Exercise-induced neuronal effects and the 5-HT3 receptor

Makoto Kondo, Shoichi Shimada

Department of Neuroscience and Cell Biology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Correspondence: Makoto Kondo
E-mail: mkondo@anat1.med.osaka-u.ac.jp
Received: April 09, 2015
Published online: April 19, 2015

Fourteen subtypes of the serotonin (5-hydroxytryptamine, 5-HT) receptor have been delineated, and these subtypes are assigned to seven 5-HT receptor subfamilies (5-HT1-7). Among the 5-HT receptor subfamilies, the 5-HT type 3 (5-HT3) receptor is the only ionotropic receptor. Previous studies have reported abundant expression of the 5-HT3 receptor in the hippocampus, and the involvement in the mood and memory. However, possible roles of the 5-HT3 receptor in hippocampal neurogenesis remains unknown. We performed immunohistochemical analyses of adult hippocampal neurogenesis in the 5-HT3A receptor-deficient mice (htr3a−/− mice). We found that basal cell proliferation and neurogenesis in the hippocampal dentate gyrus of htr3a−/− mice were normal. Exercise is known to increase hippocampal neurogenesis, cause antidepressant effects and enhance learning ability. Immunohistochemical and behavioral analyses of htr3a−/− mice revealed that a lack of the 5-HT3 receptor led to a blockade of the exercise-induced neurogenesis in the hippocampus and antidepressant effects, but not of enhanced learning ability. Moreover, we have shown that the 5-HT3 receptor agonist enhanced cell proliferation in the hippocampal dentate gyrus. Our results indicate that the 5-HT3 receptor is indispensable for increased hippocampal neurogenesis and antidepressant effects induced by exercise.

Keywords: Exercise, serotonin; 5-HT3 receptor; hippocampal neurogenesis; antidepressant effects; learning enhancement

serotonin is thought to be one of the most important molecules that mediate these beneficial effects induced by exercise [25,26], because the levels of serotonin in the hippocampus increase following exercise [27,28,29,30]. Thus, we have intended to examine possible relationships of the 5-HT3 receptor with enhanced hippocampal neurogenesis and behavioral effects induced by exercise. In our recent study titled “the 5-HT3 receptor is essential for exercise-induced hippocampal neurogenesis and antidepressant effects [31]”, we have used the 5-HT type 3A receptor subunit-deficient mice (htr3a-/− mice) [32], and performed immunohistochemical and behavioral analyses under exercise condition.

At first, we investigated possible roles of the 5-HT3 receptor in basal cell proliferation and adult neurogenesis in the hippocampus. We performed bromodeoxyuridine (BrdU) labeling in the dentate gyrus of the hippocampus in wild-type and htr3a-/− mice. The intraperitoneal injection of BrdU was done once a day during the first four days (day 1- day 4). Cell proliferation was assessed on day 5, and hippocampal neurogenesis was did on day 29, respectively. We found that there were no significant differences between wild-type and htr3a-/− mice, in the number of BrdU-positive cells (cell proliferation) on day 5 or BrdU/NeuN-double-positive cells (neurogenesis) on day 29. Our data indicate that the 5-HT3 receptor is not necessary for cell proliferation and adult neurogenesis in the dentate gyrus of the hippocampus at baseline [31].

Next, we tested whether the 5-HT3 receptor has possible roles in exercise-induced cell proliferation in the hippocampal dentate gyrus. Mice were housed in a non-exercise (standard) cage or in an exercise one for six days (day 1-day 7). The BrdU injection was performed three times on day 6. We assessed hippocampal cell proliferation 24 hours after the first injection of BrdU (day 7). After exercise for six days, wild-type mice showed a significant increment in the number of BrdU-positive cells in the hippocampal dentate gyrus, as previously described [14,26,33,34]. As contrasted with wild-type mice, there was no significant increment in the number of BrdU-positive cells in htr3a-/− mice that exercise for six days. In addition, the BrdU-positive cells were further analyzed for the expression of doublecortin (DCX), which is an immature neuronal marker. Exercise for six days significantly increased the number of BrdU/DCX-double-positive cells in the hippocampal dentate gyrus of wild-type mice, as described previously [20]. As contrasted with wild-type mice, we found no significant increment in the number of BrdU/DCX-double-positive cells in htr3a-/− mice that exercise for six days. Meanwhile, wild-type and htr3a-/− mice under exercise conditions displayed a similar running distance for six days. Our results suggest that the 5-HT3 receptor is essential for the enhanced cell proliferation in the hippocampal dentate gyrus induced by exercise [31].

Then, we further examined possible roles of the 5-HT3 receptor in hippocampal neurogenesis. The effects of 5-HT3 receptor stimulation on hippocampal cell proliferation were investigated. Saline or SR 57227A [35], which is the selective 5-HT3 receptor agonist, was administered intraperitoneally, and BrdU was injected 2 hours after SR 57227A or the saline administration. Cell proliferation analysis was performed 24 hours after BrdU injection. In wild-type mice, SR 57227A treatment significantly increased the numbers of BrdU-positive and BrdU/DCX-double-positive cells in the hippocampal dentate gyrus. As contrasted with wild-type mice, significant increases in the numbers of BrdU-positive and BrdU/DCX-double-positive cells were not seen in htr3a-/− mice after SR 57227A treatment. Our results indicate that the stimulation of the 5-HT3 receptor induces neurogenic response in the dentate gyrus of the hippocampus [31].

