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BLOCKADE OF THE DORSAL HIPPOCAMPAL DOPAMINE D1 RECEPTORS INHIBITS THE SCOPOLAMINE-INDUCED STATE-DEPENDENT LEARNING IN RATS

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Abstract—In the present study, we investigated the possible role of the dorsal hippocampal (CA1) dopamine D1 receptors on scopolamine-induced amnesia as well as scopolamine state-dependent memory in adult male Wistar rats. Animals were bilaterally implanted with chronic cannulae in the CA1 regions of the dorsal hippocampus, trained in a step-through type inhibitory avoidance task, and tested 24 h after training for their step-through latency. Results indicated that pre-training or pre-test intra-CA1 administration of scopolamine (1.5 and 3 μg/rat) dose-dependently reduced the step-through latency, showing an amnestic response. The pre-training scopolamine-induced amnesia (3 μg/rat) was reversed by the pre-test administration of scopolamine, indicating a state-dependent effect. Similarly, the pre-test administration of dopamine D1 receptor agonist, 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SKF38393; 1, 2 and 4 μg/rat, intra-CA1), could significantly reverse the scopolamine-induced amnesia. Interestingly, administration of an ineffective dose of scopolamine (0.25 μg/rat, intra-CA1) before different doses of SKF38393, blocked the reversal effect of SKF38393 on the pre-training scopolamine-induced amnesia. Moreover, while the pre-test intra-CA1 injection of the dopamine D1 receptor antagonist, R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390; 0.1 and 0.5 μg/rat, intra-CA1), resulted in apparent memory impairment, microinjection of the same doses of this agent inhibited the scopolamine-induced state-dependent memory. These results indicate that the CA1 dopamine D1 receptors may potentially play an important role in scopolamine-induced amnesia as well as the scopolamine state-dependent memory. Furthermore, our results propose that dopamine D1 receptor agonist, SKF38393 reverses the scopolamine-induced amnesia via acetylcholine release and possibly through the activation of muscarinic receptors.

Key words: scopolamine, dopamine D1 receptors, dorsal hippocampus, state-dependent memory, inhibitory avoidance memory, rat.

INTRODUCTION

Acetylcholine (ACh) activity seems essential to learn multiple tasks (Blokland, 1995; Robinson et al., 2011). Cumulative evidence indicates that acetylcholinesterase inhibitors, which enhance the availability of ACh in the synaptic cleft, improve performance in several cognitive models both in rodents and humans, whereas anticholinergic drugs are shown to impair learning and memory function upon a variety of tasks (Fibiger et al., 1991; Gallagher and Colombo, 1995; Power et al., 2003; Azami et al., 2010; Mahmoodi et al., 2010; Pakpour et al., 2010; Jamali-Raeufy et al., 2011). While both nicotinic and muscarinic receptors of the dorsal hippocampus are involved in learning and memory processes (Rezayof et al., 2008), the role of the muscarnic ACh receptors in learning and memory has been emphasized more (Power et al., 2003; Azami et al., 2010; Mahmoodi et al., 2010; Pakpour et al., 2010; Jamali-Raeufy et al., 2011).

Similar to ACh, dopamine (DA) is known to significantly contribute to learning and memory (Jay, 2003; Wittmann et al., 2005; Nasehi et al., 2010). Several studies have suggested that the entry of information into the long-term memory in the hippocampus is affected by the neuromodulatory signals from dopaminergic projections (Gasbarri et al., 1994; Jay, 2003; Wittmann et al., 2005).

A substantial body of evidence shows the complex interaction between cholinergic and dopaminergic systems (Levin and Rose, 1991; Hersi et al., 1995b;

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Abbreviations: ACh, acetylcholine; ANOVA, analysis of variance; CA1, dorsal hippocampal; cAMP/PKA, cyclic AMP/protein kinase A; DA, dopamine; intra-CA1, intra-dorsal hippocampal; SCH23390, R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; SKF38393, 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride.

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Gasbarri et al., 1997). For instance, intraperitoneal administration of scopolamine decreases DA release in the hippocampus (Memo et al., 1988), whereas, the D1 receptor agonist, 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SKF38393) increases in vivo hippocampal ACh release and the D1 receptor agonist, R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390) inhibits ACh release in the hippocampus (Hersi et al., 1995a,b). Furthermore, the continuous intravenous infusion of the muscarinic cholinergic receptor agonist is shown to alter the cholinergic and dopaminergic receptors' density in monkey's brain (Hartvig et al., 2002). In addition, evidence suggests that some anti-dementia drugs such as Ginkgo biloba leaf extract enhance patients' memory performance by means of increasing DA and ACh release in the hippocampus or other sites of the brain (Kehr et al., 2012; Zurkovsky et al., 2012; Shi et al., 2013).

