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# Attenuation of scopolamine-induced spatial memory deficits in the rat by cholinomimetic and non-cholinomimetic drugs using a novel task in the 12-arm radial maze

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**Abstract.** The effects of cholinomimetic and non-cholinomimetic agents on spatial memory using a novel task in the 12-arm radial maze were investigated. The task was designed to reduce the tendency to use non-spatial strategies. Animals were repeatedly trained to retrieve food rewards from three arms, until a criterion level of performance was reached. Scopolamine (0.03 and 0.1 mg/kg SC), but not N-methylscopolamine (0.1 mg/kg SC) disrupted performance of this task. Physostigmine (0.3 mg/kg SC) and pilocarpine (30 mg/kg SC) completely reversed the deficit of performance produced by scopolamine. Furthermore, the ACE inhibitor Hoe 288 (10 nmol ICV) and the angiotensin $AT_1$ receptor antagonist losartan (10 mg/kg SC) also significantly attenuated the scopolamine-induced deficit. These results show that this novel task in the radial maze is sensitive to the disruptive effects of scopolamine and can identify cognitive enhancing effects of both cholinomimetic and non-cholinomimetic drugs. Thus, this maze task provides a useful model for the evaluation of novel cognitive enhancing agents.

**Key words:** Radial maze – Spatial memory – Scopolamine – Cholinomimetics – ACE inhibitors – Angiotensin II antagonists – Rat

A progressive decline of cognitive function is a widely accepted clinical feature of age-associated dementing illnesses such as Alzheimer's disease (Liston 1979; Collerton 1986). Pathological evidence implicates the loss of cognitive abilities in association with a decline in the function of ascending cholinergic systems (Perry et al. 1978; Collerton 1986; Gottfries 1990). Such evidence is supported by numerous clinical studies in normal subjects showing that the cholinergic antagonist scopolamine produces amnesic effects similar to those identified in Alzheimer's disease (see Kopelman 1986; Sahakian 1987 for reviews). In addition, cognitive improvements have most reliably been obtained following treatment with cholinomimetic agents (Christie et al. 1981; Thal et al. 1983; Summers et al. 1986). However, the use of such agents is limited by unpleasant side effects or poor bioavailability (Fitten et al. 1990; Levy 1990) and as a result, there is a continuing requirement for effective agents with other modes of action to be identified.

The aim of the present study was to validate a novel procedure using the 12-arm radial maze. The radial maze, in which rats are required to search for food and subsequently remember its location, has been used as a way of measuring the spatial mapping abilities of rodents (Olton and Samuelson 1976; Olton et al. 1977; Burešová and Bureš 1982). Scopolamine challenges have been used in many studies in order to assess the possible role of cholinergic mechanisms in maintaining accurate spatial memory, and the performance deficits that accompany scopolamine treatment are now well established (Eckerman et al. 1980; Stevens 1981; Godding et al. 1982; Wirsching et al. 1984). Therefore, the use of scopolamine provides a convenient model to investigate the ability of novel cholinomimetic and other agents to improve spatial memory. However, there is considerable controversy concerning the dose of scopolamine required to induce a deficit of spatial performance. In addition, the behavioural basis of this deficit has not been well defined. There is evidence to show that the use of high doses of scopolamine can induce deficits which may be, in part, mediated by the peripheral effects of anticholinergics (see Levin 1988). Furthermore, in procedures designed to measure both working and reference memory, some workers have shown that low doses of scopolamine selectively impair working memory, while reference memory is only impaired by higher doses of scopolamine (Wirsching et al. 1984; Beatty and Brierley 1985). Thus, one criterion for establishing a valid scopolamine model in the radial maze for novel drug evaluation is sensitivity to low doses of the antimuscarinic. One factor which may influence the sensitivity of radial maze performance to

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scopolamine is the ability of rats to adopt non-spatial strategies. Rats have been shown to solve maze problems by consistently choosing either the adjacent or adjacent-but-one arm in a particular direction (Eckerman et al. 1980; Watts et al. 1981; Peele and Baron 1988). Watts et al. (1981) have shown that animals using non-spatial strategies are relatively resistent to the disruptive effects of scopolamine, compared to those using spatial discrimination involving a complex of intra- and extra-maze cues. Furthermore, confinement of rats to the central area of the maze between each choice reduces the likelihood that animals will resort to non-spatial patterns of behaviour to solve the maze and enhances the disruptive effect of scopolamine (Stevens 1981; Peele and Baron 1988).

