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Excitatory effect of histamine on neuronal activity of rat globus pallidus by activation of H_2 receptors in vitro

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Abstract

Previous studies have revealed distribution of histaminergic fibers and presence of histamine receptors in globus pallidus (GP). In this study, the brain slice preparation of adult rats was used to examine the effect of histamine on the spontaneous unitary discharge of GP neurons and the underlying receptor mechanism. Ninety-five GP neurons were extracellularly recorded from 42 slices containing the GP, of which 87 (91.6%) were excited by the stimulation of histamine. The histamine-induced excitation was concentration-dependent and persisted in low Ca^{2+}/high Mg^{2+} medium ($n = 9$), demonstrating that the action of histamine on the GP neurons was postsynaptic. The excitatory effect of histamine on the GP neurons was not blocked by selective histamine H_1 receptor antagonist triprolidine ($n = 16$) or chlorpheniramine ($n = 6$), but was effectively suppressed by ranitidine, a highly selective histamine H_2 receptor antagonist ($n = 21$). On the other hand, highly selective histamine H_2 receptor agonist dimaprit mimicked the excitatory effect of histamine on the GP neurons ($n = 23$), while histamine H_1 receptor agonists, including 2-pyridylethylamine ($n = 22$), 2-thiazolyethylamine ($n = 9$) and betahistine ($n = 9$), did not cause GP neurons any response. The dimaprit-induced GP neuronal excitation was effectively antagonized by selective histamine H_2 receptor antagonist ranitidine ($n = 14$) but not influenced by selective histamine H_1 receptor antagonist triprolidine ($n = 12$). Moreover, adenylate cyclase (AC) activator forskolin ($n = 7$) was observed to evoke GP neurons an excitatory response, whereas the histamine-induced excitation was effectively reduced by H-89 ($n = 9$), a selective and potent inhibitor of protein kinase A (PK_A). Finally, it was noted that neurons of both subdivisions of the GP, the internal (GPi, $n = 35$) and external (GPe, $n = 60$) segment, showed no differences in their responses to stimulations of the tested histaminergic reagents. These results demonstrated that histamine excited GP (including GPi and GPe) neurons via histamine H_2 receptors and H_2 receptors linked intracellular G-protein-AC-PK_A signaling pathway, suggesting that the hypothalamic histaminergic afferent fibers innervating GP may play an important modulatory role in motor control through its excitatory effect on GP neurons.

Keywords: Histamine; Histamine receptors; Globus pallidus; Hypothalamic histaminergic projections; Motor control

1. Introduction

The globus pallidus (GP), a substructure of the basal ganglia, has been considered to play an important role in the control of movement. It is well known that there are two major afferent pathways to the GP, the GABAergic

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striatopallidal (Bolam and Smith, 1990) and the glutamatergic subthalamopallidal inputs (Kita and Kitai, 1991; Smith et al., 1998). In fact, besides these inhibitory and excitatory neurotransmitter systems that are believed to transmit discrete signals from the striatum and subthalamic nucleus to the GP, various neurotransmitter/neuromodulator systems arising from other brain regions also innervate the GP. Several studies reported that dopamine (Filion, 1979; Nakanishi et al., 1985), enkephalins (Smith et al., 1998), neurotensin, serotonin and substance P (Chen and Yung, 2004) modulated activity of the GP neurons. In addition, it has been documented that the GP receives histaminergic fibers arising from the tuberomammilary nucleus of the posterior hypothalamus (Steinbusch et al., 1986; Airaksinen and Panula, 1988; Airaksinen et al., 1989; Panula et al., 1989). By using immunocytochemistry, autoradiographic mapping and in situ hybridization, some authors also revealed the presence of histamine receptors in two parts of the GP, the internal segment (GPi) and the external segment (GPe) (Martinez-Mir et al., 1990, 1993; Pollard et al., 1993; Honrubia et al., 2000; Anichtchik et al., 2001).

