The role of brain 5-HT7 receptor-ERK system in the formation of stress adaptation in mice

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A growing body of evidence suggests that impairment of the ability to adapt to stress may contribute to some stress-related psychiatric disorders such as anxiety and depression. The multifaceted effects of 5-HT are mediated by a family of at least 14 structurally and pharmacologically distinct 5-HT receptor subtypes. Among them, although the 5-HT1 and 5-HT2 receptor subtypes have received particular attention due to their implication in several psychiatric disorders, the roles of other subtypes have hardly been investigated. In the present study, we examined whether brain 5-HT7 receptors are involved in the formation of stress adaptation. Male ICR mice were either exposed to repeated restraint stress for 60 or 240 min/day (stressed group) or left in their home cage (non-stressed group) for 1 or 14 days. The emotionality of mice was estimated in the hole-board test. The levels of 5-HT7 receptor expression and extracellular signal-regulated kinase 1/2 (ERK) phosphorylation were assessed by western blot analysis. 4-(2-Diphenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1-piperazinehexanamide (LP 12), a selective 5-HT7 receptor agonist, was injected immediately after the daily exposure to restraint stress for 60 min induced a decrease in head-dipping behavior in the hole-board test. This emotional stress response was not observed in mice that had been exposed to repeated restraint stress for 60 min/day for 14 days, which confirmed the development of stress adaptation. In contrast, mice that were exposed to restraint stress for 60 min/day for 14 days did not develop the stress adaptation, and continued to show a decrease in head-dipping behavior. The 5-HT7 receptor expression as well as ERK phosphorylation were increased in the frontal cortex and hippocampus of stress-adaptive, but not stress-maladaptive, mice. The decrease in head-dipping behavior of stress-maladapted mice induced by exposure to unadaptable stress were alleviated by repeated treatment with LP 12 immediately after daily exposure to stress. The present findings suggest that the brain 5-HT7 receptor-ERK system may play an important role in the formation of stress adaptation. Furthermore, stimulation of 5-HT7 receptors may have a beneficial effect on stress adaptation and alleviate emotional abnormality under conditions of excessive stress.