In the present study, we have investigated the effect of scopolamine compared with its non-brain penetrating quaternary analogue N-methylscopolamine, using a novel procedure in a 12-arm radial maze. The procedure was designed to reduce the likelihood that the animals would adopt non-spatial strategies to solve the task. This was achieved by baiting only 3 of the 12 arms of the maze, in a configuration which allowed the task to be solved more effectively with the use of spatial memory rather than non-spatial strategies. The nature of the performance deficit produced by scopolamine, in terms of specific changes in working or reference memory, is discussed. In addition, we have evaluated the ability of cholinomimetic agents, pilocarpine and physostigmine to reverse the scopolamine-induced performance deficit. Cholinomimetic agents have been shown to reverse performance deficits of radial maze performance induced by chemical lesions of ascending cholinergic pathways (Murray and Fibiger 1985; Tilson et al. 1988). In addition, cholinomimetic agents have been shown to reverse a scopolamine-induced cholinergic deficit in primate models (Bartus 1978; Rupniak et al. 1989). However, results from radial maze studies showing the ability of these agents to reverse a scopolamine-induced deficit have not been reported (see Sarter et al. 1992). Additional studies using other types of maze have shown cholinomimetic agents to be ineffective in reversing a scopolamine-induced memory deficit (Shannon et al. 1990).

In view of the unpleasant side-effects of muscarinic agonists and cholinesterase inhibitors, the search for agents acting more specifically has expanded. Over recent years, interest in the renin-angiotensin system in the brain has increased (see Moore and Gershon 1990) and a number of studies have focused on the influence of this system in cognition. Administration of inhibitors of angiotensin converting enzyme (ACE), such as captopril, SQ29852 and Hoe 288, have been reported to enhance performance in a number of cognitive tasks (Usinger et al. 1988; Costall et al. 1989). Furthermore, the development of non- peptide angiotensin II antagonists, showing selectivity for the $AT_1$ and $AT_2$ angiotensin II receptor subtypes (Bumpus et al. 1991) has provided useful tools with which to investigate the role of angiotensin in learning and memory processes. Losartan (DuP 753) is the prototype $AT_1$ receptor selective antagonist (Chiu et al. 1990) and has previously been reported to enhance habituation in the mouse (Barnes et al. 1991). Other $AT_1$ receptor selective antagonists have also been shown to reverse a renin-induced deficit of passive avoidance in the rat (DeNoble et al. 1991). In the present studies, we have evaluated the ability of Hoe 288 and losartan to reverse a scopolamine-induced performance deficit in the radial maze.

## Materials and methods

*Subjects.* Male Lister-hooded rats (Glaxo bred) (250–300 g) were used in all experiments. The animals were housed in groups of four per cage, under a 12-h light/dark cycle with lights on 0600 to 1800 hours. Animals were maintained on a 23-h food deprivation schedule with access to food (SDS Rat and Mouse Diet No. 1) for 1 h per day immediately after testing. Water was allowed ad libitum.

*Surgery.* In studies involving the administration of substances directly into the cerebral ventricles (ICV), rats were subjected to stereotaxic surgery for the chronic implantation of guide cannulae positioned bilaterally at the level of the lateral ventricle (Ant 6.1, Vert 3.9, Lat $\pm$1.5; Paxinos and Watson 1982). Animals were anaesthetised with pentobarbitone sodium (Sagital, RMB Animal Health Ltd) (60 mg/kg IP) and were placed in a Kopf stereotaxic frame. Bilateral guide cannulae, held in Perspex holders were implanted and maintained in acrylic dental cement (Medway Dental Supplies Ltd). The guide cannulae were maintained patent with stainless steel stylets. Animals were subsequently allowed at least 7 days recovery prior to the experiment.

