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Research report

Effects of ventral pallidal D1 dopamine receptor activation on memory consolidation in morris water maze test

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HIGHLIGHTS

- D1 dopamine receptor agonist SKF38393 was microinjected into the ventral pallidum.
- SKF38393 in lower doses enhances memory consolidation in spatial learning.
- SKF38393 in lower doses increases stability of the memory trace against extinction.
- D1 dopamine receptor antagonist SCH23390 pretreatment eliminates SKF38393 effects.

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ABSTRACT

In the present experiments, in adult male Wistar rats, the effect of microinjection of the D1 dopamine receptor agonist SKF38393 into the ventral pallidum on memory consolidation, as well as on resistance of the resulting memory trace against extinction were investigated in Morris water maze test. SKF38393 was applied in three doses (0.1, 1.0 or 5.0 μg in 0.4 μl physiological saline, respectively). To clarify whether the effect of the agonist was specific, in a separate group of animals, the D1 dopamine receptor antagonist SCH23390 (5.0 μg in 0.4 μl physiological saline) was administered 15 min prior to 1.0 μg agonist treatment. In another group of animals, the same dose of antagonist was applied by itself.

The two lower doses (0.1 and 1.0 μg) of the agonist accelerated memory consolidation relative to controls and increased the stability of the consolidated memory trace against extinction. Antagonist pretreatment eliminated the effects of the agonist, thus confirming that the effect was selectively specific to D1 dopamine receptors. Our findings indicate that the ventral pallidal D1 dopamine receptors are intimately involved in the control of the consolidation processes of spatial memory.

1. Introduction

It is well known that the mesolimbic dopaminergic system (MLDS) arising from the ventral tegmental area (VTA) plays important role in motivation, reinforcement, learning and memory processes [1,2]. Dopamine released from the endings of the MLDS modulates synaptic plasticity [3,4].

The ventral pallidum (VP), receiving terminal elements of the MLDS, has reciprocal connections with several important brain regions essential for reinforcement, learning and memory [5–7]. The VP is the main target area of projection fibers from the nucleus accumbens (these fibers are predominantly GABAergic ones), and the VP also receives strong glutamatergic innervations from the prefrontal cortex and amygdala [8,9]. Although the VP has no direct connection to the hippocampus, this latter can influence ventral pallidal activity via the nucleus accumbens [10].

The VP is innervated by the dopaminergic fibers of the VTA, and in turn, the VP sends GABAergic fibers to the originating areas of the MLDS [5,11–13]. It has been shown that in the VP both D1 and D2 dopamine receptor subtypes are found, however, receptor density of the former is much higher compared to the latter [14–17]. VP neurons respond to both local and systemic application of dopamine and its agonists [18–22]. Local application of the D1 dopamine receptor agonist SKF38393 and the D2 dopamine receptor agonist quinpirole evoke, in most cases, opposite changes in the firing rate of VP neurons [18]. Systemically administered SKF38393

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increases firing rate of the cells in the VP, the quinpirole, however, was demonstrated to suppress firing rate [20]. Nevertheless, it is important to note that most VP neurons do not respond to quinpirole, suggesting a low density of D2 receptors in this forebrain region [18].

Increasing amount of information is available about the role of VP dopamine and its receptors mainly in motor behavior, and, to a more limited extent, in motivation and reward/positive reinforcement processes. Dopamine administration at low doses into the VP increases locomotor activity [23]. It has been shown that microinjection of the D1 dopamine receptor agonist SKF38393 into the VP generally increased, while that of the D2 dopamine receptor agonist quinpirole rather decreased locomotion [24]. Thus, it is reasonable to suppose, that the above locomotor effects of dopamine are exerted predominantly via D1 dopamine receptors of the VP. It has also been demonstrated that psychostimulants such as amphetamine and cocaine injected into the VP induce place preference [25]. Acquisition of place preference evoked by the dopamine reuptake inhibitor cocaine can be blocked by 6-hydroxydopamine [26]. The D1 and D2 dopamine receptor antagonists increased the threshold of intracranial self-stimulation and decreased the maximal rate of it [27].

Putting it all together, VP dopamine appears to be fundamental in the organization of motivated behaviors, but little is known yet about its exact role in learning and memory processes. Our recent results demonstrate that the D1 dopamine receptor agonist SKF38393 dose-dependently improves memory consolidation and retention in inhibitory avoidance learning [28].

Considering the data above, the present experiments, by using the Morris water maze paradigm, were designed to investigate the role of D1 dopamine receptor subtype of the VP in the consolidation of spatial memory.

