylscopolamine and physostigmine on a visual discrimination procedure using rats. *V* = drug vehicle; * = significant difference to vehicle control ($P = 0.05$). For further details see also Tables 1 and 2 and text under Materials and methods and Results sections

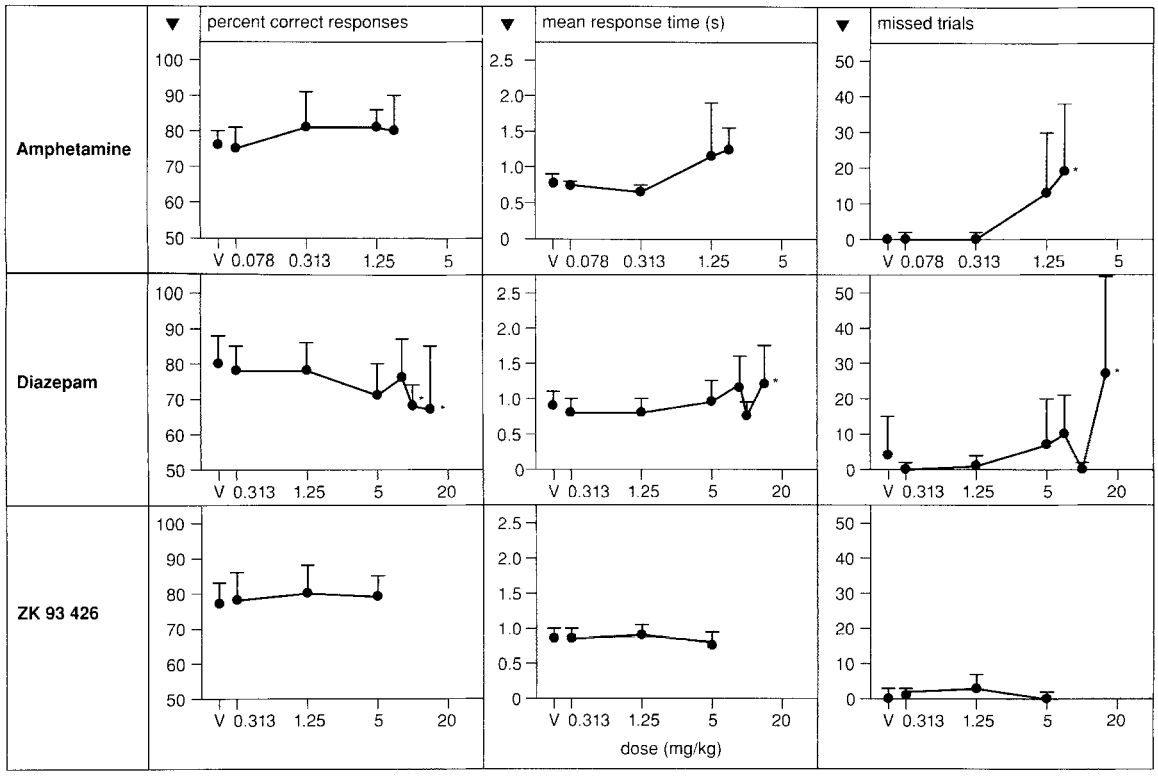

Fig. 2. The effects of amphetamine, the full benzodiazepine receptor agonist diazepam, and the benzodiazepine receptor antagonist ZK 93426. *V* = drug vehicle; * = significant difference to vehicle control ($P = 0.05$). For further details see also Tables 1 and 2 and text under Materials and methods and Results sections

Table 3. Summary of the *F*-values for main and interaction effects of the 2-factor repeated measure ANOVAs performed on the accuracy (as measured by % correct scores) and latency to respond in the delayed visual discrimination procedure

		% Correct	Latency
Scopolamine			
Dose	F (4,171)	56.11***	25.25***
Delay	F (3,171)	39.36***	3.87*
Dose × delay	F (12,171)	1.61	0.66
Methylscopolamine			
Dose	F (3,105)	45.94***	30.96***
Delay	F (3,105)	36.2***	3.22*
Dose × delay	F (9,105)	1.12	0.26
Diazepam			
Dose	F (4,190)	26.33***	33.97***
Delay	F (3,190)	74.3***	0.11
Dose × delay	F (12,190)	1.34	0.72
ZK 93 426			
Dose	F (3,165)	2.57	18.18***
Delay	F (3,165)	52.17***	1.61
Dose × delay	F (9,165)	0.96	0.16

