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The Effects of ACE Inhibitors Captopril and SQ29,852 in Rodent Tests of Cognition

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COSTALL, B., J. COUGHLAN, Z. P. HOROVITZ, M. E. KELLY, R. J. NAYLOR AND D. M. TOMKINS. *The effects of ACE inhibitors captopril and SQ29,852 in rodent tests of cognition.* PHARMACOL BIOCHEM BEHAV **33**(3) 573–579, 1989.—The ACE inhibitors captopril and SQ29,852 enhanced a habituation response to bright illumination in young adult and aged mice measured in a two-compartment light/dark test box. The treatments also antagonised a scopolamine-induced impairment and SQ29,852 was approximately 100 times more potent than captopril. In rats trained on a reinforced alternation paradigm in a T-maze, aged rats, as compared to young adults, showed a reduction in choice performance which was antagonised by SQ29,852. The impairment in choice performance in the T-maze induced by scopolamine in young adult rats was antagonised by SQ29,852 whilst captopril only delayed the onset of the scopolamine-induced impairment. SQ29,852 also antagonised scopolamine-impaired escape latency in a spatial learning/memory paradigm in a water-maze test. The effects of SQ29,852 in the rat were achieved within a somewhat restricted dose range. The ability of captopril and SQ29,852 to increase performance in the behavioural tests is discussed in terms of an antagonism of angiotensin converting enzyme to remove an inhibitory role of angiotensin II on central cholinergic function.

ACE inhibitors Captopril SQ29,852 Mouse habituation T-maze Water-maze Rat Cognition

ANGIOTENSIN converting enzyme (ACE) inhibitors such as captopril inhibit the conversion of angiotensin I to angiotensin II in body tissues and are used in the treatment of heart failure and hypertension (8). Anecdotal reports of a mood-elevating effect of captopril (5,18) find some support in a 'quality of life study' employing a multicentre randomised double-blind clinical trial where captopril treatment induced a sense of well-being (4). It has been hypothesised that this effect may result from a direct action on the central nervous system involving an inhibitory effect on the metabolism of enkephalin or other peptides, an action via noradrenergic regulation, an effect on ACTH secretion or an effect in the circumventricular organs to regulate peptide diffusion (6). It remained uncertain as to whether the feeling of 'well being' reflected an antidepressant, an anxiolytic action or an improvement in ability to perform daily tasks (a cognitive improvement). However, a secondary analysis of the data on cognitive performance in patients who participated in the quality of life study conducted by Croog and colleagues (4) has clearly shown that captopril significantly improved cognitive performance measured using the Trail Making Test from the Halstead-Reitan test battery (15). Furthermore, the captopril-induced increase in cognitive performance occurred in cognitively-impaired patients and independently of blood pressure control.

In preclinical studies the ability of captopril to delay the extinction of a conditional avoidance response in rats may also indicate an action on cognitive processes (17) and in this respect, the ability of angiotensin II and related peptides to disrupt passive avoidance, operant or retention behaviour in the rat and rabbit may be particularly relevant (9–11). The present experiments were designed to further investigate the effects of captopril and the novel ACE inhibitor SQ29,852 in models of cognitive performance in the mouse and rat.

METHOD

Experimental Animals

Male albino B.K.W. mice (25–30 g, 6 to 8 weeks old, i.e., "young adult") and (33–38 g 8 to 10 months old, i.e., "aged") were housed in groups of 10 and given free access to food and water. Mice were kept on a 12-hr light/dark cycle with lights off at 07.00 a.m.

Male Lister Hooded rats (250–300 g, 11 to 15 weeks old, i.e., "young adult," and 350–400 g, 13 to 17 months old, i.e., "aged") were housed in groups of 5 and given free access to food and water ad lib or until the start of behavioural testing (see below). Rats were kept on a 12-hr light/dark cycle with lights off at 0900 hr. The temperature was maintained at 21 ± 1°C.

Mouse Habituation Test

Testing was carried out daily between 0830 and 1230 hr. Mice

were taken from a dark home environment in a dark container to the experimental room maintained in low red lighting, and placed into the centre of the white section of a white and black test box. The box ($45 \times 27 \times 27$ cm high) was divided. Forty percent of the area was painted black and illuminated under a red light (60 W, 0 lux) and the other painted white and brightly illuminated with a white light (1×60 W, 400 lux) located 17 cm above the box. Access between the two areas was enabled by a 7.5×7.5 cm opening located at floor level in the centre of the partition. Behaviour was assessed via remote video-recording and the latency to move from the white to the black section was measured. The brightly lit area of the black and white test box has aversive properties, mice normally distributing their behaviour preferentially in the black compartment (3). On repeated daily testing mice habituate to the test system with a reduced latency in movement from the white to the black section.