*Apparatus.* The radial maze, elevated 50 cm above the floor, consisted of a central platform, 46 cm in diameter, surrounded by 12 equally spaced radial arms. Each arm was 55 cm in length, 10 cm in width and at the distal end, contained a plastic food well where food rewards (45 mg precision pellets, banana flavour, Bioserv, USA) were placed. The side walls of each arm were raised 6 cm above the level of the maze for the first 20 cm of arm length, ensuring rats returned to the central platform between each arm selection. The maze was surrounded by a variety of extra-maze cues, consisting of black and white boards, tables and chairs. The animals were observed through a one-way window by the experimenter in an adjacent room.

*Procedure.* To familiarise the rats with the maze, prior to training, each animal received three trials of habituation, each on separate days. On these days, all 12 arms of the maze were baited with food rewards and each animal was individually placed on the central platform and allowed to explore the maze for a period of 5 min.

When the rats had learned the association of arms with reward, training commenced. Each animal was assigned three maze arms which together served as the baited set. This set of arms was the same throughout the experiment for any rat, although it was different for each animal. The variation of the baited set for different animals limited the development of odour-cues within the maze as well as controlling for any directional preferences with respect to the extra-maze cues. At the start of each trial, each rat was placed individually at the end of one of the nine unbaited arms and was allowed to search the maze. The trial was complete when all rewards had been retrieved, after 24 arm entries or after 5 min, which ever occurred first. Each animal received four trials each day, with a 10-min inter-trial interval. During each trial, choice accuracy was assessed by measuring the number of errors made, that is any entries into the unbaited set or any re-entries into the unbaited or baited arms. Total errors made over the four trials were then calculated. For some analyses, total errors were also subdivided into entries into the unbaited set (reference memory errors), re-entries into the unbaited set (re- entry reference memory errors) or re-entries into the baited set (working memory errors). Animals were trained until a criterion level of performance was reached (approxi-

mately 10 days). The criterion was no more than 12 total errors per day. The latency to complete each trial was recorded and expressed as time per arm entry in order to identify changes in locomotor ability.

There are two important features of this task. The first is that the three baited arms were separated by two, three and four unbaited arms within each set, for example, 1 4 9, 2 5 10, 3 6 11. Consequently, if the rat adopted a strategy of repeatedly making 30° turns (adjacent arm entries) or even 60°, 90°, or 120° turns, more total errors would be made up to completion of the trial than if the rat were to use spatial methods and as a result, animals would unable to reach the defined criterion. The second is that the unbaited arm used as the initial starting point on each trial was assigned randomly and varied from trial to trial. Therefore, the rat was required to identify its different spatial starting position for each trial and make a different first choice. Furthermore, the use of an unbaited arm rather than the central platform as the initial starting point reduced the likelihood that some rats would be given an unintentional advantage by facing the animal close to the entrance of one of the baited arms.

*Experimental design.* After reaching criterion, drug treatment commenced. Each experiment was conducted using a Latin square design, such that by completion of the experiment, all animals had been tested under each treatment condition. A drug-free training day was allowed between testing days to re-establish baseline performance.

*Statistical analysis.* Statistical analyses of total errors and time per arm entry used analysis of variance, followed by Duncan's or Dunnett's test. An assumption of normality was not acceptable for errors per trial, working memory errors, reference memory errors and re-entry reference memory errors and hence analysis of variance was not appropriate. Furthermore, the error variability (i.e. variability between animals within the treatment groups) was greater than expected from a Poisson distribution. Thus, in these cases a modified analysis of deviance was used followed by Dunnett's test. Significant differences are indicated at the 5% and 1% levels.

