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ScienceDirect
Neurobiology of Learning and Memory 87 (2007) 218–224
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Effect of chronic angiotensin converting enzyme inhibition on spatial memory and anxiety-like behaviours in rats

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Received 30 June 2006; revised 8 August 2006; accepted 23 August 2006
Available online 2 October 2006

Abstract

Angiotensin converting enzyme inhibitors (ACEis) are widely used anti-hypertensive agents that are also reported to have positive effects on mood and cognition. The present study examined the influence of the ACEi, perindopril, on cognitive performance and anxiety measures in rats. Two groups of rats were treated orally for one week with the ACEi, perindopril, at doses of 0.1 and 1.0 mg/kg/day. Learning was assessed by the reference memory task in the water maze, comparing treated to control rats. Over five training days both perindopril-treated groups learnt the location of the submerged platform in the water maze task significantly faster than control rats. A 60 s probe trial on day 6 showed that the 1.0 mg/kg/day group spent significantly longer time in the training quadrant than control rats. This improved performance in the swim maze task was not due to the effect of perindopril on motor activity or the anxiety levels of the rats as perindopril-treated and control animals behaved similarly in activity boxes and on the elevated + maze. These results confirm the anecdotal human studies that ACEis have a positive influence on cognition and provide possibilities for ACEis to be developed into therapies for memory loss.

Keywords: Angiotensin converting enzyme; Angiotensin converting enzyme inhibitor; Hypertension; Memory; Water maze; Alzheimer's disease; Vascular dementia

1. Introduction

Angiotensin converting enzyme (ACE) inhibitors (ACEis) constitute a family of drugs used to treat high blood pressure and heart failure. By blocking the formation of angiotensin II (Ang II), the active component of the renin–angiotensin cascade (RAS), they significantly decrease blood pressure and systemic vascular resistance (Dendorfer, Dominiak, & Schunkert, 2005; Nicholls et al., 1994; and Ruilope et al., 2005). Many of the earlier studies on the central effects of ACEi treatment were anecdotal reports from patients of mood elevation, a feeling of "well-being" and better of "quality of life" scores (Croog et al., 1986; Currie, Lewis, McDevitt, Nicholson, & Wright, 1990; Germain & Chouinard, 1988, 1989; and Zubenko & Nixon, 1984). However, in 2002, Amenta and colleagues reviewed the majority of controlled clinical trials assessing the influence of anti-hypertensive treatment on cognitive function in patients with essential hypertension. They concluded that ACEi treatment (including perindopril, captopril, and lisinopril) positively influenced cognitive function independent of their blood pressure lowering effects, with patients displaying better results than those on diuretics and β-blockers (Amenta, Mignini, Rabbia, Tomassoni, & Veglio, 2002).

Most animal studies to date on the cognitive effects of ACEis have focused on animal models of cognitive deficit. Streptozotocin-diabetic rats, which have impaired memory in the water maze task, demonstrated improved performance after enalapril treatment (Manschot et al., 2003),

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1074-7427/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2006.08.010

while lifetime treatment with captopril significantly attenuated age-related memory impairment in old spontaneously hypertensive rats (SHR) and Wistar–Kyoto rats (WKY) (Wyss, Kadish, & van Groen, 2003). Captopril and SQ29,852 reversed memory deficits induced by scopolamine in the habituation response to bright illumination in a conditioned avoidance task and alternation paradigm in a T-maze (Costall et al., 1989).

The purpose of the present study was to determine the effect of ACE inhibition on spatial learning in the water maze paradigm in normal rats using an ACEi, perindopril, which we have previously shown has the ability to cross the blood–brain barrier (Jenkins, Mendelsohn, & Chai, 1997; Jenkins, Wong, Howells, Mendelsohn, & Chai, 1999; Sakaguchi, Chai, Jackson, Johnston, & Mendelsohn, 1988). We have previously demonstrated that this ACEi at a dose of 1 mg/kg/day for one-two weeks can successfully reduce ACE levels in the circumventricular organs and structures within the blood–brain barrier such as the paraventricular and supraoptic hypothalamic nuclei and the striatum (Sakaguchi et al., 1988). Furthermore, one week of oral perindopril treatment modified the neurotransmitter, dopamine content and the neuropeptide, preproenkephalin mRNA levels (Jenkins et al., 1997; Jenkins et al., 1999) in the striatum.