T-Maze Reinforced Alternation Performance in Rats

Animals were trained on a food-reinforced alternation task using a modification of the protocol of Salamone *et al.* (13). Food was withdrawn 2 days prior to testing and animals were deprived of food for 23 hr/day. Water was available ad lib and body weight was maintained at 85%. Animals were taken from the holding room to the dimly-lit test room 30 min before testing. Experiments were carried out between 0800 and 1500 hr using an elevated T-maze. The start arm measured 80×10 cm and the side arms were 60×10 cm with food wells 3 cm deep at each end. The T-maze was elevated 30 cm above the ground.

On day 1 each rat was allowed 10 min habituation to the maze. Both food wells were baited with banana-flavoured pellets and pellets were also scattered along the approach arm. The rats were then subject to a period of reinforced alternation training, days 2–5 being designated "pretraining" days with days 6–9 "training" days. All reinforced alternation training consisted of paired trials (each pair consisting of a 'run'). The first trial was the 'forced' trial in that one arm was blocked whilst the other arm was baited. The second trial of the pair was a "choice" trial in which reward pellets were placed in the arm opposite to that reinforced in the first trial of the pair. A correct choice was when the rat entered the arm and passed a point 20 cm along the arm containing the food in the choice trial. In addition to correct/incorrect choice, latency to reward was recorded for both forced and choice trials.

Four runs/day were carried out on pretraining days (intertrial interval 0 sec, interrun interval 30 sec) and 6 runs/day during training (intertrial interval 30 sec; interrun interval 60 sec). The number of lefts and rights was random (following Gellerman Schedule) and was balanced across the test groups.

Water Maze Performance in Rats

Rats were placed in a square (120×120 cm) pool of water which contained a white painted platform located 2 cm below the surface of the water. The water was rendered opaque by the addition of a small quantity of emulsion to obscure the presence of the platform. The rats were trained to locate and escape onto the island using spatial strategies. A two-day test protocol was utilised and was a modification of the method of Morris (12).

Day 1. Each rat was placed on the island for 30 sec immediately before testing commenced. The island was kept in a constant position for each rat (the position was randomised and balanced across the groups) but each rat began each trial at a different corner in the pool (the positions balanced across the groups). A training trial began with the animal being lowered into the pool, the animal close to and facing the corner designated for the trial. The timer and tracking device was started and the time recorded for the animal to escape from the water onto the platform. The rat remained on the platform for 10 sec before being placed in the pool for trial 2. On each trial the rat was allowed a maximum 100 sec to find the island and the latency, swim speed and % time spent in the island quadrant were measured. If the rat failed to find the island in 100 sec it was placed on it for 10 sec and then removed. Each rat received 6 trials on day 1. A 7th trial with a black visible island was also carried out to ensure that no visual/locomotor effects were influencing performance.

Day 2. The same procedure was carried out as that of day 1, the basis of the test being that rats had formed a strategy to find the island on day 1 which could be disrupted by drug treatments.

Statistical Analysis

Data was analysed by two-way analysis of variance (ANOVA) with repeated measures and/or Dunnett's *t*-test as indicated in the Results section.

Drugs

Scopolamine HBr and N-methyl scopolamine HBr (Sigma), SQ29, 852 [(5)-1-[6-amino-2[(hydroxy) (4-phenylbutyl)phosphinyl]oxy)-1-oxo-nexy]-2-proline] and captopril (Squibb) were all dissolved in normal saline. Doses of drugs are expressed as the base. All drugs were administered in a volume of 1 ml/kg (rat) or 1 ml/100 g (mouse) body weight by the intraperitoneal route. Dose schedules are indicated in the Results section.

RESULTS

Mouse Habituation Test

Habituation profile of young adult and aged mice. Naive young adult and aged mice placed into the centre of the white section of the black and white test box moved within 10 to 12 sec into the black section. On daily testing young adult animals habituated to the test system, moving by the 5th day within 2 to 4 sec into the black section. In contrast, the slight reduction of some 10% in the latency of movement of aged mice into the black section over the 7-day period failed to achieve significance (Fig. 1).

Influence of Captopril and SQ29,852 on Basal Learning and Scopolamine Impairment

In preliminary studies doses of captopril (0.05 mg/kg b.i.d.) and SQ29,852 (0.0005 mg/kg b.i.d.) were carefully selected as the lowest doses capable of influencing the latency of movement on continued treatment. This avoided the possibility of the use of doses of captopril and SQ29,852 that might have an acute effect to directly modify aversive responding or exploratory behaviour in the black and white test box, to obscure an interpretation of the present results.