Administration of scopolamine, a muscarinic cholinergic receptor antagonist, is shown to impair memory performance in different models of memory assessment (Collerton, 1986; Jensen et al., 1987; Quartermain and Leo, 1988; Azami et al., 2010). Scopolamine, may be utilized as a useful pharmacological tool to produce a partial model of the aging and (Alzheimer's) dementia (Bartus, 2000). This model is frequently employed as a simple and quick way for testing cognition-enhancing properties of new drugs (Snyder et al., 2005; Klinkenberg and Blokland, 2010). When a compound is found effective in restoring the scopolamine-induced amnesia in animals, it might possibly improve cognitive functions in healthy participants or in patients diagnosed with impaired memory function (Snyder et al., 2005; Klinkenberg and Blokland, 2010). According to some reports, memory impairment induced by the intraperitoneal injection of scopolamine can be ameliorated by the intra-ventral hippocampal injection of D2 receptor agonists (Fujishiro et al., 2005). Yet, the involvement of D1 dopaminergic receptors of the dorsal hippocampus on amnesia induced by scopolamine cannot be excluded. Given the fact that D1 receptor agonists increase the ACh release (Hersi et al., 1995a,b) and scopolamine could decrease DA release in the hippocampus (Memo et al., 1988), the present study was designed to investigate the effects of the bilateral intra-dorsal hippocampal (intra-CA1) microinjections of D1 receptor agonist and antagonist agents on scopolamine-induced amnesia as well as scopolamine state-dependent memory, using an inhibitory avoidance task.

EXPERIMENTAL PROCEDURES

Animals

Adult male Wistar rats (Pasteur institute, Tehran, Iran) weighing 220–270 g at the time of surgery were used. They had free access to food and water, were housed four in a cage, and kept at (22 ± 2) °C under a 12/12 h light–dark cycle (light beginning at 7:00 a.m). All experiments were carried out during the light phase between 8:00 and 14:00. Experimental groups comprised eight rats and each animal was tested once. All procedures were performed in accordance with the institutional guidelines for animal care and use.

Surgery

Animals were anaesthetized by intraperitoneal (i.p.) injection of ketamine/xylazine mixture (100 and 10 mg/kg, respectively) and placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) with a flat-skull position and the incisor bar −3.3 mm relative to the interaural line. After making a midline surgical incision, the skin and underlying periosteum were retracted. Two holes were drilled in the skull, as described in previous studies (Ishikawa et al., 1982; Packard and White, 1991), at stereotaxic coordinates of AP: −3 to −3.5 mm (depending on body weight and age) posterior to the bregma, and L: ±1.8–2 mm from midline according to the atlas of Paxinos and Watson (2006). According to the Paxinos atlas, these coordinates correspond to the length of 9 mm for bregma-lamda interval, thus, as we measured this interval in each rat's skull, we considered a ratio to locate the actual sites for cannulae implantation. Two guide cannulae (22 gauge) were inserted into the holes. For animals receiving bilateral injections into the dorsal hippocampal (CA1) area of the hippocampus, the guide cannulae were advanced 2.8–3 mm below the bregma through the holes drilled at the above-mentioned coordinates. The guide cannulae were anchored with a jeweler's screw, and the incision was closed with dental cement. After surgery, stainless steel stylets (27 gauge) were inserted into the guide cannulae and left in the place until injections were made to keep them patent prior to the injections. All animals were allowed 1 week to recover from surgery and to get cleared from anesthetics' effects.

Drugs and microinfusions

The drugs included scopolamine hydrobromide (Tocris, Bristol, BS11 0QL, UK), SKF38393 and SCH23390 (Sigma, St Louis, CA, USA). All drugs were dissolved in sterile saline and were injected into the CA1 region of the dorsal hippocampus. For bilateral drug infusion, the animals were gently restrained in hand; the stylets were removed from the guide cannulae and replaced by 27-gauge injection needles (1 mm below the tip of the guide cannula). The injection solutions were administered at a total volume of 1 μl/rat (0.5 μl in each side) over a 60-s period. Injection needles were left in place for an additional 60 s to facilitate the diffusion of the drugs.

Inhibitory avoidance apparatus

We used a step-through inhibitory avoidance apparatus consisting of two compartments of the same size ($20 \times 20 \times 30\ cm^3$). In the middle of a dividing wall, there was a guillotine door ($7.9\ cm^2$) which could be lifted manually. The walls and floor of one compartment consisted of white opaque resin, while the other