Therefore, in view of our previous reports on the CNS effects of perindopril, and anecdotal evidence from patients on ACE inhibitor therapy we investigated the effect of two chronic doses of perindopril given orally on spatial learning in the water maze in rats. Further, we assessed the effect of this drug on motor activity, stress and anxiety measures.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats weighing between 250 and 320 g at the time of drug treatment were used in this study. The animals were housed individually under diurnal light conditions (12 h light/12 h dark) and testing was carried out during the light phase. Animals were given free access to food throughout and water intake was monitored daily. All experiments were carried out in accordance with the Prevention of Cruelty to Animals Act and the NH&MRC Code of Practice for the Use of Animals for Scientific Purposes of Australia.

2.2. Drug treatments

Treated rats received perindopril (Coversyl®, Servier, Cedex, France) at either a dose of 0.1 or 1.0 mg/kg/day via the drinking water for one week before behavioural testing began, and during the 6 days of behavioural testing. Control animals received water alone.

Thirty six rats ($n = 12$/treatment group) were subjected to the water maze task. One rat was removed from the control cohort after failing to locate the platform position throughout the 20 trials over five days. A further 36 rats ($n = 12$/treatment group) were run through the activity and elevated plus maze.

2.3. Water maze task

The water maze task was adapted from (Morris, Garrud, Rawlins, & O'Keefe, 1982). The test apparatus was a circular pool (144 cm in diameter, cm deep) made of dark green plastic and mounted cm above the floor. The pool was filled with water (24 ± 1 °C) made opaque by the addition of 1 l of full cream milk. The pool was situated in the centre of a room (326 × 305 × 250 cm) that contained prominent visual extramaze cues such as posters on the wall and a grey-coloured door. Lighting was provided by four 240 V, 150 W halogen lamps in each corner of the room, generating 180 lux. The escape platform was made of clear perspex (12 cm diameter, located 1 cm below the water surface). A video camera was mounted on the ceiling above the pool and was connected to a video recorder and tracking device (Ethovision, Noldus, Wageningen, The Netherlands), which permitted automated tracking of the path taken by the rat.

Testing commenced 1 week after drug treatment was initiated. Four start positions (NE, NW, SE, and SW) were allocated relative to the experimenter. Each rat was placed in the pool facing the wall at one of the four start positions. The rat was required to swim to an underwater platform, which was positioned in the same quadrant throughout the acquisition sessions. Each group of animals were divided into four subgroups, and each subgroup was required to search for the platform in a different quadrant of the maze (N, S, E, and W). Each of the four trials every day was started from a different location on the edge of the pool and the order in which the start positions were used varied day to day. The testing regime for all groups was four trials per day for 5 consecutive days. Each acquisition trial was terminated either when the rat located the platform or after 120 s has elapsed. If the rat was unable to locate the platform after 120 s it was placed on the platform. Rats remained on the platform for 30 s, and then returned to a warm box underneath a heatlamp. Following an intertrial interval of 2 min, the next trial was run. Following these five sessions a probe trial was conducted on day 6. All rats were first given one normal acquisition trial in which the platform was located in the training quadrant as usual. Then the platform was removed from the maze, and the swim path and distance swum in each of the four quadrants was recorded over 60 s. For this probe trial, each rat was placed at a start position directly opposite to where the platform had been located.

2.4. Spontaneous locomotor activity

Activity was measured in a novel arena (Coulbourn Instruments, Philadelphia, USA) measuring 40.64 × 40.64 × 40.64 cm. Activity was measured when pairs of photobeams spaced 2.54 cm apart providing a 1.27 cm spatial resolution were crossed. Data was collected and analysed using TruScan Photo Beam Activity system (Coulbourn Instruments, Philadelphia, USA). Each rat was placed in the arena for 10 min. Data was gathered in 2 intervals of 5 min each.

2.5. Elevated plus maze

The elevated plus maze consisted of two open arms (70 × 10 cm) with a 5 cm high surrounding wall and two enclosed arms (70 × 10 cm) with a 27 cm high surrounding wall. The arms extended from a central platform (10 × 10 cm). The floors of the open and closed arms were white laminate, the open arm walls were clear perspex, and the closed arms walls dark grey perspex. The maze was elevated 85 cm above the ground. The maze was located in the centre of a room (410 cm × 420 cm × 270 cm), which was lit by eleven circular 250 V, 300 W lights from above, generating 124 lux. A video camera was mounted on the ceiling above the maze and was connected to a video recorder and television, for analysis of behaviour.

Naive rats were placed on the central platform facing one of the closed arms and behaviour investigated for 10 min.

2.6. Data analysis

For the water maze study, latency to find the position of the platform was determined using analysis of variance (ANOVA) considering two factors: group and day. The probe trial time spent in each quadrant was also analysed using ANOVA considering two factors: group and quadrant. When appropriate, simple effects for each group were analysed as recommended by (Winer, 1971). All factors for activity (swim speed in water