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Influence of nitric oxide agents in the dorsal hippocampus of mice on anxiogenic-like effect induced by histamine

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ABSTRACT

Histaminergic receptors and neuronal nitric oxide synthase (nNOS) are co-expressed at high levels in the hippocampal neurons and alter anxiety-like behaviors in rodents. Since the dorsal hippocampus may be involved in modulation of anxiety-like behaviors, the aim of the present study was to assess whether the nitric oxide (NO) system in the dorsal hippocampus affects anxiety-like behaviors induced by histaminergic agents in mice. The effects of the NO precursor, L-arginine and NOS inhibitor, L-nitro-amino-methyl-ester (L-NAME) on histamine, pyrilamine and ranitidine responses in elevated plus maze (E.P.M.) in mice were investigated. Intra-CA1 microinjection of histamine (9 μg/mouse) or H1 receptor antagonist, pyrilamine (3, 6 and 9 μg/mouse), but not H2 receptor antagonist, ranitidine decreased the percentage of open arm time (%OAT) and open arm entries (%OAE), without affecting locomotor activity, suggesting an anxiogenic-like response. Both L-arginine (0.4 and 0.8 μg/mouse) and L-NAME (40 ng/mouse) when injected into the dorsal hippocampus induced anxiety-like behaviors, but the drugs reversed the anxiogenic response induced by the effective dose of histamine (9 μg/mouse) or pyrilamine (9 μg/mouse). Our results also indicated that intra-CA1 administration of L-arginine and L-NAME, in the presence or absence of ranitidine, exerted an anxiogenic effect. The results may indicate a modulatory role for NO in the dorsal hippocampus in the anxiogenic-like response induced by histamine or pyrilamine.

1. Introduction

The biogenic amine histamine is an important neurotransmitter–neuromodulator in both the peripheral and the central nervous systems which are involved in sleep–wake cycle, emotion, appetite control, locomotor activity, stress-related behaviors, learning, and memory through different histamine receptor types (Brown et al., 2001; Leurs et al., 1994; Malmberg-Aiello et al., 2002; Privou et al., 1998; Schwartz et al., 1991; Zarrindast et al., 2005a). Ample evidence has shown that histamine release is a sensitive indicator of stress (Mazurkiewicz-Kwilecki and Taub, 1978; Yoshitomi et al., 1986). In rats, incomplete lesions of tuberomammillary rostroventral E-2 subregion, from which histaminergic fibers arise, can induce anxiolytic-like effects in the E.P.M. test (Frisch et al., 1998). Furthermore, the clinically effective anxiolytic drugs such as diazepam and buspirone decrease the turnover rate of brain histamine in mice and rats (Chikai et al., 1993; Oishi et al., 1992). Three different H1, H2 and H3 histaminergic receptors have been identified to date in the CNS (Hill et al., 1997). H1 and H2 receptors were found to be post-synaptic, while H3 receptors are localized pre-synaptically which function as auto- and hetero-receptors (Hill et al., 1997). These metabotropic G-protein coupled receptors differ in pharmacology, cellular transduction processes and localization (Haas and Panula, 2003), but all three forms of histamine receptors are expressed in the hippocampus (Josselyn and Nguyen, 2005; Lintunen et al., 1998), which play an important role in anxiety and the modulation of memory (Dere et al., 2010). The stimulation of histamine H2 receptors activates adenylyl cyclase which induces the accumulation of cAMP and subsequently activates protein kinase A (Josselyn and Nguyen, 2005). The histamine H1 receptors' stimulation activates phospholipase C which leads to increase in intracellular calcium levels and cAMP levels (Haas and Panula, 2003). In addition, histamine H1 receptor activation induces the production of arachidonic acid and nitric oxide (Haas and Panula, 2003). In this way, H1 receptor activation may be

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able to modulate transmitter release since both arachidonic acid and nitric oxide (NO) have been proposed to act as retrograde messengers. Thus, the H1 receptors' stimulation activates pre-synaptic and post-synaptic intracellular signaling cascades (Haas and Panula, 2003). On the other hand, there are reports indicating that the activity of histaminergic neurons seems to be permanently modulated by endogenous NO (Philippu and Prast, 2001; Zarrindast et al., 2011).

NO is synthesized by a group of enzymes, termed NO-synthase (NOS), which catalyzes the conversion of L-arginine to L-citrulline, producing NO as a by-product (Moncada, 1993). Neuronal NOS is found mostly in neuronal cell bodies, dendrites, and axons, and is abundantly expressed in the CNS, including the cerebral cortex, hippocampus, striatum, hypothalamic and amygdaloid nuclei, and mesencephalon (Vincent and Kimura, 1992) structures that are believed to participate in the modulation of anxiety-like states in the brain. Considerable evidence indicates that NO mediates anxiety-related behaviors in rodents (Calixto et al., 2001; De Oliveira et al., 1997; Dunn et al., 1998; Eroglu and Caglayan, 1997; Faria et al., 1997; Guimaraes et al., 2005; Podhorna and Brown, 1999, 2000; Yildiz et al., 2000). Furthermore, activation of the NO system in the brain has been shown after aversive stimuli, such as restraint stress (Krukoff and Khalili, 1997), exposure to the E.P.M. (Beijamini and Guimaraes, 2006a), and exposure to a live cat (Beijamini and Guimaraes, 2006b).

