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Activation of TrkB–Akt Signaling Rescues Deficits in a Mouse Model of SCA6

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Introduction

Spinocerebellar ataxia 6 is a rare neurodegenerative disease caused by cytosine, adenine, guanine (nucleotide) (CAG) repeat expansion mutation in CACNA1A gene.[1] Mutation in the CACNA1A gene leads to a protein abnormality. This disease impairs the muscle coordination typically starting in middle age. Currently, there is no treatment available for SCA6.[2] Previous studies have shown that the mice model of SCA6 develops muscle dysfunction at the age of 7 months and Purkinje cell loss at the age of 2 years.[3] These studies suggested that there is time gap between the onset of neuron loss and muscle coordination deficit. Therefore, it might be possible that early motor coordination impairments occur due to cerebellar function instead of cell death in patients with SCA6. Furthermore, this disease might be reversible by rescuing cerebellar function before the degeneration of Purkinje cells.

Neurotrophic factors like brain derived neurotrophic factor (BDNF) play an important role in the survival and development of the nervous system.[4] Previous studies have shown that there is a reduction in the level of BDNF in the cerebellum of postmortem SCA6 patients and several mouse models of SCA6.[5] Therefore, it might be possible that BDNF signaling deficit play a role in pathophysiology of SCA6.

Exercise has a positive impact on the overall health of the individual. Exercise found to play a neuroprotective role by increasing the level of BDNF which leads to the enhancement of hippocampal neurogenesis.[6]

Hence, this study aimed to investigate the effect of exercise-induced BDNF singling pathway on the pathophysiology of SCA6 mouse model and supplementation of 7,8-dihydroxyflavone (7,8-DHF) an agonist of TrkB, can reverse the disease pathology.

Study Design

All experiments were formed after getting approval from McGill Animal Care Committee according to Animal Care guidelines provided by the Canadian Council. A knock-in mice model of SCA6 with 84 CAG repeat expansion at CACNA1A locus was included in the study. Mice were allowed to perform voluntary running using running wheels in cages and were acclimatized to exercise on the treadmill. The treadmill exercise was provided for 6 weeks (Fig. 1), 20 min daily with speed of 6 m/min for 5 minutes, 10 m/min for 5 minutes, and 1 m/min for 5 minutes. In some cases, SCA6 mice were compared with wild-type, and in another, in order to examine the role of BDNF-TrkB signaling pathway at the onset and progression of SCA6, the following experiments were performed:

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- Immunohistochemistry
- Image acquisition and analysis
- Accelerating rotarod
- Acute slice preparation
- Electrophysiology
- Enzyme-linked immunosorbent assay
- Reverse phase protein array
- Western blotting

Results

- To investigate the level of BDNF and TrkB in a mouse model of SCA6, ELISA, and IHC were performed. It was analyzed at 5–6 months (pre-onset), 7 months (disease onset), 12 months (advance disease stage) of age. It was found that decrease in concentration of BDNF at the age of 7 months and 12 months in SCA6 mouse as compared with wild-type. It indicates that the level of BDNF and its receptor was reduced at an early stage of SCA6 progression.
- To analyze the effect of exercise on BDNF levels in SCA6 mouse, 1 month of exercise was provided to mouse at the age of 6 months. It was found that after exercise, the concentration of BDNF was increased in SCA6 mouse model. Therefore, exercise enhances the level of BDNF in SCA6 mouse model.
- Exercise also alleviates motor coordination and Purkinje cell firing deficits in SCA6 mouse. To analyze this, 1 month of exercise was provided to SCA6 mouse, after that rotarod test was performed for 5 days. It was found that after exercise, motor coordination deficit was rescued in SCA6 exercise mouse as compared with SCA6 sedentary mouse. It was also found that exercise also