*Drugs.* Drugs were obtained from the following sources. Scopolamine hydrochloride, N- methylscopolamine bromide (NMS), pilocarpine hydrochloride, physostigmine salicylate (Sigma), Hoe 288 (kindly donated by Hoechst) and losartan potassium (kindly donated by Dupont Merck Pharmaceutical Company). For all experiments, scopolamine, NMS, pilocarpine, physostigmine and losartan were administered subcutaneously (SC) in a dose volume of 1 ml/kg. Scopolamine and NMS were administered 30 min prior to testing, pilocarpine and physostigmine, 25 min and losartan, 120 min. Due to limited drug supplies, Hoe 288 was administered ICV (10 nmol in 2 µl, 30 min prior to testing). All doses of drugs were expressed as the base.

## Results

### *Experiment* 1: *Comparison of the effect of scopolamine and N-methylscopolamine*

In this experiment, the effect of scopolamine (0.1 mg/kg), compared to saline and NMS (0.1 mg/kg) was investigated. Mean total errors and mean times per arm entry were measured and the results are shown in Fig. 1*a* and *b*, respectively. The total number of errors made under scopolamine was significantly greater than that following saline or NMS (0.1 mg/kg) ($P<0.01$). There was no significant difference in total errors between saline and NMS treatments ($P>0.05$). In contrast, the time per arm entry was significantly increased by both muscarinic antagonists compared to saline treatment ($P<0.01$), although the increase in time per arm entry produced by NMS treatment was significantly less than that produced by scopolamine ($P<0.01$).

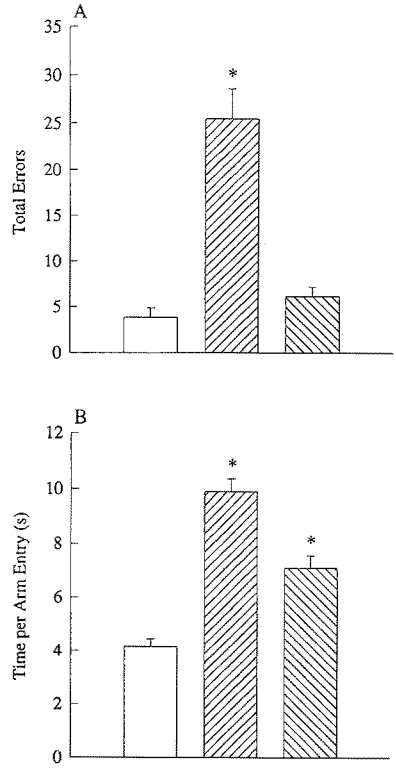


**Fig. 1. A,B** Effect of scopolamine and N-methylscopolamine on performance in the 12-arm radial maze. **A** Total errors. **B** Time per arm entry. Each bar represents mean values (± SEM) following saline (□), scopolamine 0.1 mg/kg (▨) or N-methylscopolamine 0.1 mg/kg (▧). $n=12$. *$P<0.01$ (compared to saline)

### *Experiment* 2: *Dose-relationship of scopolamine and effect of physostigmine and pilocarpine*

To investigate the sensitivity of radial maze performance to the disruptive effect of scopolamine, the effect of a lower dose of scopolamine (0.03 mg/kg) was compared to 0.1 mg/kg. In the same experiment, the ability of the cholinomimetic agents physostigmine and pilocarpine to attenuate the scopolamine deficit was examined. The results obtained are shown in Fig. 2. As in experiment 1, scopolamine (0.1 mg/kg) significantly increased the number of total errors, compared to saline ($P<0.01$). A disruptive effect was also produced by 0.03 mg/kg scopolamine, although this effect was significantly less than that produced by 0.1 mg/kg scopolamine ($P<0.01$). As seen with scopolamine 0.1 mg/kg in experiment 1, scopolamine 0.03 mg/kg also increased the time per arm entry from 10.3 ± 1.04 (following saline) to 18.3 ± 1.99 (following scopolamine) ($P<0.05$). Furthermore, the effects of scopolamine (0.03 and 0.1 mg/kg) to impair performance were significantly attenuated by physostigmine (0.3 mg/kg) ($P<0.01$). Pilocarpine (30 mg/kg) also completely re-

