



Editorial

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Physical Activity and Brain Plasticity

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Recent research suggests that the brain has capable of remarkable plasticity and physical activity can enhance it. In this editorial letter, we summarize the role of hippocampal plasticity in brain functions. Furthermore, we briefly sketched the factors and mechanisms of motion that influence brain plasticity. We conclude that physical activity can be an encouraging intervention for brain restoration through neuronal plasticity. At the same time, we suggest that a mechanistic understanding of the beneficial effects of exercise should be accompanied in future studies.

[Key words] Physical activity, Neurogenesis, Brain plasticity, Hippocampus

Studies have demonstrated that physical activity affects brain plasticity, cognition and mood¹⁻⁴. Indeed, animal experiments and clinical studies show tremendous biological and psychological benefits of physical activity, and accompanying structural and functional changes in the various brain regions^{5,6}. In recent years, the effect of physical activity on memory improvement in neurodegenerative diseases patients has attracted attention⁷. The circuits of the limbic system are known to regulate learning and memory function^{8,9}. Subjects with cognitive impairment have been shown to have reduced volume in the hippocampus and forebrain¹⁰⁻¹². Adult neurons have been thought to be unable to be replaced by new cells because cell division is over, but recent studies have found that new neurons are born (neurogenesis) in select regions of the adult brain and may contribute to maintenance of neuronal function¹³. Experiments utilizing the thymidine analog bromodeoxyuridine (BrdU) to label dividing cells and several genetic markers have revealed that hippocampal dentate gyrus is one of the brain regions showing the neurogenesis in mature animals, and this was conserved in rodents, primates, and humans^{13,14}. Adult neurogenesis was also proven in bird studies; a comparison of hippocampus size and number of neurons with a long-traveled migratory bird and a non-traveling migratory bird also shows that hippocampus may be important for memory and experience¹⁵. In addition, chickadees exhibit enhanced neurogenesis when they store seeds for winter¹⁶.

Neuronal plasticity is key feature for the cognition and it is regulated by neurogenesis, synapse formation, angiogenesis and changes in neurotransmitter system^{3,6,9}. Animal experiments using voluntary wheel cages and treadmills have reported that exercise increases the proliferation of neurons in the hippocampus of rodents³. Exercise induces the changes of the neurotransmitter systems such as serotonin and acetylcholine and the release of factors such as BDNF and IGF-1^{2,17}. Along with these changes, exercise improves the cognitive functions such as spatial and executive functions^{18,19}. These changes may also be very effective interventions in aging and degenerative brain disease models^{20,21}.

Recent studies have shown that exercise promotes the release of factors such as peripheral BDNF²², IRSIN²³, IGF²⁴, and Cathepsin B⁵, which are systemically delivered to the brain and may play a role in cognitive function. Furthermore, we found that conditioned media which containing secreted proteins from skeletal muscle cells could influence adult hippocampal neural progenitor cell (aNPC) differentiation²⁵. Exercise induced neurogenesis can be also affected through epigenetic modifications²⁶ or the balance of intestinal microflora²⁷. In fact, even though the mechanisms are not clearly investigated, there are reports demonstrating exercise affects intestinal microorganisms²⁸ or brain epigenetics²⁹. There has been little research on the effects of metabolites on the brain and nerve system. Studies have shown that these metabolites are not only end products during metabolism but also act as hormones in a variety of physiological and pathological conditions as a signaling material^{30,31}. In the near future, exercise-induced changes in these biological markers may be the candidate target of new exercise mimetics and may play an important role in proposing or prescribing exercise appropriate to the individual's health status. Most of the cross sectional studies investigating changes in the human brain after exercise have limitations in observing the neuronal adaptation during or after exercise. Future studies are needed to understand the effects and mechanisms of exercise from a systemic and longitudinal view. Moreover, human studies are needed to show that exercise is important for the learning and memory function via hippocampal neurogenesis.

