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Hippocampal α-adrenoceptors involve in the effect of histamine on spatial learning

Anahita Torkaman-Boutorabi [a], Fatemeh Danyali [b], Shahrbanoo Oryan [b], Mohaddeseh Ebrahimi-Ghiri [c], Mohammad-Reza Zarrindast [a,d,e,f,g,*]

[a] Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Biology, Sciences and Research Branch, Islamic Azad University, Tehran, Iran
[c] Department of Biology, Faculty of Basic Sciences, University of Zanjan, Zanjan, Iran
[d] Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran
[e] School of Cognitive Sciences, Institute for Research in Fundamental Sciences, Tehran, Iran
[f] Institute for Cognitive Science Studies, Tehran, Iran
[g] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

HIGHLIGHTS

- Phenylephrine or clonidine induced a dual response in training phase.
- Prazosin impaired while yohimbine or histamine facilitated spatial learning.
- Subthreshold dose of phenylephrine reversed histamine response at the highest dose.
- Subthreshold dose of clonidine potentiated histamine response at the lowest dose.
- Subthreshold dose of prazosin or yohimbine did not alter histamine response.

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ABSTRACT

Spatial learning is a model of higher human cognitive functions which is used for studying animal behavior. Histaminergic and noradrenergic systems play a modulatory role in learning and memory. The present study aimed to test the effects of α-adrenoceptor agonist/antagonist microinjection into the CA1 region of dorsal hippocampus on histamine-induced spatial learning facilitation in the water maze task. Pre-training intra-CA1 microinjection of α_1- or α_2-adrenergic agonist, phenylephrine (0.0025 μg/rat) or clonidine (0.05 μg/rat) decreased traveled distance and escape latency at the start of the training phase, suggesting a spatial learning facilitation; while the higher dose of the drugs (phenylephrine 0.005 μg/rat, clonidine 0.2 and 0.5 μg/rat) increased the performance level at the end of the training phase, indicating a water maze spatial acquisition impairment. However, α_1-receptor antagonist, prazosin (1 μg/rat) impaired spatial learning; α_2-receptor antagonist, yohimbine (0.25 μg/rat) facilitated spatial acquisition. Moreover, pre-training intra-CA1 microinjection of a subthreshold dose of phenylephrine (0.001 μg/rat) reversed histamine response, while ineffective dose co-administration of clonidine (0.1 μg/rat) potentiated histamine (0.01 μg/rat) response. Subthreshold dose of prazosin or yohimbine did not alter histamine response. Bilateral infusion of histamine (0.05 μg/rat) facilitated spatial learning by itself. Furthermore, the drug's injections had no effect on swimming speed on the training days of MWM. These results suggest that α-adrenergic receptors of the dorsal hippocampal CA1 regions may play an important role in histamine-induced facilitation of spatial acquisition.

1. Introduction

The hippocampus has a well-known role in spatial memory acquisition and the processing of spatial information in most of mammals [1,2]. In this structure, different neurotransmission systems are involved in the modulation of memory processes [3–6]. There is evidence that noradrenaline when injected into the amygdala [7], hippocampus and entorhinal cortex [8] enhance memory formation indicating the involvement of adrenergic receptor (AR) systems in learning and memory. The hippocampus as a major target of adrenergic system receives a dense noradrenergic innervation from the locus coeruleus (LC) [9]. The ARs comprise a family of 7-transmembrane spanning G protein-coupled receptors named: α_1-, α_2-, and β-receptors, each with three

* Corresponding author at: Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, P.O. Box 13145-784, Tehran, Iran. Tel./fax: +98 21 66402569.
E-mail address: zarinmr@ams.ac.ir (M.-R. Zarrindast).

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(perhaps more) subtypes [10]. The α_1-ARs are mainly post-synaptic, while α_2-adrenoceptors are localized both pre-synaptically and post-synaptically [11]. It has also been reported that α_1- and α_2-ARs may be situated on glial cells or non-noradrenergic nerve terminals in mammalian brain [12]. The α_1-ARs are generally coupled to Gq proteins, activate phospholipase C and phosphotidyl inositol intracellular signaling and result in the activation of protein kinase C (PKC) and the release of intracellular calcium via inositol 1,4,5-triphosphate [13]. Moreover, α_2-ARs are coupled to Gi proteins [14], which can reduce intracellular cyclic adenosine monophosphate (cAMP) production by inhibiting some adenylyl cyclase isoforms. There is a suggestion that activation of hippocampal α_1-ARs can attenuate glutamatergic neurotransmission or may potentiate the cellular consequences of NMDA receptor activation indirectly via non-neuronal mechanisms [15]. Furthermore, hippocampal α_{1A}-AR activation depolarizes a subpopulation of CA1 GABAergic interneurons [16,17]. These interneurons may express the neuropeptide somatostatin [18]. The α_{1A}-AR-mediated depolarization possibly results in GABA and somatostatin release onto nearby pyramidal neurons. Therefore, the possibility may exist that activation of the α_{1A}-AR not only modulates firing of CA1 interneurons, but also has downstream effects on pyramidal neuron activity [19]. It should be also considered that other subtypes of α_2-ARs (α_{2A}- and α_{2C}) are found in the hippocampus [20].