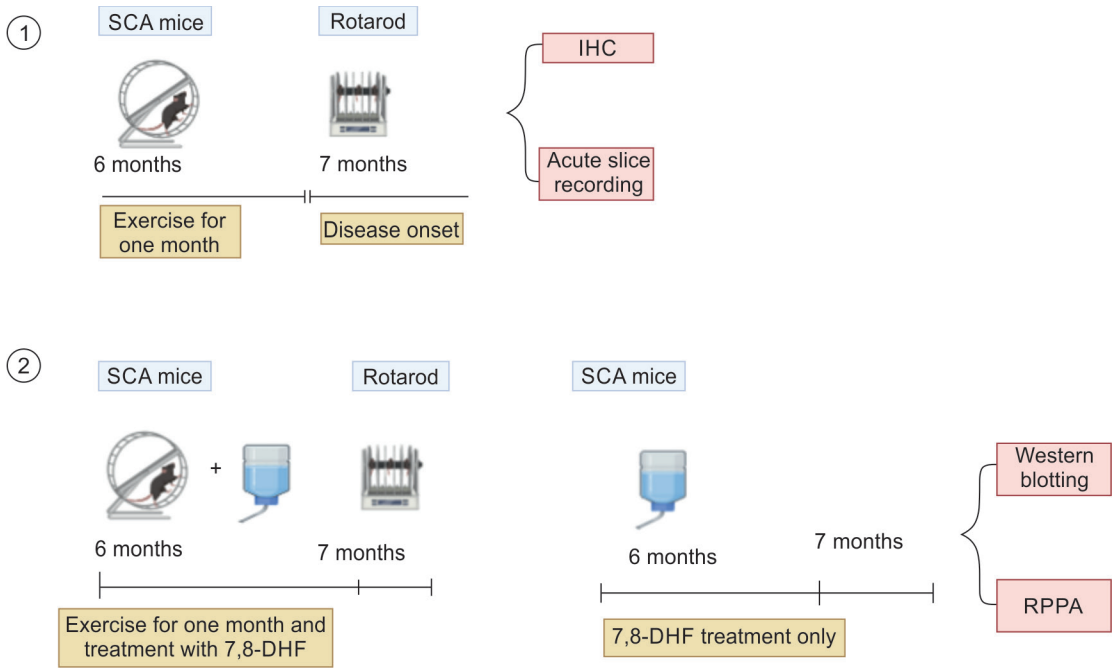

Fig. 1: Schematic of exercise regimen and 7,8-DHF administration

rescue the frequency of Purkinje cell firing deficit in SCA6 exercise mouse as compared with sedentary. Therefore, exercise rescued ataxia in SCA6 mouse by restoring the BDNF signaling pathway.

- Exercise might improve motor coordination and frequency of Purkinje cell firing in SCA6 mouse by BDNF-TrkB pathway. To analyze this, SCA6 mouse was provided with 7,8-DHF an agonist of TrkB in drinking water for 1 month. It was found that administration of 7,8-DHF gave a similar kind of result as provided by exercise. Exercise+ SCA6, SCA6+ 7,8-DHF, Exercise +SCA6 + 7,8-DHF in all of these scenarios gave similar kind of results. This indicates that both exercise and 7,8-DHF improve motor coordination via TrkB signaling pathway.
- To investigate whether 7,8-DHF had any effect on TrkB signaling, immunoblotting was performed. It was found that administration of 7,8-DHF enhances the level of TrkB, pTrkB, and pAkT in SCA6 + 7,8 DHF mouse as compared with SCA6 mouse. When 7,8-DHF was provided before the onset of disease, there was improvement in motor coordination. Therefore, 7,8-DHF was found to improve motor coordination, frequency of Purkinje cell firing, Akt signaling pathway.

Implication

This study has shown improvement in motor coordination, Purkinje cell firing deficit via activation of TrkB–Akt pathway after administration of 7,8-DHF in SCA6 mouse. So, 7,8-DHF can as potential therapeutic drug for SCA6. This study indicates that drugs which target TrkB–Akt signaling pathway may be beneficial for the treatment of SCA6 in humans. Furthermore, TrkB–Akt pathway may be a potential therapeutic target for SCA6.

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