In young adult mice, the daily treatment with captopril and SQ29,852 enhanced habituation to the test system, reducing the latency of movement into the black section by the 3rd or 4th day (Fig. 1). The administration of scopolamine (0.25 mg/kg) to the young adult mice on the 6th day impaired habituation to the test box, increasing the latency of movement into the black section 2-fold. Captopril and SQ29,852 prevented the effect of scopolamine (Fig. 1).

In aged mice, the daily treatment with captopril and SQ29,852 reduced the latency of movement into the black section. Even on the first day of testing mice moved more quickly than untreated animals into the black section and this achieved significance using SQ29,852. Habituation to the test box occurred rapidly, by the 3rd

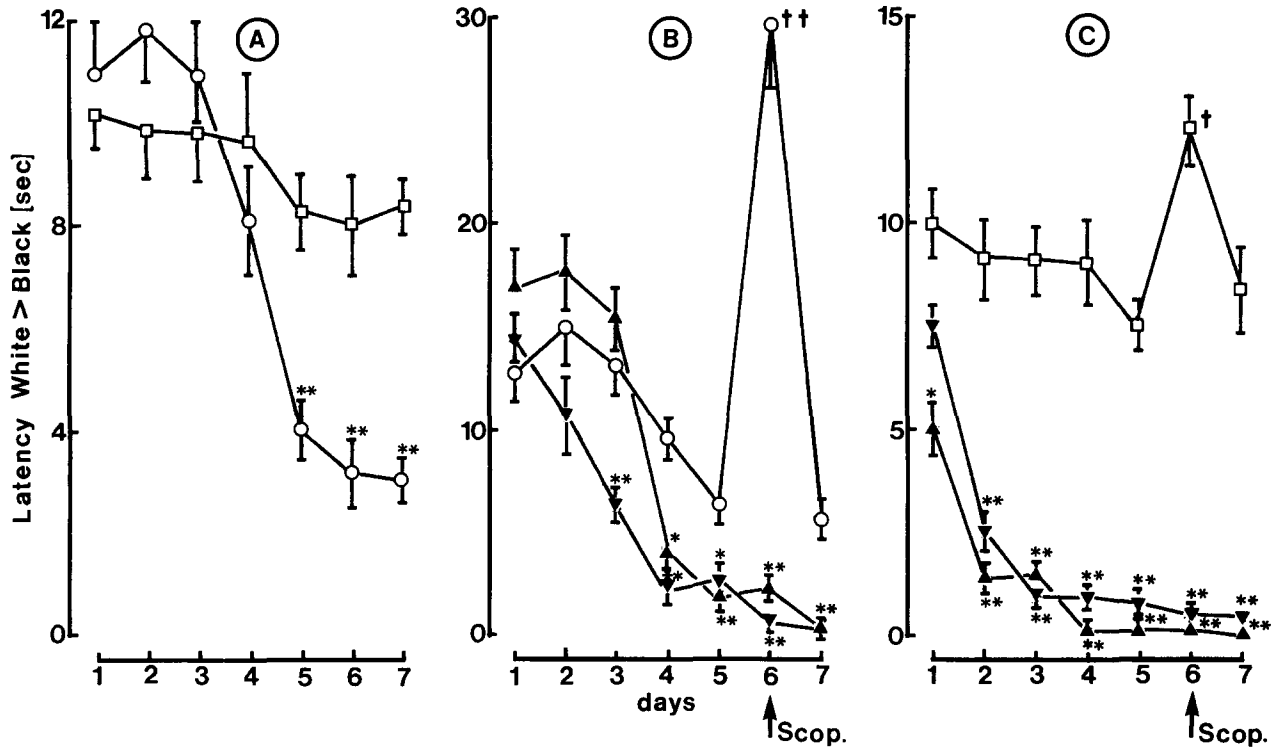

FIG. 1. The effect of captopril and SQ29,852 to enhance mouse habituation responding in a black and white test box, and to prevent a scopolamine-induced impairment. (A) Young adult (○) and aged (□) mice received vehicle injections; (B) young adult mice received injections of vehicle (○), captopril (0.05 mg/kg IP b.i.d. ▼) or SQ29,852 (0.0005 mg/kg IP b.i.d. ▲); and (C) aged mice received injections of vehicle (□) captopril (0.05 mg/kg IP b.i.d. ▼) or SQ29,852 (0.0005 mg/kg IP b.i.d. ▲). In B and C animals receiving vehicle or drug injections were challenged with a single treatment of scopolamine (Scop. 0.25 mg/kg IP B, 0.1 mg/kg IP C) on the 6th day (↑). Significant differences in the latency of initial movement from the white to the black area between A, aged and young adult mice and B, C: drug treatments with captopril and SQ29,852 compared to control (vehicle) values are indicted *$p<0.01$ and **$p<0.001$ (Dunnett's t-test); a significant increase in the latency of movement induced by scopolamine relative to vehicle controls is indicated †$p<0.05$ and ††$p<0.001$ (Dunnett's t-test).