On the other hand, histamine has been shown to modulate learning in different behavioral tasks, but the exact mechanisms involved are controversial. Histamine acts through four distinct types (H1 to H4) and G protein-coupled receptors and several associated second messengers. Both H1 and H2 receptors excite or potentiate excitatory impulses [21–23], while H3 activation elicits autoinhibition of tuberomammillary nucleus neurons and inhibits the synthesis and release of histamine or other neurotransmitters such as glutamate, acetylcholine, and noradrenaline [21,24,25]. H4 type is expressed in peripheral tissues like bone marrow and leukocytes [26]. It has been suggested that histamine activates hippocampal pyramidal cells in slices via H2 receptors [27]. The decrease in calcium-activated potassium conductance [28], increase in neuronal excitability [29], and control of high-frequency oscillations [30,31] are mediated by histamine in the hippocampus, which also can enhance N-methyl-D-aspartate (NMDA)-mediated responses [32,33]. In fact, histamine is able to modulate the threshold for induction of NMDA receptor-dependent long-term potentiation (LTP) in the CA1 region [34], a form of synaptic plasticity that is considered a cellular correlate of memory formation [35].

In addition, ample evidence has confirmed the existence of an interaction between the adrenergic and histaminergic systems [36,37]. Shelton and McCarthy reported that hippocampal astrocytes have histamine receptors coupled to Ca^{2+}. Given that Ca^{2+} elevations may trigger astrocytes to release glutamate, affecting neuronal activity [38]. They also suggested that α_1-ARs in the hippocampal astrocytes are regulated during development.

Since the hippocampus [39] plays important roles in memory formation of the spatial learning task which is an approved model to hippocampus-dependent learning task, and it is a major target of adrenergic and histaminergic systems, therefore, we aimed to examine the effects of bilateral microinjections of α_1- or α_2-adrenergic receptor agents into the CA1 region of the dorsal hippocampus on histamine-induced memory acquisition facilitation.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (Pasteur Institute; Tehran, Iran), weighing 200–240 g at the time of the surgery were used as subjects. The animals were housed four per standard rat cage, in a room with a 12/12 h light/dark cycle (lights on 7:00 h) and controlled temperature (22 ± 1 °C). Commercial rodent pellets and tap water were available ad libitum except for the times of experiments. Animal care was according to the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Surgery and microinjection

Under deep anesthesia (50 mg/kg of ketamine and 5 mg/kg of xylazine), the animals were placed in a stereotaxic frame. The animals were bilaterally implanted with 22-gauge guide steel cannulae into the CA1 region of dorsal hippocampus according to the atlas of Paxinos and Watson [40]. Stereotaxic coordinates for the CA1 region of the dorsal hippocampus were: AP: −3.3; ML: 2; and DV: −2.8. Cannulae were secured to anchor jewelers' screws with dental acrylic. Stainless steel stylets (27-gauge) were placed in the guide cannulae in order to prevent clogging until each animal was given the CA1 injections. All animals were allowed a 7 day recovery period from surgery and to clear the anesthetic. For drug injection, the stylets were gently removed from the guide cannulae and replaced by 27-gauge injection needles. Considering that the guide cannulae were implanted 1 mm above the CA1, the injection needles were 1 mm longer than those. Each injection unit was connected by polyethylene tubing to 2 μl Hamilton syringe. The CA1 was injected with a 0.5 μl solution for over a 60 s period. In order to prevent backflow through the needle track, the injection needles were left in place for an additional 60 s to allow for diffusion.

2.3. Drugs

The drugs included histamine dihydrochloride (Sigma, St. Louis, CA, USA), yohimbine (Tocris, UK), phenylephrine hydrochloride, prazosin hydrochloride and clonidine hydrochloride (Sigma, UK). All drugs were dissolved in sterile saline and were injected into the CA1 region of dorsal hippocampus.

2.4. Behavioral training and evaluation

Briefly, the Morris water maze included a black-painted circular pool (136 cm diameter, 60 cm height), filled to a depth of 35 cm with water (22 ± 2 °C). This pool was divided to four equal quadrants and a hidden platform (10 cm in diameter), made of Plexiglas, was located 1 cm under the water surface in the center of South-West quadrant (target quadrant). After recovery from stereotaxic surgeries, training of animals was started and continued for 4 consecutive days (each day included one block of 4 trials). Each trial was started by placing the animal in one of the four quadrants. The animals were allowed to swim in the pool during a period of 90 s and find the hidden platform. If an animal did not find the platform within this period, it was manually guided to the platform by the investigator. The rats rested 30 s between two consecutive trials and all trials were conducted at about the same time of the morning. Directions of the rats were recorded by a video camera located just above the center of the maze. The camera was connected to a computer. Spatial acquisition was evaluated by a video tracking system (Noldus Information Technology, Wageningen, The Netherlands) through measuring escape latency (time to find the platform), traveled distance (path length to reach the platform), and swimming speed.

2.5. Drug treatment

Eight animals were used in each experimental group. In the experiments where the animals received one or two injections, the control groups also received one or two saline injections. The intervals of drug administration were based on our previous studies in order to obtain a maximum response.

2.5.1. Experiment 1: Effect of pre-training intra-CA1 microinjection of phenylephrine, prazosin, clonidine or yohimbine on spatial acquisition

The animals received different doses of phenylephrine (0.001, 0.0025 and 0.005 μg/rat), prazosin (0.1, 0.5 and 1 μg/rat), clonidine