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REFERENCES

- van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci*. 2005;25:8680-5.
- Moon HY, Kim SH, Yang YR, Song P, Yu HS, Park HG, Hwang O, Lee-Kwon W, Seo JK, Hwang D, Choi JH, Bucala R, Ryu SH, Kim YS, Suh PG. Macrophage migration inhibitory factor mediates the antidepressant actions of voluntary exercise. *Proc Natl Acad Sci U S A*. 2012;109:13094-9.
- Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. *Curr Top Behav Neurosci*. 2013;15:189-210.
- Chang H, Kim K, Jung YJ, Kato M. Effects of acute high-intensity resistance exercise on cognitive function and oxygenation in prefrontal cortex. *J Exerc Nutrition Biochem*. 2017;21:1-8.
- Moon HY, Becke A, Berron D, Becker B, Sah N, Benoni G, Janke E, Lubojko ST, Greig NH, Mattison JA, Duzel E, van Praag H. Running-Induced Systemic Cathepsin B Secretion Is Associated with Memory Function. *Cell Metab*. 2016;24:332-40.
- Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108:3017-22.
- Radak Z, Hart N, Sarga L, Koltai E, Atalay M, Ohno H, Boldogh I. Exercise plays a preventive role against Alzheimer's disease. *J Alzheimers Dis*. 2010;20:777-83.
- Vivar C, Peterson BD, van Praag H. Running rewires the neuronal network of adult-born dentate granule cells. *Neuroimage*. 2016;131:29-41.
- Greenwood PM, Parasuraman R. Neuronal and cognitive plasticity: a neurocognitive framework for ameliorating cognitive aging. *Front Aging Neurosci*. 2010;2:150.
- Khan UA, Liu L, Provenzano FA, Berman DE, Profaci CP, Sloan R, Mayeux R, Duff KE, Small SA. Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nat Neurosci*. 2014;17:304-11.
- Grothe MJ, Heinsen H, Amaro E, Jr, Grinberg LT, Teipel SJ. Cognitive Correlates of Basal Forebrain Atrophy and Associated Cortical Hypometabolism in Mild Cognitive Impairment. *Cereb Cortex*. 2016;26:2411-26.
- Mueller SG, Schuff N, Yaffe K, Madison C, Miller B, Weiner MW. Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. *Hum Brain Mapp*. 2010;31:1339-47.
- Gage FH. Adult neurogenesis in mammals. *Science*. 2019;364:827-28.
- Moon HY. Differential expression of genes in the subgranular zone and granular cell layer of the hippocampus after running. *J Exerc Nutrition Biochem*. 2018;22:1-6.
- Healy SD, Gwinner E, Krebs JR. Hippocampal volume in migratory and non-migratory warblers: effects of age and experience. *Behav Brain Res*. 1996;81:61-8.
- Barnea A, Nottebohm F. Seasonal recruitment of hippocampal neurons in adult free-ranging black-capped chickadees. *Proc Natl Acad Sci U S A*. 1994;91:11217-21.
- Guerrieri D, Moon HY, van Praag H. Exercise in a Pill: The Latest on Exercise-Mimetics. *Brain Plast*. 2017;2:153-69.
- Weinstein AM, Voss MW, Prakash RS, Chaddock L, Szabo A, White SM, Wojcicki TR, Mailey E, McAuley E, Kramer AF, Erickson KI. The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain Behav Immun*. 2012;26:811-9.
- Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ. Running enhances spatial pattern separation in mice. *Proc Natl Acad Sci U S A*. 2010;107:2367-72.
- Kannangara TS, Lucero MJ, Gil-Mohapel J, Drapala RJ, Simpson JM, Christie BR, van Praag H. Running reduces stress and enhances cell genesis in aged mice. *Neurobiol Aging*. 2011;32:2279-86.
- Marlatt MW, Potter MC, Bayer TA, van Praag H, Lucassen PJ. Prolonged running, not fluoxetine treatment, increases neurogenesis, but does not alter neuropathology, in the 3xTg

- mouse model of Alzheimer's disease. *Curr Top Behav Neurosci*. 2013;15:313-40.
22. Nascimento CM, Pereira JR, Pires de Andrade L, Garuffi M, Ayan C, Kerr DS, Talib LL, Cominetti MR, Stella F. Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different bdnf Val66Met genotypes. *J Alzheimers Dis*. 2015;43:81-91.
 23. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, Gonçalves RA, Clarke JR, Beckman D, Staniszewski A, Berman H, Guerra LA, Fornoy-Germano L, Meier S, Wilcock DM, de Souza JM, Alves-Leon S, Prado VF, Prado MAM, Abisambra JF, Tovar-Moll F, Mattos P, Arancio O, Ferreira ST, De Felice FG. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med*. 2019;25:165-75.
 24. Stein AM, Silva TMV, Coelho FGM, Arantes FJ, Costa JLR, Teodoro E, Santos-Galduróz RF. Physical exercise, IGF-1 and cognition A systematic review of experimental studies in the elderly. *Dement Neuropsychol*. 2018;12:114-22.
 25. Moon HY, Javadi S, Stremlau M, Yoon KJ, Becker B, Kang SU, Zhao X, van Praag H. Conditioned media from AICAR-treated skeletal muscle cells increases neuronal differentiation of adult neural progenitor cells. *Neuropharmacology*. 2019;145:123-30.
 26. Sun J, Sun J, Ming GL, Song H. Epigenetic regulation of neurogenesis in the adult mammalian brain. *Eur J Neurosci*. 2011;33:1087-93.
 27. Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *J Neuroinflammation*. 2019;16:53.
 28. Motiani KK, Collado MC, Eskelinen JJ, Virtanen KA, Löytyniemi E, Salminen S, Nuutila P, Kalliokoski KK, Hannukainen JC. Exercise Training Modulates Gut Microbiota Profile and Improves Endotoxemia. *Med Sci Sports Exerc*. 2020;52:94-104.
 29. Fernandes J, Arida RM, Gomez-Pinilla F. Physical exercise as an epigenetic modulator of brain plasticity and cognition. *Neurosci Biobehav Rev*. 2017;80:443-56.
 30. Lauber SN, Gooderham NJ. The cooked meat derived genotoxic carcinogen 2-amino-3-methylimidazo[4,5-b]pyridine has potent hormone-like activity: mechanistic support for a role in breast cancer. *Cancer Res*. 2007;67:9597-602.
 31. Morali G, Lemus AE, Munguia R, García GA, Grillasca I, Pérez-Palacios G. Hormone-like behavioral effects of levonorgestrel and its metabolites in the male rat. *Pharmacol Biochem Behav*. 2002;73:951-61.