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Performance- and task-dependent effects of the dopamine D_1/D_5 receptor agonist SKF 38393 on learning and memory in the rat

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Abstract

Dopamine D_1/D_5 receptor agonists may enhance cognition by mimicking dopamine's neurophysiological actions on the processes underlying learning and memory. The present study examined the task- and performance- dependence of the cognitive effects of a partial agonist at dopamine D_1/D_5 receptors, SKF 38393 [(±)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrobromide], in rats. Spatial working memory was assessed in a T-maze, spatial reference memory in a water maze and habituation learning in a novel environment, a hole board. The muscarinic acetylcholine receptor antagonist scopolamine (1.5 mg/kg, i.p.) was used to cause an impairment of performance of these learning tasks. Administration of SKF 38393 (6 mg/kg, i.p.) alone had no significant effect on spontaneous alternation in the T-maze, latency to escape to a hidden platform in the water maze or the habituation of spontaneous behaviour in the hole board. In contrast, in scopolamine-treated rats, whereas SKF 38393 prevented the scopolamine-induced deficit in the T-maze, it exacerbated the impairment in the water maze and did not significantly alter the disruption of habituation. These results suggest that dopamine D_1/D_5 receptor activation has performance- and task-dependent effects on cognitive function.

Keywords: Morris water maze; T-maze; Hole board; Scopolamine; Reference memory; Working memory; Novelty habituation

1. Introduction

Dopamine plays a significant role in memory processes especially in three inter-connected brain regions: the striatum, the hippocampus and the prefrontal cortex (see Jay, 2003; Lisman and Grace, 2005 for a review). Age-related disruption of the dopaminergic system in Parkinson's disease patients is associated with loss of episodic memory and executive functions (Owen, 2004; Erixon-Lindroth et al., 2005). Studies in monkeys and rodents have shown that the disruption of striatal dopaminergic transmission caused performance deficits in several learning tasks (e.g. Roeltgen and Schneider, 1994; Aosaki et al., 1994; Schneider and Pope-Coleman, 1995; Mura and Feldon, 2003; Da Cunha et al., 2003). Dopamine loss in the prefrontal cortex causes profound working memory deficits in monkeys and rats (Brozoski et al., 1979; Simon et al., 1980). Although less well characterized, neurotoxic lesions of mesohippocampal dopaminergic neurons in the rat impair the retention of spatial information in a water maze (Gasbarri et al., 1996).

Recently, Lewis et al. (2005) have shown that, in Parkinson's disease patients, working memory but not attention deficits were attenuated following administration of L-DOPA, giving support for the development of dopamine-based memory enhancing drugs. Dopamine has five main receptor subtypes and several investigations have shown therapeutic potential for agents boosting dopaminergic mechanisms including pharmacological targeting of specific dopamine receptor subtypes (Mehta and Riedel, 2006). There is extensive evidence that activation of dopamine D_1/D_5 receptors mediates many of the mnemonic actions of dopamine making these receptors attractive targets (Castner and Williams, 2007; El-Ghundi et al., 2007). Intrahippocampal injections of dopamine D_1/D_5 receptor agonists improve spatial working memory in the win-shift eight-arm radial maze (Packard and White, 1991). However, Wilkerson and Levin (1999) reported no significant effects of dopamine

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D_1/D_5 receptor agonists on a working memory task when injected in the ventral hippocampus. Recent studies have shown that systemic or bilateral intra-prefrontal cortical infusions of a dopamine D_1/D_5 receptor agonist in rats has delay-dependent opposite effects on performance of a wide variety of memory tasks (Chudasama and Robbins, 2004; Hotte et al., 2005). Generally, the facilitatory effects of dopamine D_1/D_5 receptor agonists on memory tasks are observed when performance is not optimal at long delays. Since studies in deficit models are potentially of more clinical relevance, the ability of dopamine D_1/D_5 receptor agonists to reverse cognitive impairment has also been studied. Age-related deficits in spatial maze learning have been shown to be attenuated by a dopamine D_1/D_5 receptor agonist (Hersi et al., 1995; Bach et al., 1999) possibly due to increased acetylcholine release in the hippocampus (Hersi et al., 1995) or frontal cortex (Di Cara et al., 2006) reversing an age-associated decline of the cholinergic system (Bartus et al., 1982). Indeed impairments in radial maze and passive avoidance learning caused by cholinergic hypofunction can be attenuated by dopamine D_1/D_5 agonists (Levin and Rose, 1991; McGurk et al., 1992; Steele et al., 1997). However, it is not known if the facilitatory effects of dopamine D_1/D_5 receptor agonists in cholinergic memory deficit models are task-dependent.