day animals moving into the black section within 1 to 3 sec and, by the 4th day of treatment, animals receiving captopril or SQ29,852 moved into the black either immediately or within 1 or 2 sec. The administration of scopolamine (0.1 mg/kg) on the 6th day of testing caused a significant but modest delay in movement into the black section as compared to the response obtained on the previous day. This impairment was not observed in mice receiving treatment with captopril or SQ29,852 (Fig. 1).

Effects of Captopril and SQ29,852 on Scopolamine-Induced Impairments in a T-Maze Reinforced Alternation Task in Young Adult Rats

Scopolamine-induced disruption of reinforced alternation performance was characterised by a significant reduction in the % correct responses (see below). A dose of 0.25 mg/kg IP b.i.d. scopolamine was selected as the minimal dose causing a maximal reduction of some 60% correct responses compared to vehicle controls (Fig. 2). N-Methylscopolamine (0.25 mg/kg IP b.i.d.) was ineffective. SQ29,852 (0.005–0.5 mg/kg IP b.i.d.) antagonised the scopolamine-induced impairment and at 0.005 and 0.05 mg/kg IP b.i.d. the choice performance indicated by % correct response was not significantly different from that of vehicle control animals (two-factor ANOVA with repeated measures, Factor A = drug treatments and Factor B = time in days) revealed significant effects of drug [$F(4,24) = 56.34$, $p<0.01$, time, $F(7,42) = 25.31$, $p<0.01$, and a significant drug × time interaction, $F(28,168) = 1.03$, $p<0.05$; further data analysis using Dunnett's t-test revealed significant effects of scopolamine and the antagonism of these effects by SQ29,852, see Fig. 2]. Lower and higher doses of SQ29,852 (0.0005 and 1.0 mg/kg IP b.i.d.) were ineffective in this model (Fig. 2). Captopril (0.1 and 1.0 mg/kg IP b.i.d.) failed to antagonise the scopolamine-induced impairment, but at 1.0 mg/kg b.i.d. delayed the onset of impairment as seen by a nonsignificant change from control values on days 1 and 2 of treatment (two-factor ANOVA, Factor A = drug treatment and Factor B = time in days) revealed significant effects of drug, $F(4,24) = 39.61$, $p<0.01$, and time, $F(7,42) = 13.82$, $p<0.01$, and significant drug × time interaction, $F(28,168) = 1.79$, $p<0.05$; further data analysis using Dunnett's t-test revealed effects to be significant (see Fig. 2). Both captopril (1.0 mg/kg IP b.i.d.) and SQ29,852 (1.0 mg/kg IP b.i.d.) administered alone failed to modify basal performance (Fig. 2).

Effects of Captopril and SQ29,852 on Performance of Aged Rats in a T-Maze Reinforced Alternation Task

Aged rats showed a reduction in choice performance of some 30% compared to the performance of young adult animals as assessed using two-way ANOVA followed by Dunnett's t-test (see below). The reduced performance of aged rats was significantly improved by treatment with SQ29,852 (0.005 mg/kg IP b.i.d.),