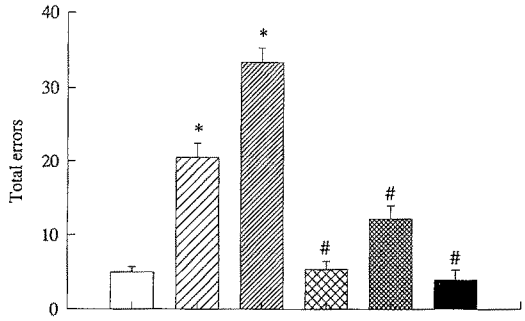


**Fig. 2.** Effect of scopolamine, physostigmine and pilocarpine on performance in the 12-arm radial maze. Each bar represents mean total errors (±SEM) following saline (□), scopolamine 0.03 mg/kg (▨), scopolamine 0.1 mg/kg (▨), scopolamine 0.03 mg/kg plus physostigmine 0.3 mg/kg (▨), scopolamine 0.1 mg/kg plus physostigmine 0.3 mg/kg (▩) or scopolamine 0.1 mg/kg plus pilocarpine 30 mg/kg (■). $n=16$. *P<0.01 (compared to saline). #$P<0.01$ (compared to appropriate scopolamine)

versed the effect of 0.1 mg/kg scopolamine. The number of total errors made under pilocarpine/scopolamine treatment was not significantly different from vehicle control ($P>0.05$). The effects of physostigmine or pilocarpine administered alone could not be tested, because of the presence of severe side-effects occurring in the absence of scopolamine.

To investigate whether the disruptive effect of scopolamine was seen in all trials, the data from this experiment were further examined to measure errors per trial. This analysis revealed no significant differences in the number of errors made per trial in either scopolamine treatment group ($P>0.05$). Further, a significant effect of scopolamine (0.03 or 0.1 mg/kg) compared to saline was seen in all trials ($P<0.05$) Thus, in all future experiments, data is expressed as mean total errors per day.

In an attempt to define the nature of the scopolamine deficit in more detail, the data from experiment 2 were separated into working memory errors, reference memory errors and re- entry reference memory errors. Scopolamine dose- dependently increased the number of working and re-entry reference memory errors compared to saline ($P<0.01$), and although scopolamine also increased reference memory errors, there was no significant difference between the two scopolamine doses ($P>0.05$) (Fig. 3). The effects of physostigmine and pilocarpine were also similar against all measures.

*Experiment* 3: *Dose-relationship of pilocarpine*

This experiment investigated the effect of two doses of pilocarpine (10 and 30 mg/kg) against scopolamine (0.1 mg/kg). As in experiment 2, 30 mg/kg pilocarpine completely reversed the disruptive effect of scopolamine ($P<0.01$). The lower dose of pilocarpine (10 mg/kg) also partially reversed the effect of scopolamine ($P<0.05$), although the magnitude of the effect was less (Fig. 4*a*). Mean times per arm entry are shown in Fig. 4*b*. While scopolamine increased time per arm entry above saline ($P<0.01$) (as in experiment 1), only the lower dose of pilocarpine (10 mg/kg) attenuated this effect ($P<0.05$)