Given these considerations, the present study was designed to compare the behavioural effects of a dopamine D_1/D_5 receptor agonist in a range of learning tasks in the presence and absence of deficits induced by a muscarinic acetylcholine receptor antagonist. We tested reference and working memory in the Morris water maze and the T-maze, respectively (e.g. Morris, 1984; Olton and Samuelson, 1976). We also tested habituation learning, which is one of the most elementary forms of novelty learning (Dai et al., 1995), in a hole-board apparatus. We chose to study a partial agonist, SKF 38393 (O'Boyle and Waddington, 1984; O'Boyle and Lawler, 1996), at a dose that had no observable effects on general behavioural activity since full agonists have profound effects on spontaneous behaviour that potentially confound interpretation of any effects on memory and learning tasks (Salmi and Ahlenius, 2000; Isacson et al., 2004).

2. Materials and methods

2.1. Animals

Male Wistar rats aged from 6 to 7 weeks, weighing approximately 250 g at the beginning of the experiment (Bioresources Unit, Dublin, Ireland) were studied. Animals were housed in pairs and maintained on a 12 h/12 h light/dark schedule, at a temperature of 18–20 °C, with ad libitum access to food and water. Experiments started 48 h after the animals arrived to the housing facility. All procedures were licensed by the Irish Government Department of Health and Children.

2.2. Experimental design and drug treatments

The experiment was designed to determine the effects of the dopamine D_1/D_5 receptor partial agonist SKF 38393 [(±)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrobromide] (Tocris Cookson, Bristol, UK) on the performance of behavioural tasks carried out in a Morris water maze, a hole-board and a T-maze. The behavioural effects of SKF 38393 were tested in non-impaired controls and in scopolamine-treated animals (scopolamine hydrobromide, also Tocris Cookson). SKF 38393 was dissolved in saline and scopolamine in water. The animals were randomly assigned to one of four treatment groups, each group receiving two injections: (1) a group that received water and saline injections, termed the "Veh+Sal" group; (2) a group that received water and 6 mg/kg SKF 38393, termed the "Veh +SKF 38393" group; (3) a group that received 1.5 mg/kg scopolamine and saline, termed the "Scop+Sal" group; and (4) a group that received 1.5 mg/kg scopolamine and 6 mg/kg SKF 38393, termed the "Scop+SKF 38393" group. Animals received two intraperitoneal (i.p., 1 ml/kg) injections in quick succession 30 min before behavioural testing began. Injections of SKF 38393 and scopolamine were given in random order. The dose and method of administration of SKF 38393 were chosen on the basis of pilot studies and the results reported by Levin and Rose (1991).

2.3. Morris water maze

In this test, the animals were required to find a submerged platform in a pool (diameter: 200 cm, height: 50 cm) filled with water (water level: 30 cm; water temperature: approx: 25 °C), within 120 s. Rats were given 4 trials a day for five consecutive days. If a rat did not find the platform within 120 s this value was assigned as the escape latency for the trial. On the fifth day, a probe trial was carried 3 h after the last acquisition trial. In probe trials, the platform was removed, and the animals were allowed to swim for 60 s. A latency of 60 s was assigned to rats that did not reach the platform location within the trial duration. Values measured were "escape latency" (time to get to the location where the platform had been positioned during acquisition, "time in target quadrant", "time in opposite quadrant", "quadrant bias" (time spent in the target quadrant vs. time spent in the opposite quadrant), "mean swim speed", "time in periphery" and "total distance travelled". The latter was used as a measure of search strategy efficiency (Spowart-Manning and van der Staay, 2005). Both quadrant bias and time in periphery were presented as a percentage of total trial time. The software package used to track the animals and to analyze data was *Ethovision*, Version 3.0, Noldus, The Netherlands.

2.4. Hole-board task

The apparatus design, validated by File and Wardill (1975) was derived from the hole board introduced by Boissier et al. (1964). This apparatus can be thought of as an open field with some modifications aimed at increasing the motivation of an animal to explore. The hole board consisted of a wooden box 60×60×43 cm, in which the inside walls and floor were painted white. The bottom of the box had 4 circular holes, each 4 cm in diameter, whose centre was located 18 cm away from each of two adjacent walls. A grid was also drawn on the floor. The experiments were carried out in a dimly lit room. Rats were kept in the room for at least 30 min before the first trial.