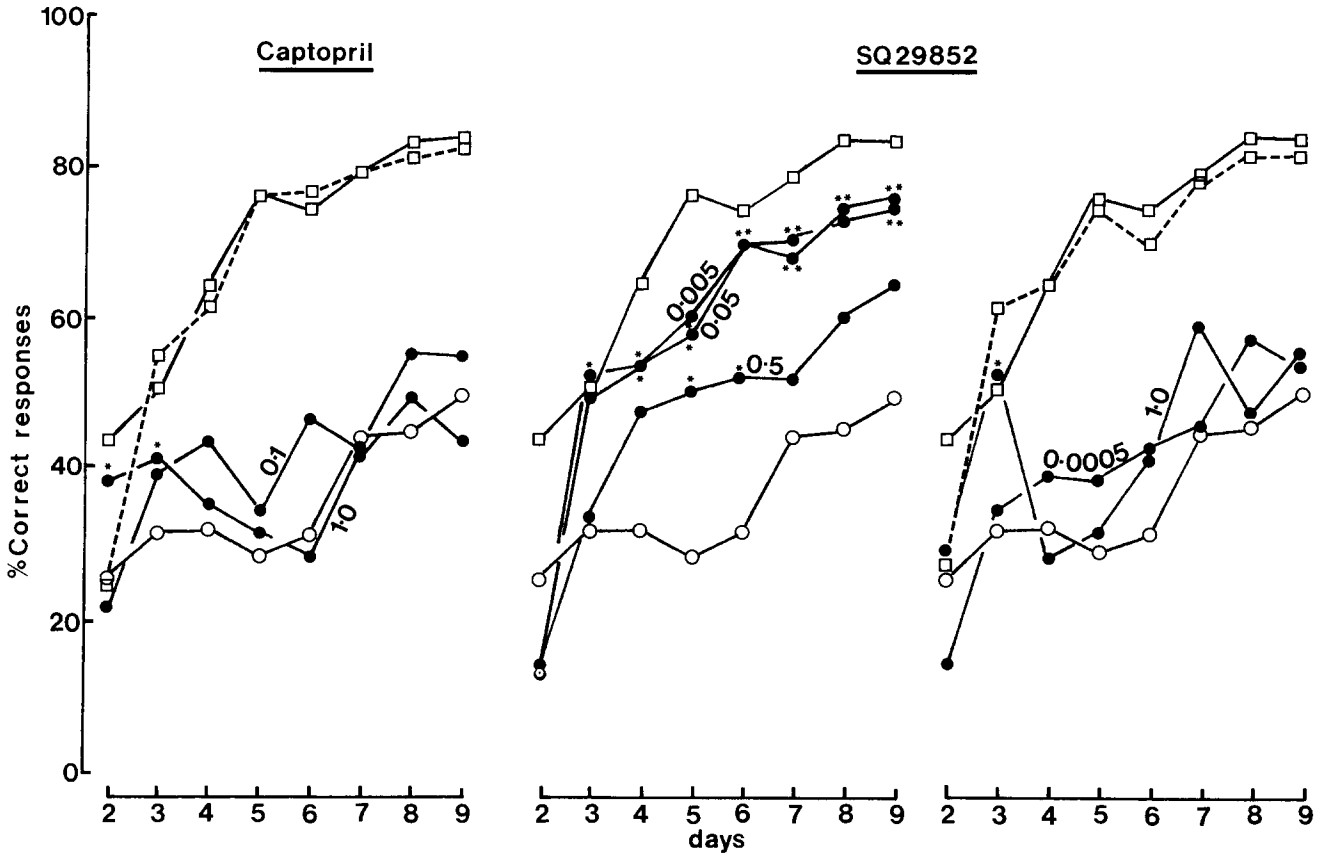

FIG. 2. Effects of captopril and SQ29,852 on scopolamine-induced impairment in a T-maze reinforced alternation task in the rat. Young adult animals received daily treatment with captopril or SQ29,852 (□---□, 1.0 mg/kg IP b.i.d.) or vehicle (□—□), scopolamine (○, 0.25 mg/kg IP b.i.d.) or scopolamine plus captopril or SQ29,852 (● mg/kg IP b.i.d. doses indicated) for 9 days and data is presented following a 1-day habituation to the test apparatus. Data obtained was analysed by two-way ANOVA followed by Dunnett's *t*-test, n = 10. A significant antagonism by SQ29,852 of the scopolamine-induced impairment is indicated $*p<0.05$ and $**p<0.01$; a significant impairment in choice performance induced by scopolamine relative to vehicle controls was obtained at $p<0.05$–0.001 on all other values without asterisks.

the deficit between the young adult and aged animals being reduced by 50%. However, the more modest improvements of 20 to 30% observed using 0.0005 and 0.05 mg/kg SQ29,852 did not achieve significance, and higher doses were ineffective (two-factor ANOVA, with repeated measures, Factor A = age/drug treatment, Factor B = time in days) revealed significant effects of age/drug, $F(5,30) = 16.78$, $p<0.01$, and time, $F(7,42) = 27.85$, $p<0.01$; further data analysis using Dunnett's *t*-test revealed significant effects between the test groups (see Fig. 3). Captopril (0.025–1.0 mg/kg IP b.i.d.) failed to modify choice performance in aged rats (Fig. 3). Latency to reward was not modified by treatments with captopril or SQ29,852 in either young adult or aged rats.

Effect of SQ29,852 on Scopolamine-Induced Impairment of Rat Performance in the Water Maze

On the first day of testing the trend for scopolamine (0.25 mg/kg IP b.i.d.) to increase the escape latency failed to achieve significance. The trend for the administration of scopolamine alone, or in combination with SQ29,852 to reduce the % time in the island quadrant, also failed to achieve significance. On the second day, the continued treatment with scopolamine significantly impaired to escape latency by 62% and % time in the island quadrant by 40%. SQ29,852 (0.005 mg/kg IP b.i.d.) significantly antagonised the scopolamine-induced deficit such that the performance to escape and the % time in the island quadrant were indistinguishable from values determined for vehicle-treated control animals. The higher dose of SQ29,852 (0.05 mg/kg IP b.i.d.) failed to modify the scopolamine-induced impairment in this test (Fig. 4). The lack of effect of drug treatments on swim speed and the ability to locate the black visible island indicated an absence of effect on visual and locomotor performance.

