The effects of alpha-2 adrenoceptor antagonist, atipamezole, on spatial learning in scopolamine-treated and aged rats

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Summary. In order to study whether noradrenergic drugs improve age-related cognitive dysfunctions the present experiments investigated whether atipamezole, a selective and specific alpha-2 antagonist, improves spatial learning impairment due to cholinergic blockade (scopolamine 0.8 mg/kg) or aging in rats. Previously, it has been shown that atipamezole dose-dependently (0.03–3.0 mg/kg) increases the turnover of noradrenaline in rat brain. According to the present results, atipamezole (0.1, 0.3, 0.6 mg/kg) did not affect spatial learning/memory when assessed in a free swim trial of the water maze task in control rats. Furthermore, atipamezole (0.1, 0.6 mg/kg) did not improve learning deficit in scopolamine treated young rats. Higher doses (~> 1.0 mg/kg) of atipamezole could not be tested, because they induce floating behaviour in rats. In aged rats, which were screened to be impaired in the initial acquisition of the water maze task, 0.3 mg/kg atipamezole impaired further learning of this task. Because previous studies suggest that age-related learning impairment in the water maze may be, at least partly, due to a cholinergic deficit, the present results suggest that atipamezole which increases the release of noradrenaline in brain does not alleviate this learning deficit.

Keywords: Aging, alpha-2 adrenoceptor antagonist, noradrenergic system, rat, spatial learning/memory.

Introduction

Aging can be associated with disorders in memory functions. Cholinergic and noradrenergic dysfunctions have received much attention as a neurobiological background of age-related memory impairment (Bartus et al., 1982; Arnsten and Goldman-Rakic, 1987). Interactions between cholinergic and noradrenergic systems may play an important role in memory dysfunctions; a partial norad-
renergic lesion aggravated cholinergic blockade (scopolamine)-induced deficits of rats in the performance of radial arm maze and water maze tasks assessing spatial memory (Decker and Gallagher, 1987; Riekkinen Jr. et al., 1990a). Spatial memory is also worse in aged rats, and this deficit has been proposed to be a good model of memory impairment in aged subjects (Gallagher and Pelleymounter, 1988).

Electrophysiological (Aghajanian and Rogawski, 1983) and neurochemical studies (Langer, 1981) have shown that the firing rate of the locus coeruleus and the release of noradrenaline is regulated by alpha-2 adrenergic autoreceptors. The blockade of those autoreceptors increases the release of noradrenaline in brain. Atipamezole which is a selective and specific alpha-2 adrenergic antagonist (Virtanen et al., 1989), increased dose-dependently (0.03–3 mg/kg) the turnover of central noradrenaline (Scheinin et al., 1988). The present experiments were undertaken to study whether pharmacological activation of the noradrenergic system would improve age-related impairment of spatial learning and memory. Thus, we examined whether atipamezole improves age-related learning deficit of rats in a water maze task. Since the acquisition deficit of this task may vary considerably between individuals (Gage et al., 1984), we screened a population of aged rats for impairment in the initial acquisition of the water maze task before testing the effects of atipamezole on further learning of this task. In order to investigate whether atipamezole could improve learning impairment following cholinergic dysfunction, we also studied the effects of atipamezole on water maze performance in rats treated with a muscarinic antagonist (scopolamine) which is a widely used model of amnesia (Smith, 1988).

Materials and methods

Animals

In experiment 1, young (4 months old) male rats were used. In experiment 2, young (4 months old, n = 9) and aged (18 months old, n = 59) male Kuo:Wistar rats were used. The rats were housed in light period (0700–2100), temperature (21 °C) and humidity (50–60%) controlled environment.

Behavioral training

The water maze apparatus (the pool and video tracking system) used to assess spatial learning and memory has been described previously (Riekkinen et al., 1990b). The rats were trained to find a submerged platform, the position of which was kept constant in the pool during training. The free swim trial (probe trial) was used to measure the spatial bias (percentage of the total distance swum in the previous training quadrant). The spatial bias in the probe trial is an index of memory: the higher the spatial bias, the better memory is assessed as being.

In experiment 1, the rats were trained for 10 days (two trials/day, maximum duration 90 seconds). The free swim trial was the second trial of the 10th training day. In experiment 2, young and aged rats were screened for the initial acquisition of water maze task for four days (2 trials/day, maximum 70 seconds). In this experiment, we used a shorter training time, because aged rats were used. The aged rats were considered to be impaired in the