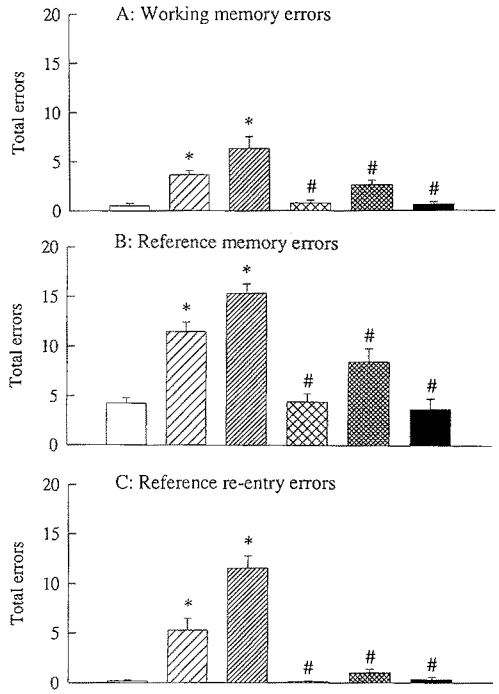


**Fig. 3.** Effect of scopolamine, physostigmine and pilocarpine on working memory errors (**A**), reference memory errors (**B**) and reference re-entry memory errors (**C**) in the 12-arm radial maze. Each bar represents mean total errors (±SEM) following saline (□), scopolamine 0.03 mg/kg (▨), scopolamine 0.1 mg/kg (▨), scopolamine 0.03 mg/kg plus physostigmine 0.3 mg/kg (▨), scopolamine 0.1 mg/kg plus physostigmine 0.3 mg/kg (▩) or scopolamine 0.1 mg/kg plus pilocarpine 30 mg/kg (■). $n=16$. *P<0.01 (compared to saline). #$P<0.01$ (compared to appropriate scopolamine)

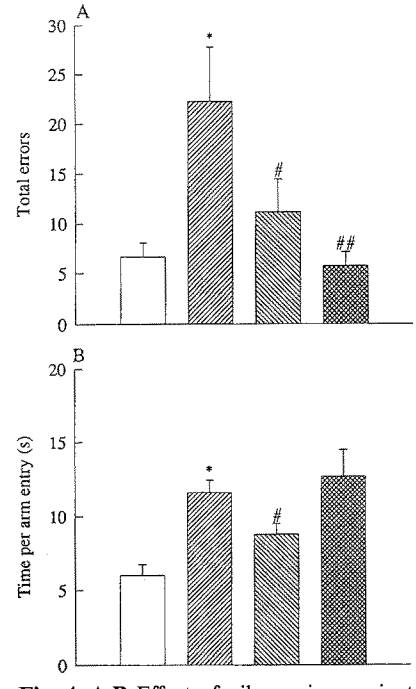


**Fig. 4. A,B** Effect of pilocarpine against the scopolamine-induced performance deficit in the 12-arm radial maze. **A** Total errors. **B** Time per arm entry. Each bar represents mean values (±SEM) following saline (□), scopolamine 0.1 mg/kg (▨), scopolamine 0.1 mg/kg plus pilocarpine 10 mg/kg (▨) or scopolamine 0.1 mg/kg plus pilocarpine 30 mg/kg (▩). $n=12$. *P<0.01 (compared to saline). # $P<0.05$, # # $P<0.01$ (compared to scopolamine)

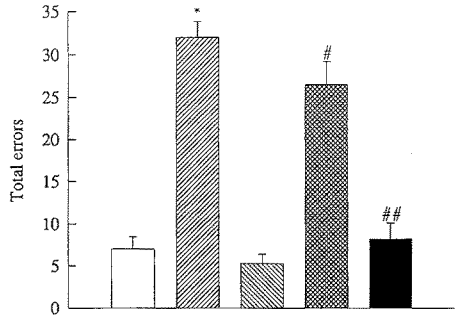


**Fig. 5.** Effect of Hoe 288 against the scopolamine-induced performance deficit in the 12-arm radial maze. Each bar represents mean total errors (±SEM) following saline (□), scopolamine 0.1 mg/kg (▨), Hoe 288 10 nmol ICV (▧), scopolamine 0.1 mg/kg plus Hoe 288 10 nmol ICV (▩) or scopolamine 0.1 mg/kg plus pilocarpine 30 mg/kg (■). $n=15$. *P<0.01 (compared to saline). # $P<0.05$, # # $P<0.01$ (compared to scopolamine)

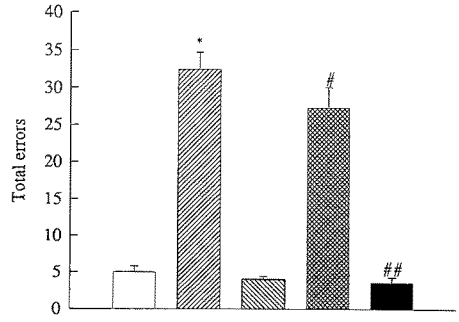


**Fig. 6.** Effect of losartan against a scopolamine-induced performance deficit in the 12-arm radial maze. Each bar represents mean total errors (±SEM) following saline (□), scopolamine 0.1 mg/kg (▨), losartan 10 mg/kg (▧), scopolamine 0.1 mg/kg plus losartan 10 mg/kg (▩) or scopolamine 0.1 mg/kg plus pilocarpine 30 mg/kg (■). $n=14$. *P<0.01 (compared to saline). # $P<0.05$, # # $P<0.01$ (compared to scopolamine)