Newly generated granule cells in the dentate gyrus are functionally integrated into the brain neural network and augment the functional capacity of the hippocampus [36]. Thus, we investigated whether the exercise-induced increment in hippocampal granule cells is observed in wild-type and htr3a-/− mice. Mice were housed in a non-exercise (standard) cage or in an exercise one for three weeks (day 1-day 22). The BrdU injection was performed once a day during the first four days (day 1-day 4). We assessed the BrdU-positive granule cells in the hippocampal dentate gyrus on day 22. Exercise for three weeks caused a significant increment in the number of BrdU/NeuN-double-positive cells in the hippocampal dentate gyrus of wild-type mice, as previously described [14,33,34]. As contrasted with wild-type mice, not significant increment in the number of BrdU/NeuN-double-positive cells was observed in htr3a-/− mice that exercise for three weeks. Meanwhile, wild-type and htr3a-/− mice under exercise conditions showed a similar running distance for three weeks. Our data indicate that the 5-HT3 receptor is indispensable for the exercise-induced increase in the dentate granule cells of the hippocampus [31].

Finally, we examined whether the 5-HT3 receptor plays a role in exercise-induced behavioral effects, such as antidepressant effects and learning improvement. To investigate possible roles of the 5-HT3 receptor in the antidepressant effects caused by exercise, the forced swim test and the tail suspension test were performed. These behavioral tests are useful for assessment of depressive-like behavior of rodents [37]. Exercise for three weeks induced a significant reduction of the immobility time measured in the
forced swim test and the tail suspension test in wild-type mice. This indicated a decrease in depressive-like behavior [21,22]. No significant differences were found in the immobility time of the forced swim test and the tail suspension test between wild-type and htr3a-/- mice under no-exercise conditions. After three weeks of exercise, as contrasted with wild-type mice, there were no significant reductions in immobility time of both tests in htr3a-/- mice. Meanwhile, no significant differences in spontaneous activity were found between wild-type and htr3a-/- mice after exercise for three weeks.

We next tested possible roles of the 5-HT3 receptor in learning enhancement induced by exercise. We performed the contextual fear conditioning test, which is one of the most useful tests assessing hippocampus-dependent memory. After exercise for three weeks, wild-type mice showed a significant enhancement of contextual freezing responses 24 hours after conditioning, as described previously [38]. Under no-exercise conditions, wild-type and htr3a-/- mice displayed a similar contextual fear learning ability, as described previously [10,11]. Intriguingly, after exercise for three weeks, htr3a-/- mice showed a significant enhancement of contextual freezing responses, like wild-type mice. Collectively, our results from behavioral tests suggest that the 5-HT3 receptor is indispensable for exercise-induced antidepressant effects, but is not necessary for augmentation of learning ability [31].

The involvement of serotonin in hippocampal neurogenesis and antidepressant-like behavior has been studied [39,40,41-47]. Because the levels of serotonin in the hippocampus increase after exercise [27,28,29,30], serotonin has been suggested to be an important molecule in exercise-induced behavioral and morphological changes. However, it remained uncertain how serotonin acts in animal brains under exercise condition. In our recent study [31], we found that the 5-HT3 receptor is indispensable for exercise-induced hippocampal neurogenesis and antidepressant effects, but is not necessary for learning enhancement. Our results suggest that the 5-HT3 receptor is the pivotal target of action of serotonin in hippocampal neurogenic responses and antidepressant-like behavior that are caused by exercise. This is the first study of a critical 5-HT receptor subtype which plays essential roles in the morphological changes and behavioral effects in reaction to exercise stimulation. Our study could provide a further insight into the mechanisms of the morphological and behavioral changes induced by exercise.

Many studies have indicated that adult hippocampal neurogenesis could contribute to enhance hippocampal function [48,49,50,51]. Actually, previous reports have shown that augmented hippocampal neurogenesis is necessary for the behavioral effects of antidepressants which target the serotonin system in brains [41,42,43]. In our recent study [31], we showed that htr3a-/- mice did not exhibit enhanced hippocampal neurogenesis and antidepressant effects caused by exercise. The evidence that lack of the 5-HT3 receptor leads to loss of both increased hippocampal neurogenesis and antidepressant effects caused by exercise indicates that these two biological events could be related causally. In other words, antidepressant-like behavior caused by exercise could be mediated by a 5-HT3 receptor-dependent enhancement of hippocampal neurogenesis. Our results support the idea that increased adult neurogenesis of the hippocampus is necessary for exercise-induced antidepressant effects [52,53]. Our results suggest that exercise-induced augmentation of hippocampal neurogenesis regulated by the 5-HT3 receptor might result in enhancement of synaptic plasticity in the brain neuronal network [15,54]. Subsequently, this would appear as behavioral changes, such as antidepressant-like behavior, in response to exercise stimuli. As exercise has beneficial effects on brain diseases [12,13], the 5-HT3 receptor could be a potential target which merits further research.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by JSPS KAKENHI Grant Number 26860926, and grants from the Uehara Memorial Foundation, the Japan Prize Foundation, Brain Science Foundation, the Sakamoto Research Foundation of Psychiatric Diseases, Takeda Science Foundation, and the Ichiro Kanehara Foundation, Kanae Foundation, Suzuken Memorial Foundation, Meiji Yasuda Life Foundation, and Nakatomi Foundation.

References


38. Greenwood BN, Strong PV, Foley TE, Fleshner M. A behavioral analysis of the impact of voluntary physical activity on...