DISCUSSION

In the present study the ACE inhibitors captopril and SQ29,852 were shown to enhance performance in tests of cognitive function in the rodent. Using a two compartment light/dark test box to measure habituation in young adult mice, the mildly aversive, brightly-lit environment ensured that mice placed into the white brightly-lit area would move into the black section. On repeated daily testing an habituation to the procedure was apparent by the 3rd to 5th day, mice moving with a reduced latency into the black environment. Treatment with either captopril or SQ29,852 facilitated the habituation response by the 3rd or 4th day of testing, and such treatments antagonised the impairment caused by the administration of scopolamine.

Aged animals perform less well in tests of cognitive function (2) and aged mice failed to habituate to the test procedure, although their initial performance was comparable to that of young adult mice, indicating that the impairment was not the conse-

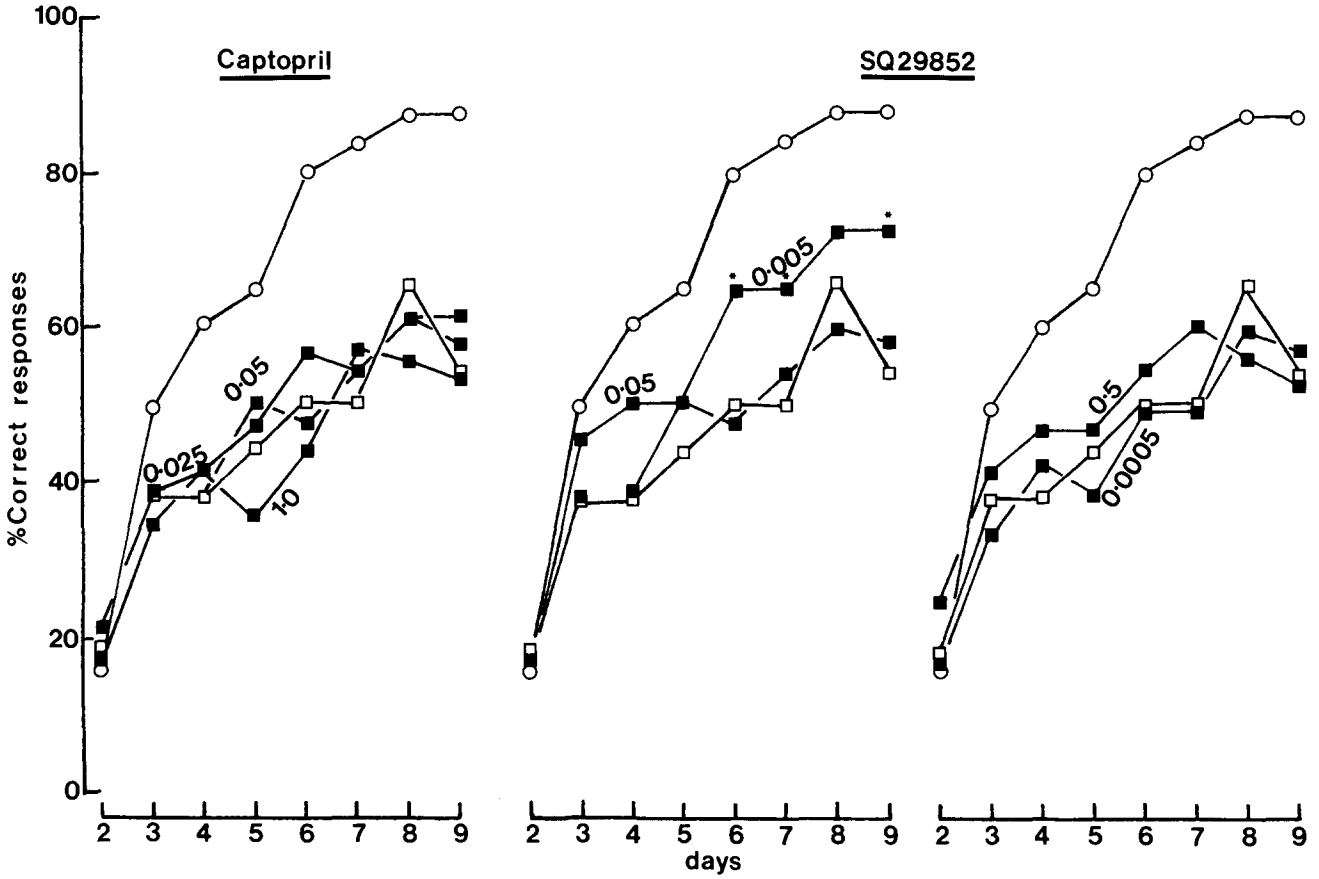

FIG. 3. Effects of captopril and SQ29,852 in aged rats in a T-maze reinforced alternation task. Aged rats received daily treatment with captopril or SQ29,852 (■, mg/kg IP b.i.d. doses indicated) or vehicle (□) for 9 days, young adult rats were used as a 'reference control' and received vehicle (○), and data is presented following a 1-day habituation to the test apparatus. Data obtained was analysed by two-way ANOVA followed by Dunnett's *t*-test. n = 7–10. A significant improvement in choice performance induced by SQ29,852 in aged rats compared to vehicle-treated aged rat controls is shown $*p<0.05$.

quence of a slowness in movement. Aged animals also proved more sensitive to the toxic effects of scopolamine necessitating the use of a lower dose which, nevertheless, was sufficient to induce an impairment in performance. Aged mice treated with captopril or SQ29,852 showed a rapid habituation response evident by the first or second day of treatment, and the habituation pattern was not disrupted by scopolamine. Therefore, as found in the young adult mice, captopril and SQ29,852 can also prevent the impairments caused by scopolamine in aged mice. It is also an interesting observation that the habituation response of aged mice treated with captopril or SQ29,852 was achieved significantly more rapidly than in young adult animals, with or without treatment with captopril or SQ29,852.

