Neuroscience Research 64 (2009) 385–390

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Chewing rescues stress-suppressed hippocampal long-term potentiation via activation of histamine H1 receptor

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ARTICLE INFO

Article history:
Received 8 January 2009
Received in revised form 19 March 2009
Accepted 13 April 2009
Available online 22 April 2009

Keywords:
Chewing
Coping
Histamine H1 receptor
Hippocampus
Long-term potentiation
Pyrilamine
Stress
Tuberomammillary nucleus

ABSTRACT

We have previously found in rats that chewing, an active behavioral strategy to cope with a stressful situation, rescues long-term potentiation (LTP) in the hippocampus through activating stress-suppressed *N*-methyl-D-aspartate (NMDA) receptor function. To further examine the mechanisms underlying this ameliorative effect of chewing, we studied the involvement of the histaminergic system, which has been shown to be activated by mastication, in the LTP of hippocampal slices of rats that were allowed to chew a wooden stick during exposure to immobilization stress. Chewing failed to rescue stress-suppressed LTP in the rats treated with histamine H1 receptor (H1R) antagonist pyrilamine (5 mg/kg, i.p.) before exposure to stress, although administration of pyrilamine did not affect LTP in naive rats and in stressed rats that did not chew. However, when pyrilamine was administrated immediately after exposure to stress, chewing rescued LTP whose magnitude was statistically comparable to that in the rats that chewed without drug treatment. These results suggest that chewing-induced histamine release in the hippocampus and the subsequent H1 receptor activation may be essential to rescue stress-suppressed synaptic plasticity.

1. Introduction

In general, exposure to severe stress causes prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis, which in turn causes the adrenal cortex to secrete corticosterone, which finally disrupts fundamental cellular processes in the central nervous system. Especially in the hippocampus, an excessive corticosterone level causes a Ca^{2+} influx into neurons via activation of glucocorticoid receptors (GR) (Elliott and Sapolsky, 1993) and attenuates cellular excitability (Joëls and de Kloet, 1991), which selectively weakens the long-term potentiation (LTP) of hippocampal neurons that depends on the *N*-methyl-D-aspartate receptor (NMDAR) (Foy et al., 1987; Wiegert et al., 2005). We have recently found that chewing during a stressful event ameliorates the stress-induced impairment of LTP in hippocampal CA1 neurons by rescuing NMDAR function (Ono et al., 2008). However, the rescue mechanism remains to be elucidated.

The mesencephalic trigeminal nucleus (Me5) receives chewing-related proprioceptive sensory afferents of the trigeminal nerve from the jaw-closing muscle spindle and the periodontal ligaments (Luschei, 1987). A subpopulation of the Me5 neurons projects its fibers into the tuberomammillary nuclei (TMN) of the posterior hypothalamus where cell bodies of histaminergic neurons are localized (Ericson et al., 1989, 1991). Indeed, activation of the Me5 by mastication increases extracellular concentration of histamine (HA) in the hypothalamus to control satiety (Fujise et al., 1998; Sakata et al., 2003), suggesting the facilitative effect of chewing on histaminergic neurons in the TMN. The axons of histaminergic neurons in the TMN innervate practically the entire brain, including the hippocampus (Köhler et al., 1985; Inagaki et al., 1988; Panula et al., 1989; Brown et al., 2001) and the electrical stimulation of the TMN facilitates extracellular concentration of HA in the hippocampus (Mochizuki et al., 1994). Thus, a chewing-induced increase of the HA level in the hippocampus probably restores the stress-attenuated NMDAR to normal function and thereby rescues LTP.

At the present time, there are three known mechanisms by which HA facilitates NMDAR function *in vitro*. First, HA can stimulate the activity of phospholipase C through histamine H1 receptor (H1R) which is associated with the $G_{q/11}$ protein, followed by intracellular production of two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3)

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doi:10.1016/j.neures.2009.04.011

(Leurs et al., 1994). DAG and IP_3 further potentiate the activity of protein kinase C and increase intracellular Ca^{2+}, respectively, both of which increase the excitability of NMDAR (MacDonald et al., 2001; Markram and Segal, 1992). Payne and Neuman (1997) have shown that applying HA increases NMDA current in the hippocampal CA1 neurons, an effect that is reduced in a concentration-dependent manner by H1R antagonists but neither by histamine H2 receptor (H2R) nor by histamine H3 receptor (H3R) antagonist. Second, activation of H2R, which is associated with the G_s protein, stimulates adenylate cyclase to enhance the production of second messenger cyclic adenosine 3',5'-monophosphate (cAMP) (Selbach et al., 1997). An elevation in intracellular cAMP concentrations further activates protein kinase A, increasing charge transfer and Ca^{2+} influx through NMDARs (Raman et al., 1996). Third, HA acts directly on the polyamine binding site of NMDAR to enhance its function (Bekkers, 1993; Vorobjev et al., 1993). Taken together, these reports further strengthen the hypothesis that HA participates in the rescue of stress-attenuated NMDAR function.

