PROCEEDING

Effects of forced swimming stress on rat brain function

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Abstract : Chronic stress has been reported to be an essential factor for depression. In this study, the effect of forced swimming stress on neurotransmitters and cellular signaling pathway contributing to brain functions was investigated using the forced swimming test (FST) in order to understanding of mechanisms to regulate stress signals in brain. Antidepressant drug, imipramine, significantly reduced the immobility time of male rats in the FST by 85% at a dose of 15mg/kg for 2 weeks. This result indicated that the swimming stress caused a depressed state in the rats without administration of imipramine. Swimming stress significantly lowered the serotonergic ratio and also markedly enhanced the phosphorylation of ERK1/2 in the hypothalamus region compared to the rats without FST. These phenomena may be included in key mechanisms of the development of depression. J. Med. Invest. 52 Suppl. : 300-301, November, 2005

Keywords **:** *depression, forced swimming test, brain function, serotonergic ratio, ERK1/2*

INTRODUCTION

Depression represents a major public disease affecting nearly 3-5% of the world population. Chronic stress has been reported to be an essential factor for this disease (1) . One of our goals is to control the daily stress and then to prevent the depression by the strategy of nutritional science. Therefore, understanding of the mechanisms to regulate stress signals in brain may give insight into the role of nutritional factors as antidepressants. In this study, the effects of forced swimming on neurotransmitters and cellular signaling pathway contributing to brain functions were investigated, as the forced swimming test (FST) is a rodent's model often used for the screening of antidepressant drugs.

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METHODS

Male CD rats(240-280 g)from Charles River Japan Inc., Yokohama, Japan, were housed in a 12h light/dark cycle at a constant temperature of 25±1℃ with free access to food and water. All experiments were conducted in accordance with the animal experimental guidelines of The University of Tokushima. Each group (n=7) was orally administered water or antidepressant drug, imipramine(15 mg/kg body weight/day). After 2 weeks treatment, both groups were subjected to the FST for 8 min according to the method of Porsolt *et al.* (2). In the first 5 min of swimming

stress, the immobility time was counted. After the FST, every rat was sacrificed by decapitation immediately. A hypothalamus region in the rats with or without FST was collected, and the amount of neurotransmitters, serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), were measured using HPLC-coulometric array system. In addition, the activation of extracellular signal-regulated kinase (ERK) 1/2 in the hypothalamus region was measured by immunoblotting assay.

RESULTS AND DISCUSSION

Immobility time in the water+stress (WS) group was 150 sec. Administration of antidepressant drug, imipramine, for 2 weeks significantly reduced the immobility time, as reported by Butterweck *et al* (3) . These results indicate that the swimming stress caused a depressed state in the WS group. Concerning neurotransmitters in the hypothalamus region, 5-HIAA/5-HT ratio significantly decreased in the WS group due to increased 5-HT levels and decreased 5-HIAA levels compared to the rats without FST, suggesting that the decrease of the ratio possibly reflects the decline of 5-HT metabolic activity due to swimming stress. ERK1/2 was remarkably phosphorylated in the hypothalamus by the swimming stress. It should be noted that the activation of ERK1/2 has been reported to regulate a synaptic plasticity in the brain by modulating gene expression (4) .

In conclusion, swimming stress significantly lowers the 5-HIAA/5-HT ratio and also markedly enhances the phosphorylation of ERK1/2 in the hypothalamus, which is a central region for regulation of the autonomic nervous system. These phenomena may be included in key mechanisms of the development of depression.

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