SQ29,852 was also found to modify cognitive performance of the rat. In rats trained on a reinforced alternation paradigm in the T-maze, aged rats showed a 30% reduction in choice performance as compared to young adults, and there was no evidence that the choice deficit in the older animals was due to a reduced motor performance. The ability of SQ29,852 to antagonise the performance deficit in aged rats, and the impairment induced by scopolamine in young adult rats, was observed as a bell-shaped dose response curve. Captopril's only effect in the T-maze test was to delay the scopolamine-induced impairment on the first and second day of treatment. In the water maze procedure, scopolamine impaired escape latency and % time in the island quadrant and the disruptions in performnace were antagonised by a 2-day treatment with SQ29,852 at a low dose, but not at a higher dose.

The cognitive deficits associated with scopolamine use in animals and man have been linked with a central cholinergic blockade (2). Angiotensin II may cause a similar change, but by a different mechanism to inhibit the release of acetylcholine from cholinergic neurones (1). In the latter in vitro study using slices of rat entorhinal cortex, angiotensin I was shown to be ineffective, and it was suggested that, by inhibiting ACE, captopril and SQ29,852 may remove a tonic inhibitory influence of angiotensin II on the cholinergic neurone. In the mouse test, SQ29,852 was at least one hundred times more potent than captopril and is two orders of magnitude more potent to inhibit ACE (Cushman, personal communication; Barnes *et al.*, unpublished data). The increase in release of acetylcholine could enhance basal performance or act to oppose the scopolamine-induced acetylcholine receptor blockade. Such a hypothesis is in agreement with an extensive literature reporting that cholinergic agents can improve performance in cognitive tests (2). However, in the rodent behavioural tests, both captopril and SQ29,852 were effective at exceptionally small doses, doses probably less than required to inhibit ACE, at least as measured in body tissues. Thus, the relevance of an inhibitory effect of captopril and SQ29,852 on ACE to an ability to enhance cognitive events requires more detailed studies of their effects on cerebral angiotensin converting enzyme. Furthermore, it would be important in such studies to measure the effects of captopril and SQ29,852 on the metabolism