In behaving animals, NMDAR-dependent LTP in the neurons of the CA1 area in the hippocampus plays an essential role in learning and memory (Whitlock et al., 2006). HA is also one of the possible facilitators of the hippocampal memory function. Interestingly, *in vivo*, H1R-dependent enhancement of NMDAR is more likely to facilitate the hippocampal-dependent learning and memory process, rather than the H2R-dependent mechanism or the direct action on NMDAR that are also well confirmed *in vitro*. Kamei and Tasaka (1993) have reported that intracerebroventricular administration of HA or intraperitoneal administration of HA precursor histidine improved the response latency in an active avoidance task via H1R activation in old rats. Moreover, antagonism of H1R causes memory deficit in a radial maze task, which can be restored by facilitating the NMDAR function by activating either the glycine binding site or the polyamine binding site of NMDAR (Masuoka et al., 2008) and vice versa (Huang et al., 2003). These findings show that there is H1R-mediated facilitation of NMDAR function in the hippocampus, suggesting a dominant role of H1R in modulating synaptic plasticity in the hippocampus of behaving animals.

Therefore, to elucidate the involvement of H1R in the chewing-induced amelioration of hippocampal synaptic plasticity, we have examined the effect of H1R antagonism on LTP of the rats that underwent immobilization stress with chewing. We also tested H1R antagonism with two different time points of pre- and post-stress to determine how activation of the histaminergic system during chewing contributes to ameliorating the stress-suppressed LTP.

2. Materials and methods

2.1. Experiment 1: administration of pyrilamine and chewing effects on stress-suppressed hippocampal LTP

The goal of experiment 1 was to determine whether activation of H1R is crucial for ameliorative effect of chewing on hippocampal LTP in the stressed rats. To test this, we used H1R antagonist pyrilamine to block histaminergic signal transduction through H1R in the hippocampal neurons before stress.

2.1.1. Animals

We used 10-week-old male Sprague-Dawley rats in all the experiments reported here. The rats took water and food freely in a temperature-controlled room (22 ± 3 °C) with a 12 h light/dark cycle (lights on at 7:00 a.m.). All our experiments accorded with the guidelines for Animal Experimentation of Kanagawa Dental College. All efforts were made to minimize the number of animals used and their suffering.

2.1.2. Drug administration and stress protocol

We dissolved pyrilamine (5 mg/kg; Sigma–Aldrich Japan, Tokyo, Japan) in saline and intraperitoneally injected it into all of the 18 rats tested. The dose of pyrilamine was set to the amount that sufficiently inhibits H1Rs in the hippocampus (Kamei and Tasaka, 1991) but that does not affect the arousal level (Saitou et al., 1999). Fifteen minutes after the injection, we produced immobilization stress in 12 of the rats by fixing their limbs to a wooden board for 30 min in a spread-eagle, supine position. We left half of them alone for the entire immobilization period (pyrilamine administration followed by stress; STp). For the other half, we placed a wooden stick (diameter, 5 mm) near the immobilized animal's mouth (pyrilamine administration followed by stress and chewing; SCp). All the rats given a wooden stick except one responded to it by chewing on it with a rapid and repetitive sequence of jaw opening and closing movements for at least two-thirds of the total restraint period. The one rat that did not touch the offered stick was included in group STp. We returned the remaining six rats to their home cage without subjecting them to immobilization stress (control of pyrilamine administration only; CTp). We performed all drug administration and stress inducement between 10:00 a.m. and 11:30 a.m.

2.1.3. Electrophysiology

We anesthetized rats with 2-bromo-2-chloro-1,1,1-trifluoroethane (2 ml/kg; Takeda Chemical Industries, Osaka, Japan) at 24 h after the immobilization stress, the time at which the ameliorative effect of chewing on hippocampal LTP was the most prominent in our previous study (Ono et al., 2008). We decapitated and removed their brains to make transverse hippocampal slices (450 μm thick). As to the rats in group CTp that did not experience stress, we set post-injection survival time to be the same as that in the other groups (Fig. 1). We maintained the slices in a holding chamber filled with artificial cerebrospinal fluid (ACSF) containing 119 NaCl, 2.5 KCl, 26.2 $NaHCO_3$, 1 NaH_2PO_4, 1.3 $MgSO_4$, 2.5 $CaCl_2$, and 11 glucose (in mM, bubbled with 95% O_2–5% CO_2) until use. After at least 1 h of recovery time, we transferred one of the slices to an immersion-type recording chamber perfused at 1 ml/min

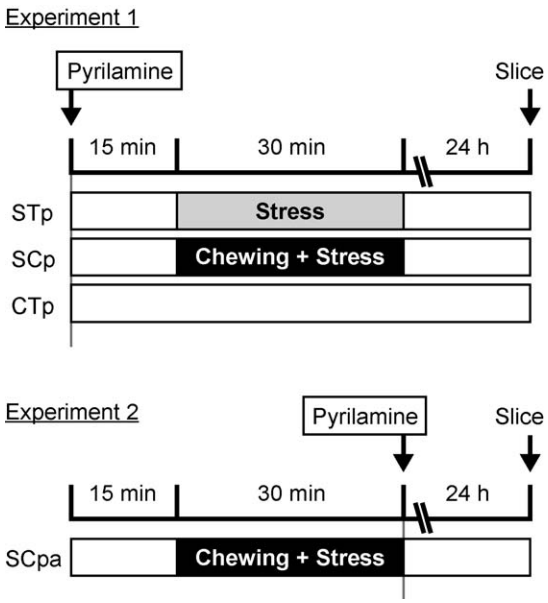

Fig. 1. Time intervals from intraperitoneal pyrilamine administration to stress exposure and from stress exposure to hippocampal slice preparation in experiments 1 and 2.