* $P<0.05$; ** $P<0.01$; *** $P<0.001$

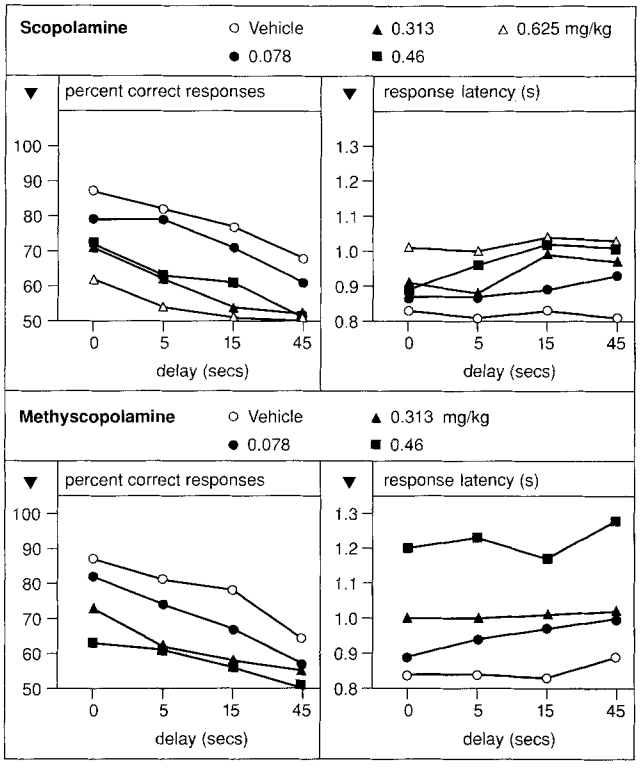

Fig. 3. The effects of the cholinergic antagonists scopolamine and methylscopolamine on accuracy and speed of responding in a delayed response visual discrimination procedure in rats. Figures show mean values for accuracy and speed of responding with different delays in the opportunity to respond after the disappearance of the stimulus. For further details see Tables 1 and 3 and text under Materials and methods and Results

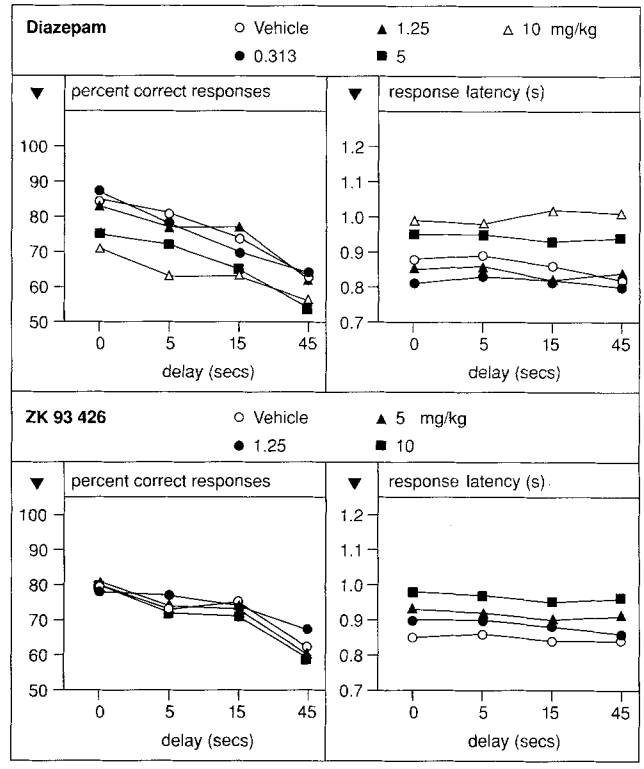

Fig. 4. The effects of the benzodiazepine receptor ligands diazepam and ZK 93426 on accuracy and speed of responding in a delayed response visual discrimination procedure in rats. Figures show mean values for accuracy and speed of responding with different delays in the opportunity to respond after the disappearance of the stimulus. For further details see Tables 1 and 3 and text under Materials and methods and Results

Amphetamine exerted a significant effect only on missed trials, the highest dose (1.75 mg/kg) causing a significant increase in failure to respond. Amphetamine exerted very disruptive effects on responding: only 5 rats from 16 completed all doses. In general slight increases in latency to respond and missed trials were observed in all rats tested, followed by an almost total failure to respond at one or two doses.

Delayed visual discrimination

The overall ANOVA F statistics are shown for all substances discussed in Table 3. Pairwise comparisons between treatments were made using the Tukey multicomparisons test (multiple test level $\alpha = 0.05$). Figures 3 and 4 illustrate the results. Data concerning missed trials are not reported.