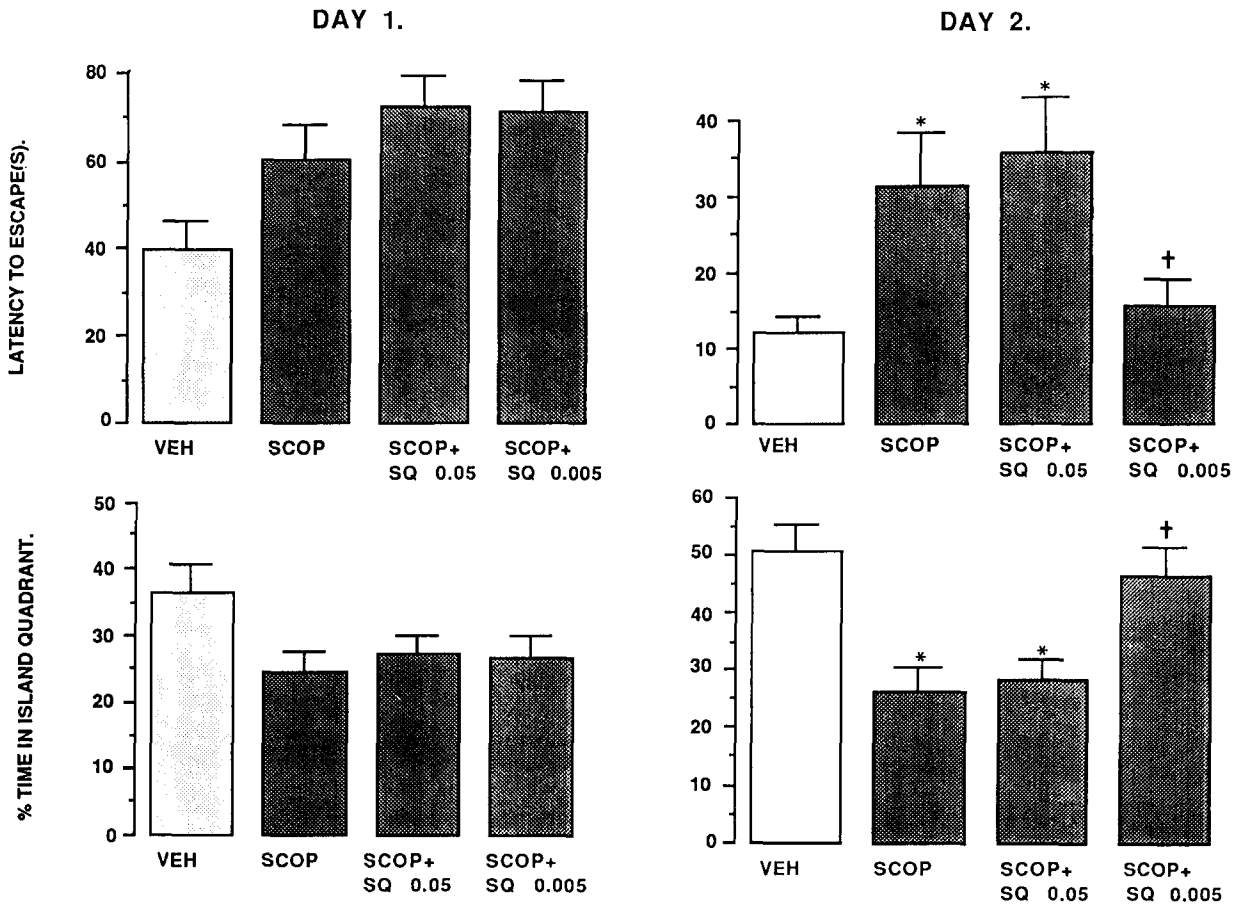

FIG. 4. Effect of SQ29,852 to inhibit scopolamine-induced impairment of rat behaviour in the water-maze test. Rats received scopolamine (0.25 mg/kg IP b.i.d.), scopolamine plus SQ29,852 (0.005 and 0.05 mg/kg IP b.i.d.) or vehicle and the latency to escape from the water onto an island, and the % time spent in the island quadrant were measured in 6 trials on the first and second days. Each value is the mean ± S.E.M. of 6 determinations. S.E.M.s for values for % time in island quadrant were calculated from original data. The significance of scopolamine/drug treatments to impair performance as compared to the performance of vehicle control animals, and the ability of SQ29,852 to inhibit the effects of scopolamine is indicated by $*p<0.05$ and $\dagger p<0.05$ respectively (Dunnett's *t*-test).

of other peptides such as bradykinin, substance P and enkephalins which are also degraded by ACE (7), and which may affect cognition (10). Indeed, Sudilovsky and colleagues (14) have recently reported a reversal by naloxone of the captopril-induced delay in the extinction of a conditioned avoidance response in the rat. It remains relevant that the diastereoisomer of captopril, epicaptopril, which lacks ability to inhibit ACE, fails to modify performance in rodent models of cognitive performance [(16), Costall *et al.*, unpublished data].

It also remains an interesting observation that the effects of SQ29,852 were observed in the rat over a narrow dose range, and there is no immediate explanation as to why the effects of SQ29,852 should decrease with increase in dose. However, if the effects of SQ29,852 are mediated via a cholinergic mechanism, it may be relevant that cholinergic agents in their own right appear to improve cognitive performance within a narrow dose range (2).

In summary, both captopril and SQ29,852 in the rodent can improve performance in tests of cognition. SQ29,852 is particularly potent in such tests and a closer analysis of a potential to modify memory, attention, visual information processing, reaction time or other components of cognition is clearly required.

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