The central histaminergic nervous system arising from the hypothalamic tuberomammilary nucleus has been demonstrated to widely innervate various brain regions and suggested to globally modulate neuronal activities and brain functions (Brown et al., 2001; Haas and Panula, 2003). A series of electrophysiological studies revealed that histamine exerted an excitatory effect on neuronal activity of some subcortical motor structures, including medial vestibular nucleus, cerebellum, red nucleus, substantia nigra and neostriatum, through its actions on H_1 and/or H_2 receptors (Munakata and Akaike, 1994; Wang and Dutia, 1995; Tang et al., 1996; Li et al., 1999; Prast et al., 1999; Sittig and Davidowa, 2001; Korotkova et al., 2002; Shen et al., 2002; Chen et al., 2003). On the other hand, an early study of autoradiographic mapping demonstrated that in comparison with normal animal models, the levels of H_2 receptors binding sites in the GP of human patients with Huntington's chorea were markedly decreased (Martinez-Mir et al., 1993); and a recent immunohistochemical study revealed that the histamine concentrations in the GPi and GPe of post-mortem brain samples of patients with Parkinson's disease (PD) were significantly increased (Rinne et al., 2002). All these data from both experimental and clinical observations strongly suggest a possible involvement of central histaminergic nervous system in the functions of GP and thus the system may play a role in motor control. However, the effect of histamine on normal GP neuronal activity and the functional significance of hypothalamic histaminergic fibers on the GP have not been experimentally explored. In the present study, we used brain slice preparation and extracellular single unit recording to examine the effects of histamine on the spontaneous neuronal firing activity of GP. The results showed that histamine exerted an excitatory effect on the GP neurons through H_2 receptors, suggesting that the central histaminergic nervous system may play a modulatory role in the motor integration through the basal ganglia macrocircuit.

2. Materials and methods

The experiments were carried out on slices of the GP of the Sprague–Dawley rats (150–250 g) of either sex. Under ether anesthesia, the animals were decapitated. The brain was immediately removed and placed in ice-cold oxygenated artificial cerebrospinal fluid (ACSF, composition in mM: NaCl 124, KCl 5, $MgSO_4$ 1.3, KH_2PO_4 1.2, $NaHCO_3$ 26, $CaCl_2$ 2.4 and D-glucose 10). According to the rat brain atlas of Paxinos and Watson (1998), the coronal brain slices (350–400 μM in thickness) containing the GP were cut with a vibroslicer (VSLM-1, Campden, UK) and transferred into a recording chamber, which was continuously perfused with ACSF equilibrated with 95% O_2/5% CO_2 (pH 7.4, 33 ± 0.2 °C, flow rate 2–3 ml/min). All slices were incubated for a minimum of 40 min before neuronal electrophysiological recording. In some experiments, a low-Ca^{2+}/high-Mg^{2+} medium was used to decrease presynaptic neurotransmitter release. In these cases, the concentration of Ca^{2+} was lowered to 0.3 mM and Mg^{2+} was raised to 9.0 mM (Jorgenson et al., 1989; Li et al., 1999; Tian et al., 2000; Shen et al., 2002; Chen et al., 2003).

Spontaneous unitary activity of the GPi and GPe neurons was recorded extracellularly from the slices by using glass microelectrodes (impedance 5–10 MΩ) filled with 2 M NaCl. Based on the rat brain atlas of Paxinos and Watson (1998), the GPi and GPe (named as medical globus pallidus (MGP) and lateral globus pallidus (LGP) in the atlas for the rat, respectively) were visually identified with the aid of a stereomicroscope (SD-3045F, Olympus, Japan). By using the following two criteria, all the recorded GPi and GPe neurons were discriminated: (i) according to the coronal planes 8.2–7.6 (GPe) and 6.8–5.8 (GPi) in the interaural reference system of the atlas, the GPe in the brain slices looks much bigger and locates more anteriorly and laterally than the GPi; (ii) the firing rate of the GPe neurons is slightly higher than that of the GPi cells (see Section 3).

Before bath application of histaminergic compounds at known concentrations, the discharge frequency of the recorded neuron was observed for at least 20 min to assure stability. Histamine or histamine receptor agonist was added to the perfusing ACSF to stimulate the recorded GP neuron for a test period of 1 min. If the GP neuron responded to the stimulation, the perfusing medium was switched from normal ACSF to the ACSF containing histamine receptor antagonist. After the slice was equilibrated with the ACSF containing the antagonist for at least 15 min, histamine or histamine receptor agonist was re-applied and effect of the antagonist on the response of GP neuron to histamine or histamine receptor agonist was observed. To further examine the mechanisms of intracellular signal transduction