There is a report showing that activation or inhibition of H1 receptors increases or decreases production and release of nitric oxide in the hippocampus respectively (Haas and Panula, 2003). Since nitric oxide may modulate anxiety-related behaviors, one may expect that this response to histamine may partly be mediated through changes in the nitric oxide levels in the dorsal hippocampus (Zarrindast et al., 2011). We examined this hypothesis in this study. For this purpose, we investigated the effects of NO agents on histamine-induced anxiety-like behaviors when microinjected into the dorsal hippocampus of mice by using the E.P.M. test which is an animal model tool for investigating and understanding the brain areas related to anxiety (Pellow and File, 1986).

2. Materials and methods

2.1. Subjects

The subjects were male albino NMRI mice (Pasteur Institute; Tehran, Iran) weighing 22–30 g. The animals were housed 10 per Plexiglas cage, in a room with controlled photoperiod (a 12-h light/dark cycle) and temperature (22 ± 2 °C). They had food and water available ad lib and were allowed to adapt to the laboratory conditions for at least 1 week before the surgery. The experiments were carried out during the light phase of the cycle. Ten animals were used in each group of experiments; each animal was used only once. Behavioral tests and animal care were conducted in accordance with the standard ethical guidelines (NIH, publication no. 85–23, revised 1985; European Communities Directive 86/609/EEC) and approved by the local ethical committee.

2.2. Surgery and microinjection

The mice were anesthetized with intra-peritoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and placed in a stereotaxic apparatus. The skin was incised and the skull was cleaned. Two 23-gauge guide cannulae were placed 1 mm above the intended site of injection according to the atlas of Paxinos and Franklin (2001). Stereotaxic coordinates for the CA1 regions of the dorsal hippocampus were AP: −2 mm from bregma, L: −1.6 from the sagittal suture and V: −1.5 mm from the skull surface (Paxinos and Franklin, 2001). The cannulae were secured to anchor jewelers' screws with dental acrylic. Stainless steel stylets (30-gauge) were inserted into the guide cannulae to keep them free of debris. All animals were allowed 1 week to recover from surgery and clear anesthetic. For drug infusion, the animals were gently restrained by hand; the stylets were removed from the guide cannulae and replaced by 30-gauge injection needles (1 mm below the tip of the guide cannulae). Bilateral microinjections of drugs into the CA1 (Intra-CA1) were in a volume of 1 μl (0.5 μl/side). Injections were made over a 60-s period, and the injection cannulae were left in the guide cannulae for an additional 60 s to facilitate the diffusion of the drugs.

2.3. Behavioral testing (elevated plus maze)

E.P.M. testing was conducted as previously described (Zarrindast et al., 2001). All behavioral testing took place in a dimly lighted room separated from the colony room. Animals were adapted to the testing room for 1 h prior to testing. The wooden apparatus consisted of two open arms (40 × 7), and two closed arms of the same size but with 10 cm high end and side walls. The arms were connected by a central 7 × 7 cm area. The mice were placed in the center of the E.P.M. with their head facing an open arm and left undisturbed for 5 min (Overton, 1966; Pellow and File, 1986; Rodgers and Johnson, 1995; Rostami et al., 2006). The mice were then removed and returned to their home cages. The maze was cleaned with a 10% chlorine bleach solution after each mouse was tested. The experimental sessions were videotaped and analyzed later. A mouse was considered to be on the central platform when at least two paws were on it (i.e. either both front paws or both hind paws and all four paws) and on an arm whenever all four paws were on it. Percentage of time spent in open arms [%OAT: (time in open arm/time in open + closed arms) × 100] and percentage of open arm entries [%OAE: (number of open arm entries/number of open + closed arm entries) × 100] were used as measures of anxiety, and the number of total arm entries was used as a measure of spontaneous locomotor activity.

2.4. Drugs

The drugs included histamine dihydrochloride, pyrilamine maleate, the histamine H1 receptor antagonist, ranitidine hydrochloride, the histamine H2 receptor antagonist (Sigma Chemical Co., USA), NG nitro-L-arginine methyl ester hydrochloride (L-NAME; Alexis Biochemicals, Lausen, Switzerland) and L-arginine (Sigma Chemical Co., USA). All drugs were dissolved in sterile 0.9% saline just before the experiment. Control animals received either saline or vehicle. The drugs were injected in a volume of 1 μl/mouse (0.5 μl/side) into the dorsal hippocampus (intra-CA1). It is important to note that the doses of drugs, sequence of and the time between drug injections were selected on the basis of a pilot study and on our previous works (Azami et al., 2010; Piri and Zarrindast, 2011; Rostami et al., 2006; Zarrindast et al., 2005a, 2011).

2.5. Experimental design

2.5.1. Experiment 1: effects of histamine on anxiety-like behaviors

Four groups of mice received saline (1 μl/mouse, intra-CA1) or histamine (3, 6 and 9 μg/mouse). In all experiments, the test session was performed 5 min after the final intra-CA1 injections. %OAT, %OAE and locomotor activity were measured as earlier described.

2.5.2. Experiment 2: effects of L-arginine in the presence and absence of histamine on anxiety-like behaviors

Eight groups of mice received saline (1 μl/mouse, intra-CA1) or histamine (9 μg/mouse, intra-CA1) 2 min before the injection of different doses of L-arginine (0, 0.2, 0.4 and 0.8 μg/mouse, intra-CA1).