*Experiment* 4: *Effect of Hoe* 288

This experiment investigated the ability of Hoe 288 (10 nmol), administered directly into the lateral ventricles, to attenuate the effect of scopolamine. While there was no effect of Hoe 288 alone ($P>0.05$ versus saline), there was a significant effect of Hoe 288 to attenuate the increase in total errors produced by scopolamine ($P<0.05$). However, this effect was only small (20%) (Fig. 5). As a control, pilocarpine (30 mg/kg) was again shown to reverse the scopolamine deficit ($P<0.05$) (as in experiments 2 and 3).

*Experiment* 5: *Effect of losartan*

This experiment investigated the effect of the $AT_1$ receptor antagonist, losartan (10 mg/kg) against scopolamine. As in experiment 4, pilocarpine (30 mg/kg) was included to show a reversal of the scopolamine deficit. While losartan failed to modify performance when administered alone ($P>0.05$), it significantly attenuated the scopolamine-induced deficit by scopolamine by 26% ($P<0.05$) (Fig. 6).

## Discussion

In the present studies, we have pharmacologically validated a novel spatial memory task using a 12-arm radial maze. The procedure used was designed to reduce the likelihood that animals would adopt non-spatial strategies. It has previously been shown that animals can effectively solve maze problems by repeatedly choosing adjacent or adjacent but one arms in a particular direction. Under such circumstances, the requirement for spatial memory is limited and the effectiveness of scopolamine to disrupt such performance is reduced (see Introduction for references). Using the present task, the configuration of the baited set of arms was designed such that if the animals adopted any type of repeated response pattern, more arm entries would be required to complete the task (and hence more errors) than if the rats used spatial memory to remember the baited arm locations. Using this task, the observation that the animals reached a criterion of less than 3 errors per trial (12 errors per day) suggests that the use of repeated response patterns of the type commonly described is limited. Furthermore, the observation that low doses of scopolamine can disrupt performance of this task provides further evidence that rats solve this task by using spatial memory. The low sensitivity of this task to scopolamine is consistent with previous work using tasks in which non-spatial responding has been reduced by confinement to the central platform in between each choice (Peele and Baron 1988). In addition, such doses are in agreement with those shown to produce cognitive deficits in other models using either rodent (Murray et al. 1991) or primate (Rupniak et al. 1989) species. However, it is interesting to note that Levin and Rose (1991) also report low sensitivity to scopolamine without using a confinement protocol, suggesting that factors other than the degree of non-spatial responding, perhaps strain differences may govern sensitivity to scopolamine.

The central nature of the performance deficit produced by scopolamine has been confirmed by the use of the quaternary non-brain penetrating muscarinic antagonist NMS. The observation that only scopolamine and not NMS increased the number of errors confirms that the changes in spatial accuracy are due to central muscarinic blockade. This observation is in agreement with others (Eckerman et al. 1979; Beatty and Bierley 1985; Hodges et al. 1991). Furthermore, in view of the observation that both scopolamine and NMS increased time per arm entry, it is likely that these changes are mediated largely by peripheral muscarinic blockade. However, as the increase in time per arm entry was greater following scopolamine treatment than following an equivalent dose of NMS, it is also likely that the additional increase in time per arm entry produced by scopolamine is due to a central action and could actually contribute to the increase in the number of errors.

