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Research Report

Protective effect of histamine microinjected into cerebellar fastigial nucleus on stress gastric mucosal damage in rats

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ABSTRACT

In the study, we investigated the effect of histamine microinjected into cerebellar fastigial nucleus (FN) on stress gastric mucosal damage (SGMD), and its mechanisms in rats. The model of SGMD was established by restraining and water (21±1 °C)-immersion for 3 h. The gastric mucosal damage index (GMDI) indicated the severity of gastric mucosal damage. Histamine or receptor antagonist was microinjected into the FN. The decussation of superior cerebellar peduncle (DSCP) and the lateral hypothalamic area (LHA) were destroyed, respectively. The pathological changes of gastric mucosa were evaluated using biological signal acquisition system, Laser-Doppler flowmeter, and western blotting. We found that the microinjection of histamine (0.05, 0.5, and 5 μg) into FN significantly attenuated the SGMD, in a dose-dependent manner, whereas, the microinjection of histamine H_2 receptor antagonist, ranitidine, and glutamic acid decarboxylase antagonist, 3-mercaptopropionic acid (3-MPA) exacerbated the SGMD. The protective effect of histamine on SGMD was abolished by electrical lesion of DSCP or chemical ablation of LHA. The microinjection of histamine decreased the discharge frequency of the greater splanchnic nerve, and the gastric mucosal blood flow was increased. In addition, the cellular proliferation was enhanced, but the cellular apoptosis was reduced in the gastric mucosa. Also the pro-apoptosis protein, Bax, and caspase-3 were down-regulated, and the anti-apoptosis protein, Bcl-2 was up-regulated following microinjection of histamine. In conclusion, the FN participated in the regulation of SGMD after histamine microinjected

Abbreviations: FN, fastigial nucleus of the cerebellum; LHA, lateral hypothalamic area; RWI, restraint and water-immersion; SGMD, stress-induced gastric mucosal damage; GMDI, gastric mucosal damage index; DSCP, decussation of superior cerebellar peduncle; SOD, superoxide dismutase; MDA, malondialdehyde; GSN, greater splanchnic nerve; GMBF, gastric mucosal blood flow; 3-MPA, 3-mercaptopropionic acid

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into FN, and cerebellar–hypothalamic circuits (include: DSCP, LHA) contribute to the process, which may provide a new therapeutic strategy for SGMD.

1. Introduction

Histamine is well-known pro-inflammatory substance that has been commonly used in allergic disease. Recently, histamine has been found to be implicated in multiple functions, such as learning, memory, and regulation of sleep/wakefulness, attention, anxiety, pain perception, homeostasis of fluid balance, appetite, and body temperature (Haas and Panula, 2003; Haas et al., 2008; Zhang and Shi, 2012). Histamine, for the first time, was demonstrated to be an important neurotransmitter/neuromodulator in learning and memory processes in mammalian brain (Brown et al., 2001). In central nervous system, histaminergic afferent fibres originating from the tuberomammillary nucleus in hypothalamus have been shown to innervate on neurons in cortices and three deep cerebellar nuclei, including cerebellar fastigial nucleus (FN), interposed cerebellar nucleus (Int), and lateral dentate cerebellar nucleus (Lat) (He et al., 2012). Autoradiographic mapping and in situ hybridization experiments have demonstrated the presence of H_1 and H_2 receptors in cerebellar cortex and deep cerebellar nuclei in rats; however, H_3 receptors are scarce in the cerebellum (Haas and Panula, 2003). In neuroanatomical studies in the last decades, cerebellum and hypothalamus have been shown to be interconnected with direct hypothalamocerebellar and cerebellohypothalamic projections via a multitude of indirect pathways (Zhu et al., 2006). The lateral hypothalamic area (LHA) has been shown to be an important site to protect brain from gastric damage (Namiki et al., 1994). Our previous studies in rat have shown that cerebellum is involved in the regulation of stress-induced gastric mucosal damage (SGMD) (Gao et al., 2011), supporting that cerebellum may also participate in the regulatory of autonomic viscera (Moers-Hornikx et al., 2011). Taken together, these pieces of evidence suggest that cerebellum plays an important role not only in subcortical locomotor centre, but also in the central integration of visceral activities.

In immunocytochemical experiments, Zhu et al. (2006) found that some of the hypothalamocerebellar fibres are histaminergic. Takemura et al. showed that fibres connecting between the tuberomammillary nucleus of the hypothalamus with cortex and deep nuclei of the cerebellum contained histamine, indicating that the hypothalamocerebellar histaminergic fibres may play a vital role in cerebellar functions (Nakamura et al., 2009). FN, one of the phylogenetically oldest nucleu in the cerebellum, is a key pivot in the ultimate outputs of the spinocerebellum. In our previous study, FN has been indicated to participate in the protection of SGMD, which might be achieved by histamine through modulating the electrophysiological properties of cerebellar nuclear neuron (Gao et al., 2011). Although evidences are accumulating on the function of histamine, its function in visceral activity regulated by the cerebellum still remains largely unknown.

In our study, histamine was microinjected into FN in restraint and water-immersion (RWI) rat model. We examined the gastric mucosal damage index (GMDI), an indicator of SGMD, the discharge frequency of greater splanchnic nerve (GSN), and the gastric mucosal blood flow (GMBF). In gastric mucosal cells, we estimated the effect of histamine on proliferation and apoptosis using TUNEL staining, immunohistochemistry staining and western blotting.

2. Results

2.1. *Histological verification*

The histological verification was performed on all target sites of electrical and chemical lesions (Fig. 1). The coronal sections stained with neutral red shows the target sites of microinjection in FN (A) and LHA (B), and damage in DSCP

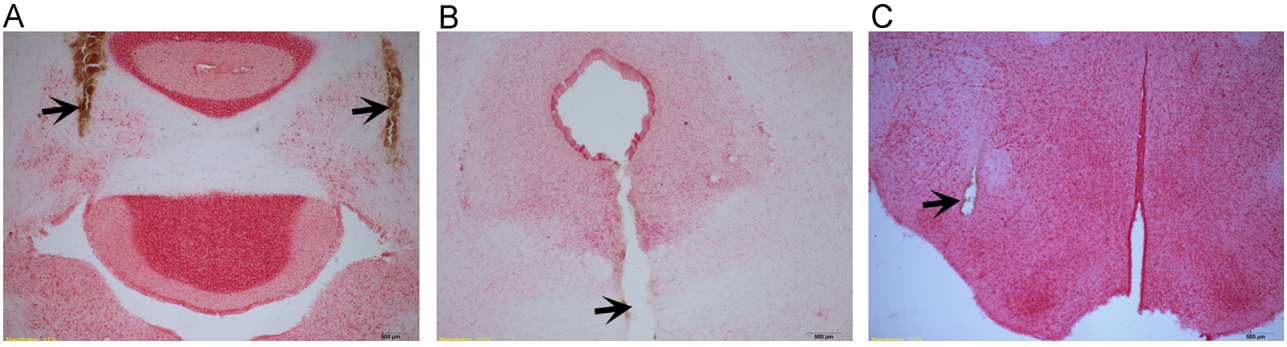

Fig. 1 – The target sites in rat brain. A: The photomicrograph microinjection site of FN; B and C: The photomicrographs of ablation sites of LHA and DSCP in the rats brains. The sections were stained with neutral red, showing the target sites (scale bar: 500 μm). The tissue ablation used the passage of DC of 1 mA for 10 s.