Scopolamine induced a significant dose-dependent parallel shift down in the delay curve; all doses tested reduced accuracy. Between consecutive control sessions, latencies to respond and missed trials were constant across delays; scopolamine increased the latency to respond more at longer than shorter delays.

Methylscopolamine also induced a similar delay independent impairment of accuracy at all doses tested. Similar effects on latency to respond and missed trials were also observed. Two animals failed to respond adequately at the higher doses and were excluded from the analysis.

Diazepam caused parallel delay independent effects on all parameters. Accuracy decreased and latencies to respond generally increased with higher doses (5 and 10 mg/kg).

ZK 93426 had no effect on accuracy at the doses tested, but the two higher doses significantly lengthened response times with respect to control.

Discussion

The effects of several centrally active drugs were investigated using a visual discrimination task. The compounds each produced different profiles of action in terms of accuracy, response latency and overall response frequency. Amphetamine increased the number of omissions without significant effects on accuracy or response latency, although some negative tendencies were observed. Physostigmine enhanced failures, and latencies to respond without significant effects on accuracy. The putative nootropic ZK 93426 had no consistent effects on performance. In the simple visual discrimination procedure, scopolamine dose dependently disrupted the ability to respond without significant effects on accuracy; in the delayed discrimination, scopolamine disrupted accuracy in a dose-, but not delay-dependent manner. Methylscopolamine similarly disrupted the ability to respond in both procedures. In contrast to scopolamine, improved accuracy at some doses of methylscopolamine was observed in the simple discrimination. In the more complex paradigm, a disruptive dose-dependent, but delay-independent, effect on accuracy was seen. All performance parameters in both paradigms were negatively affected by higher doses of diazepam.

For technical reasons, no attempt was made to prevent the animals from utilising a mediating response during the delay. Thus it cannot be formally excluded that they solve the delay by simply going to the appropriate lever immediately on making the discrimination, and simply await its reappearance. There are several reasons for believing that this may not have been the case. Firstly, performance levels declined with increasing delay; secondly, informal observations showed that the rats patrolled the cage during the delays, and thirdly, the results obtained in this task are similar to those from other studies in which mediating responses were prevented.

The effects of scopolamine and methylscopolamine in this experiment were especially interesting. Scopolamine apparently had no effect on accuracy in the simple discrimination, although in keeping with previous reports (Ksir and Slifer 1982; Viscardi and Heise 1986; van Haaren and van Hest 1989), increased omissions and response latencies were noted.

Nevertheless, several reports have documented the disruptive effects of scopolamine on discriminative performance (Hearst 1959; Milar 1981; Ksir and Slifer 1982; Viscardi and Heise 1986; van Haaren and van Hest 1989), and the reasons for the lack of an effect here require explanation. In typical auditory and visual discrimination paradigms, marked disruptive effects of scopolamine are associated with higher doses and increased task difficulty (Milar 1981). Accordingly, increasing the stimulus intensity can compensate for the effects of the drug (Evans 1975; Milar 1981). In the initial procedure, rats could regulate the length of time for which the stimulus was visible by taking longer to respond; this can be seen as analogous to increasing the strength of the stimulus. Thus, in situations where this is not possible, as in the second procedure, a decrement in performance would be expected, and was indeed observed. The results from the delayed discrimination are in full agreement with reports indicating a disruption of discriminability by scopolamine independent of delay, i.e. parallel downward shifts in the delay response function (Dunnett 1985; Kirk et al. 1988; Dunnett et al. 1989; Bushnell 1990). In contrast, at least two studies indicate that in monkeys scopolamine affects retention but not discrimination, i.e. does show delay-dependent effects (Bartus and Johnson 1976; Rupniak et al. 1990). However, in the task used in both of these studies there was an apparent ceiling effect in the control situation; delay-dependent effects were not unambiguously observed in the control condition, although in fairness the task seemed to be more difficult at longer than shorter delays. However, ceiling effects can obscure parallel shifts in performance curves. The present results confirm the generality of scopolamine's disruptive effects across modality and task type.

The peripheral effects of scopolamine are well documented and it cannot be excluded that effects on pupil size may have had some effect on the brightness discrimination. Undoubtedly the use of dry food may also have contributed to failures to respond: a dry mouth would make the food pellets unpalatable. In general all pellets delivered were eaten, which suggests that this effect had only minor consequences in this task. Furthermore, the use of liquid reinforcers in both rats (Hearst 1959) and monkeys (Evans 1975) does not prevent serious decrements in auditory or visual discrimination performance.