The ability of scopolamine to specifically disrupt working memory without significant effects on reference memory is still very much disputed. While some workers (Wirshing et al. 1984; Beatty and Bierley 1985) have shown a selective effect on working memory, this has not

been confirmed by others (Okaichi et al. 1989; Hodges et al. 1991). In the present study, although the maze procedure used was not ideally designed to assess changes in working and reference memory abilities because of the imbalance of rewarded and unrewarded arms, we identified no selectivity in the action of scopolamine to disrupt any specific type of error. In addition, we identified no differences in the types of errors made by the two doses of scopolamine used. Thus, we would also prefer to conclude, that scopolamine, even at very low doses, is capable of producing a rather general cognitive deficit. In studies which have shown a selective effect of scopolamine on working memory, it has been suggested that such an action relates to a selective blockade by scopolamine of the cholinergic terminal fields of the septohippocampal pathway (Beatty and Bierley 1985). However, from the lesion literature, there is still no firm evidence to support the dissociative functions of the septohippocampal and basal forebrain cortical pathways in mediating specific effects on working and reference memory respectively (Walker and Olton 1984; Dunnett 1985; Hepler et al. 1985; Murray and Fibiger 1985; Hagan et al. 1988). Thus, a more likely explanation for the selectivity of scopolamine on working and reference memory in some studies and not in others relates to differences in the training protocols. This is discussed in detail by Lydon and Nakajima (1992).

The ability of classical cholinomimetic agents, physostigmine and pilocarpine, in addition to the more novel non-cholinomimetic agents Hoe 288 and losartan, to reverse or attenuate the scopolamine-induced cognitive deficit of maze performance supports the use of this task to identify potential cognitive enhancing drugs. Despite the lack of previous data regarding the ability of cholinomimetics to reverse scopolamine-induced deficits of radial maze performance, physostigmine has been shown to reverse lesion-induced deficits in the radial maze (Tilson et al. 1988) and both scopolamine- and lesion- induced deficits in other models (Bartus 1978; Hagan et al. 1989; Rupniak et al. 1989). Furthermore, a number of other cholinesterase inhibitors have been shown to be equally effective (Hagan et al. 1989; Dawson et al. 1991; Murray et al. 1991). Data on the effectiveness of pilocarpine in animal models of cognition is limited. In the present study, pilocarpine was used in preference to other agonists, because of its lower efficacy and hence better tolerability (Rupniak et al. 1989) and was able to dose-dependently and completely reverse the deficit in spatial performance induced by scopolamine. In other models, pilocarpine has been reported to be only partially effective (Hagan et al. 1989; Rupniak et al. 1989).

The ability of Hoe 288 and losartan to ameliorate the scopolamine-induced cognitive deficit is in agreement with previous work (Usinger et al, 1988; Barnes et al. 1991). While full dose-response effects would be required to fully identify the extent to which these agents can improve performance in this task, doses of Hoe 288 and losartan were selected by their ability to inhibit a functional dipsogenic response following intraventricular injection of angiotensin I or II, respectively (Dennes and Barnes 1991; Dennes et al. 1992) or to displace [$^{125}$I]Sar$^{1}$Ile$^{8}$ angiotensin II binding from forebrain tissue ex vivo (Song et al. 1991b; Marshall et al. 1993). Therefore these data provide further evidence to support the involvement of the renin-angiotensin system in cognitive function. While both angiotensin $AT_1$ and $AT_2$ receptors have been located in specific forebrain regions of the rat brain (Song et al. 1991a), the mechanism by which ACE inhibitors or $AT_1$ receptor antagonists can improve cognitive performance remains to be established. Recently, Denny et al. (1991) have reported the ability of angiotensin II to inhibit hippocampal long term potentiation, a model of enhanced synaptic efficacy believed to be involved in the formation of memory. Furthermore, an interaction of angiotensin II with the cholinergic system has also been implicated (Barnes et al. 1990). While neither of these effects have yet been shown to be mediated through either $AT_1$ or $AT_2$ receptors, either may provide possible underlying mechanisms mediating the cognitive enhancing effects of the ACE inhibitors or the $AT_1$ receptor antagonists as reported in the present study and by others.

In conclusion, we have validated a novel procedure in the 12-arm radial maze which is sensitive to cholinergic and non-cholinergic drugs and which may therefore be useful for investigating the effects of drugs on cognitive spatial performance in rats.

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