Effects of the acute and chronic restraint stresses on the central histaminergic neuron system of Fischer rat

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Effects of the acute and chronic restraint stresses on the central histaminergic neuron system

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Abstract

The effects of acute and chronic restraint stresses on the brain histamine level and histamine N-methyltransferase activity in Fischer rat brain was studied. The acute restraint stress increased the histamine levels in the diencephalon and nucleus accumbens, and increased the histamine N-methyltransferase activities in the nucleus accumbens and striatum. The chronic restraint stress increased histamine N-methyltransferase activities in the nucleus accumbens and striatum. These results indicate that the acute and chronic restraint stresses increase the brain histamine turnover, which would be partly relate to the pathology of stress vulnerability.

Keywords:

histamine, histamine N-methyltransferase, histamine turnover, restraint stresses, rat brain, stress vulnerability

As a neurotransmitter or neuromodulator, neuronal histamine (HA) has a variety of physiological roles in brain functions, such as sleep-wakefulness, feeding and drinking behaviors, locomotor activities, regulation of the neuroendocrine system, body temperature, convulsion and circulation [13,15,20]. Cell bodies of the histaminergic neuron system are located exclusively in the tuberomammillary nucleus of the posterior hypothalamus, with projections througout the whole brain including the diencephalons, where the highest concentration of HA is found [18,21]. HA is inactivated by N-methyl-transferase (HMT) and metabolized to N-tele-methylhisitamine in the mammalian brain [15,20]. The hypothalamus plays an important role in response to stress [4]. It has been suggest that acute stress can influence the histaminergic nervous system in the rat brain, but, to our knowledge, there is no report on the effect of chronic restraint stress on the histaminergic nervous system [7,8]. In the present study, we examined the effects of acute and chronic restraint stresses on HA level and HMT activity in the brain of Fischer rats.

Fischer male rats weighing 190-210 g at the beginning of experiments were group-housed (five rats per cage) with free access to food and water in a room maintained at 22}2 and 65}5 humidity under a 12 hours light /12 hours dark cycle (lights on at 6:00 a.m.). Rats to be subjected to restraint stress were placed in the immobilization wire cage (15 cm length, 8 cm height and 7 cm width), and could hardly turn around themselves. In acute stress studies, they remained in that uncomfortable position for 1 hour and thereafterwere decapitated. In chronic stress studies, rats were placed in the immobilization wire cage for 1 hour everyday for 21 days and decapitated immediately after the last restraint stress. Control rats were decapitated after handling.

The brains were rapidly removed and dissected on ice into seven regional parts of the diencephalon, nucleus accumbens, striatum, amygdala, hippocampus, pons medulla, and cerebellum by the method of Glowinski and Iversen (1966). The brain regions were stored at -80 until assay. For the measurement of HA level, the frozen brain regions were homogenized in 10 volumes of 3 perchloric acid containing 5mM Na2-EDTA with a Polytron homogenizer (Kinematica, Lucerne, Switzerland) at a maximum setting for 10 sec in an ice bath, and then the homogenates were centrifuged at 10,000 g for 30 min at4. HA was measured by a sensitive HPLC-fluorometric method as described by Yamatodami et al. (1985). In brief, HA was separated on a cation exchanger, TSK gel SP2SW (Tosoh, Tokyo, Japan; particle size 5), and eluted with 0.25 M KH2PO4 as the mobile phase at a flow rate of 0.6 ml/min using a constant flow pump (model CCPM, Tosoh). HA eluate

was derivatized using an on-line automatedƒÍ-phthalaldehyde method [16], and the fluorescence intensity was measured at 450 nm with excitation at 360 nm in a spectrofluorometer equipped with a flow cell (model C-R3A, Shimadzu, kyoto, Japan) and a chromatographic data processor (model C-R3A, Shimadzu). For the measurement of HMT activity, the frozen brain regions were homogenized in 4 volumes of HMT solution (100 mM sodium phosphate buffer, pH 7.4, 10 mM dithiothreitol, 1 polyethylene glycol) in a Polytron homogenizer at a maximum setting for 10 sec in an ice bath. The homogenates were centrifuged at 10,000 g for 30 min, and the supernatants were dialyzed against an HMT solution at 4 Ž for 3 hours. The HMT reaction was carried out at 37 with 0.25 ml of a mixture containing 0.1 mM HA, 30 mM sodium phosphate buffer, 0.25 mM S-adenosyl-L-methionine, and 0.2 mM aminoguanidine and the supernatants.@Three hours later, the reaction was stopped by adding 0.03 ml of 60 perchloric acid.@Protein were determined by the method of Lowry et al. (1951) with bovine serum albumin as the standard. N-tele-Methylhistamine was separated from HA and measured by the sensitive HPLC-fluorometric method as mentioned above, except with 37.5 mM citric acid, 1.25 imidazole, and 20 methanol, pH 6.8, as the mobile phase.

Statistical analysis of the data were carried out using one-way ANOVA followed by the least significant difference test. In all cases, P values less than 0.05 were considered statistically significant.

Acute restraint stress significantly increased the HA level in the diencephalon and nucleus accumbens (table1), and significantly increased the HMT activity in the nucleus accumbens and striatum compared with control groups (table 2). Chronic restraint stress significantly increased the HMT activity in the nucleus accumbens and striatum compared with control groups (table 2), although it did not change HA levels in these regions (table 1).

In this study, we first found that acute restraint stress increased the brain HA turnover not only in the diencephalon but also in the nucleus accumbens and striatum. The increased HA level in the diencephalon, which may represent the increased HA synthesis, after acute stress is consistent with the other studies [8]. This increased HA in the diencephalon, which is the main HA synthesizing site of the brain, may be carried through axon to the nucleus accumbens and sriatum, and metabolized mainly at these sites in the acute restraint stress. Oishi et al. (1986) reported that the anxiolytic diazepam decreased the turnover rate of the central HA neuron system in mice, indicating the contribution of brain HA neuron system to anxiety. Therefore,

this increased HA turnover in the brain regions may partly relate to the etiology of anxiety in the acute stress.

In second, we also found that the increased HA metabolism in the nucleus accumbens and striatum maintained after chronic restraint stress. This is the first report about the effect of chronic restraint stress on the central HA neurons. No significant difference of HA content in diencephalon between chronic stress group and control group may relate to the lasting axonal transport from diencephalon to the nucleus accumbens and striatum in order to compensate the lasting increased HA metabolism there. The chronicrestraint stress to rat is thought to be animal model of stress-induced depression [11,22]. Many antidepressants have antihistaminergic properties and act as antagonists on histamine H1 or H2 receptor [1,2,3,9,10,14,17,19]. These lines of evidence suggest the possible contribution of central HA transmission to the etiology of stress-induced depression. Therefore, sustained increase of the HA turnover in the nucleus accumbens and striatum induced by the chronic stress may partly relate to the stress-induced vulnerability against depression.

In conclusion, the acute restraint stress increased HA turnover in the diencephalon, nucleus accumbens, and striatum.@Chronic restraint stress continuned to increase HA turnover in the nucleus accumbens and striatum.

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