2. Methods

2.1. Drugs and subjects

In the present experiments, effect of bilateral microinjection of the D1 dopamine receptor agonist (R)-(+)-SKF-38393 hydrochloride (Sigma–Aldrich Co., S101) and the D1 dopamine receptor antagonist R(+)-SCH-23390 hydrochloride (Sigma–Aldrich Co., D054) into the VP was investigated in Morris water maze test (MWM) in male Wistar rats. We used 78 animals weighing 280–320 g at the beginning of the experiments. Rats were housed individually and cared for in accordance with institutional (BA02/2000-8/2012), national (Hungarian Government Decree, 40/2013. II. 14) and international standards (European Community Council Directive,86/609/EEC, 1986, 2010). Animals were kept in a light and temperature controlled room (12:12 h light–dark cycle with lights on at 06:00 a.m., 22 ± 2 °C). Tap water and standard laboratory food pellets (CRLT/N standard rodent food pellet, Charles River Laboratories, Budapest) were available ad libitum. Food and water consumption and body weight were measured daily. All tests were performed during the daylight period of the rats between 08:00 and 17:00 h.

2.2. Surgery

Operations were carried out under anesthesia by intraperitoneal injection of a mixture of ketamine (Calypsol) and diazepam (Seduxen) mixed in a ratio of 4:1 (Calypsol, 80 mg/kg bw and Seduxen, 20 mg/kg bw, respectively; Richter Gedeon Ltd., Hungary). By means of the stereotaxic technique, 22 gauge stainless steel guide tubes were bilaterally implanted 0.5 mm above the target area (coordinates referring to the bregma: AP: −0.26 mm, ML: ±2.2 mm, DV: −7.1 mm from the surface of the dura) according to the stereotaxic rat brain atlas of Paxinos and Watson [29]. Cannulae were fixed to the skull with self-polymerizing dental acrylic (Duracryl) anchored by 2 stainless steel screws. The guide tubes, except when being used for insertion of microinjection delivery cannula, were occluded with stainless steel obturators made of 27 gauge stainless steel wire.

2.3. Morris water maze test

Experiments were carried out in a circular pool with a diameter of 1.5 m and filled with water (temperature: 23 ± 1 °C) [30]. The pool was divided into four quadrants. One of these was chosen to place a square (10 cm × 10 cm) plexiglass platform in it. The location of the platform was fixed during the experiments, except in the habituation and extinction trials when the animals swam without the presence of the platform. Surface of the water was kept 2 cm above the platform and the water was colored to make the water opaque, and the platform hidden for the animals. The pool was surrounded with external cues, which helped the orientation of the rats. These cues were kept in constant position throughout the whole experiment. The behavior of animals was recorded by a video camera and registered by a specific software (EthoVision; Noldus Information Technology, The Netherlands). One day before the start of training, rats were habituated to the pool by allowing them to perform swimming for 90 s without platform. In the morning of the first day, two trials for spatial learning (detailed below) were performed, the two trials were separated by 1 min interval. This short intertrial interval ensured the possibility to observe in the second trial the short term memory trace formed during the first trial. On the second day, 24 h later, the schedule of the first day was repeated to investigate the possible further consolidation of memory. In these trials, the latency to finding the safe platform was measured. On the third day, 24 h later, in the morning, an extinction trial was performed: the platform was removed, and the latency to the first crossing of the removed platform's place was measured. In the extinction trial, in addition to the first crossing, three other parameters were measured: number of crossings at the place of the removed hidden platform, number of the entrances into the target quadrant (where the platform was previously placed) and the time spent in the target quadrant. The same day, in the afternoon, the test trial was carried out: the platform was replaced and the latency to finding the safe platform was measured again.

The first four trials were conducted as follows: rats were placed into the water maze at randomly assigned but predetermined locations to avoid the egocentric orientation. The task required animals to swim to the hidden platform guided by external spatial cues. After finding the platform, the rats were allowed to remain there for 60 s. Animals failing to find the platform in 180 s were placed on the platform and were allowed to rest for 60 s. During the experiments, in each trial the mean swimming velocities of the animals were measured.

2.4. Microinjection protocol

The first and the second day, the two series of trials were immediately followed by the bilateral microinjection of D1 dopamine receptor agonist into the VP, that is, one experimental day one microinjection was performed. The agonist was applied in three different doses (SKF38393, 0.1 μg, 1.0 μg or 5.0 μg, in 0.4 μl physiological saline, 0.85 mM, 8.56 mM and 42.84 mM, respectively). Control animals received only vehicle (physiological saline) in all cases (0.4 μl, bilaterally). In a second experiment, D1 dopamine receptor antagonist (SCH23390, 5.0 μg in 0.4 μl physiological saline, 38.55 mM) was microinjected by itself or 15 min before the administration of 1.0 μg agonist. Solutions were kept in +4 °C