The effects of methylscopolamine in the two procedures were surprising. The decreased tendency to respond is in keeping with many previous reports (e.g. van Haaren and van Hest 1989; van Haaren et al. 1989), but the small but significant increase in accuracy in the simple discrimination, and the decrease in performance in the delayed discrimination requires examination.

There could be several explanations for the observed trade off in speed and accuracy. The absence of central

effects gives prominance to the peripheral effects of methylscopolamine; these are known to be aversive, and can be used to train conditioned place avoidance (Hughes et al. 1989). Mildly aversive effects can enhance vigilance and in some circumstances improve performance, an action probably best ascribed to the well-known Yerkes-Dobson inverted U arousal function. Thus enhanced arousal coupled with a longer stimulus presentation time could lead to a preservation of, or slightly enhanced performance.

The similarity in the action of scopolamine and methylscopolamine in the delayed discrimination is striking and was unexpected. With the exception of response disruption, performance deficits following methylscopolamine are rarely observed, although when seen they are similar in nature, but smaller in magnitude, to the effects of scopolamine (e.g., Dunnett et al. 1989; van Haaren et al. 1989). This task appears to be particularly sensitive to these two compounds, suggesting a complex interaction between the visual nature of the task, peripheral effects of both drugs on the visual system, and to the high doses involved in the study. Studies involving cholinergics acting only in the central nervous system are required to establish whether this type of visual procedure is capable of assessing central cholinergic activity.

Physostigmine affected only response latency, without influencing accuracy. Evidence from the literature that cholinergic agonists or cholinesterase inhibitors can enhance cognitive performance in animals is poor; physostigmine has been shown to enhance (Warburton and Brown 1972) or disrupt discrimination (Milar 1981), and improve (Dunnett 1985) or have no effect on delayed matching to position (Dunnett et al. 1989) at doses similar to those employed here. These inconsistencies appear to mirror the experience in the clinic (Becker and Giacobini 1988). Taken together, the presently available evidence casts doubts on the usefulness of the currently available cholinergic drugs for investigating memory.

The stimulant properties of amphetamine can sometimes lead to small improvements in performance in some tasks at low doses. In this study there were no beneficial effects of amphetamine. In keeping with previous two-choice discrimination studies, higher doses of amphetamine interfered with the ability to respond (see also Koek and Slangen 1983; Andrews and Holtzman 1988).

Diazepam failed to show delay-specific effects in these experiments. Benzodiazepines have previously been found to affect performance on visual discrimination in both man and animals (Iwasaki et al. 1976; Francis and Cooper 1979; Cole 1982, 1990; Jansen et al. 1986; Dorow et al. 1987). However, these effects do not appear to be unequivocally dose related. Interestingly, these effects are more consistently observed on single lever go/no-go tasks as opposed to the two lever go/go type tasks. This may be related to diazepam's known effects on releasing response inhibition rather than on discriminative ability per se. The results from the present experiments support the observations of Tan et al. (1990) using another benzodiazepine, chlordiazepoxide, in a delayed auditory discrimination using rats, and are similar to the results of Jansen et al. (1986) on the action of diazepam on a visual detection task in human volunteers. However, it must be noted that the clear and consistent amnestic effects of benzodiazepines in humans (e.g. Stephens et al. 1991) are not reflected in the present task.

In contrast to the amnestic effects of benzodiazepines, inverse agonists at the benzodiazepine receptor have been predicted to possess positive effects on cognition, though their anxiogenic properties (e.g. Dorow et al. 1983) can make interpretation of such effects problematic. The antagonist ZK 93426 has not been reported to possess anxiogenic effects in rats and thus might be a more suitable candidate for testing for direct effects on cognitive abilities. However, in the present procedure, there was no effect of the drug on accuracy. These data contrast with earlier studies indicating that ZK 93426 can enhance some aspects of cognitive performance in man (Duka et al. 1987) and rats (Hodges et al 1989; Sarter and Steckler 1989). In both of the latter studies, involving different types of radial arm mazes, improvements were observed only in rats in which performance had been compromised by a lesion. Thus, the lack of effect of ZK 93426 in the present study may reflect either the insensitivity of the task to the sort of cognitive effects exerted by benzodiazepine receptor ligands, or to the lack of an impairment in the animals studied. In the delayed discrimination procedure, but not in the simple visual discrimination task, a significant slowing of responding was noted; this is probably attributable to the higher doses used in the more complex task.

In summary, the present study shows the sensitivity of a conditional visual discrimination and a conditional delayed visual discrimination in rats to various drug treatments. In keeping with some previous studies, little evidence was found for drug effects on accuracy at different delays, independent of generally disruptive effects on discriminative ability and performance.

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