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Exercise and Brain Health – Implications for Multiple Sclerosis

Part 1 – Neuronal Growth Factors

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Abstract

The benefits of regular exercise to promote general health and reduce the risk of hypokinetic diseases associated with sedentary lifestyles are well recognized. Recent studies suggest that exercise may enhance neurobiological processes that promote brain health in aging and disease. A current frontier in the neurodegenerative disorder multiple sclerosis (MS) concerns the role of physical activity for promoting brain health through protective, regenerative and adaptive neural processes. Research on neuromodulation, raises the possibility that regular physical activity may mediate favourable changes in disease factors and symptoms associated with MS, in part through changes in neuroactive proteins. Insulin-like growth factor-I appears to act as a neuroprotective agent and studies indicate that exercise could promote this factor in MS. Neurotrophins, brain-derived neurotrophic factor (BDNF) and nerve growth factor likely play roles in neuronal survival and activity-dependent plasticity. Physical activity has also been shown to up-regulate hippocampal BDNF, which may play a role in mood states, learning and memory to lessen the decline in cognitive function associated with MS. In addition, exercise may promote anti-oxidant defences and neurotrophic support that could attenuate CNS vulnerability to neuronal degeneration. Exercise exposure (preconditioning) may serve as a mechanism to enhance stress resistance and thereby may support neuronal survival under heightened stress conditions. Considering that axonal loss and cerebral atrophy occur early in the disease, exercise prescription in the acute stage could promote neuroprotection, neuroregeneration and neuroplasticity and reduce long-term disability. This review concludes with a proposed conceptual model to connect these promising links between exercise and brain health.

Common symptoms of multiple sclerosis (MS), muscle weakness, spasticity, excess fatigue and depression are associated with CNS neurodegenerative processes and often result in a vicious cycle of

reduced mobility and decreased physical activity. A review of the exercise literature indicates that selected MS patients can improve their aerobic fitness, muscle strength, muscle endurance and mobility through individualised exercise training[1] and consequently may also lower their secondary disease risk related to inactivity.[2] Physical activity may promote brain health by impacting neuronal plasticity.[3] Preliminary evidence for exercise-related neuroplasticity comes from clinical research[4,5] and animal studies.[6-8]

To date, the concept of exercise neuromodulation in neurological disorders has received limited attention. However, some evidence suggests that physical activity may confer neuroprotective benefits in animal models of Parkinson's disease,[9] ischaemic stroke[10] and Alzheimer's disease.[11] In rheumatoid arthritis patients, progressive exercise training resulted in decreased disease activity and fewer swollen joints.[12] Using an animal model of MS, experimental autoimmune encephalomyelitis (EAE), Le Page and colleagues[13,14] observed that exercise did not exacerbate clinical signs of the disease. In chronic-relapsing EAE, clinical symptom onset and duration to recovery were delayed,[13] providing some preliminary evidence of a possible link between exercise and disease status. In this article, we present an overview of studies that lend support for the potential therapeutic role of exercise in MS. Further research to verify the influence of exercise on brain health in MS is needed.

Some studies suggest that physical activity may enhance cognitive function in rats and aging humans.[4,6] In rodents, exercise has been shown to impede age-related neuronal loss,[15] increase cell proliferation and neurogenesis[7] and attenuate neurological impairments in different neurodegenerative processes.[15,16] Such exercise-related changes in the CNS have implications for impacting neurological disease, although the mechanisms involved require further elucidation.

Regular physical activity may have value in MS treatment partly through exercise-mediated expression of brain growth factors.[17-22] Neurotrophic factors and neurotransmitters via cell signalling pathways mediate synaptic neuronal plasticity and cell survival in the brain throughout life.[23] These nerve growth polypeptides act on neuronal cells at specific receptors. Some of the more well characterized neurotrophic factors include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophin (NT) 3, 4 and 5.[24-26] Other factors,[27,28] in particular, insulin-like growth factor (IGF), may influence neuroprotection, regeneration and functional plasticity in the adult brain.

1. Insulin-Like Growth Factor (IGF)

IGF-I is important for normal brain development[29] with demonstrated effects on many stages of brain cell proliferation, differentiation and survival.[29] IGF-I may have similar effects on neural progenitor cells in the adult CNS as it does in the developing system.[30] In the adult brain, IGF-I is a pleiotropic peptide involved in numerous processes to maintain brain homeostasis,[31-33] acting at the cellular/molecular and systemic levels. In development, IGF-I has modulatory actions on cell survival,[34] brain growth and CNS myelination.[35-37] Evidence suggests that IGF-I may interface with other proteins to influence synaptic and cognitive plasticity.[38] IGF-I was shown to be involved with restoration of motor coordination in an animal model of cerebellar ataxia.[39] Several reports indicate that IGF-I is a potent neuroprotective agent.[40-44] Additionally, IGF-I has been shown to mediate effects on learning, memory[45,46] and behaviour.[47]

Although controversial, several lines of evidence suggest that IGF-I may be beneficial in treating MS.[48-52] In EAE, intravenous IGF-I twice daily over 8 days was found to reduce clinical deficit scores[50] and improve walking, stride length and climbing performance compared with control

rats.[50] IGF-I treatment in EAE also significantly reduced the number and area of demyelinating lesions in the spinal cord. In addition, the lesions contained axons surrounded by regenerating myelin segments instead of demyelinated axons as observed in the controls.[49] In addition, relative messenger RNA (mRNA) levels for myelin basic protein, proteolipid protein, and 2′,3′-cyclic nucleotide 3′-phosphodiesterase in lesions of IGF-I-treated rats were significantly higher than in controls.[49] Subcutaneous IGF-I injection produced similar effects as the same dose administered intravenously.[48] Lastly, tumour necrosis factor-α (TNFα) has been implicated in demyelinating injury[53,54] and IGF-I has been shown to protect myelin and oligodendrocytes from TNFα-induced damage.[55]

1.1 Exercise and IGF-I

Exercise may affect neurodegenerative processes and thus promote neuroprotection in the adult brain by modulating IGF-I.[31-33,56-59] Carro et al. found that running induced the uptake of IGF-I by specific groups of neurons throughout the brain,[56,57] and also showed that treadmill running facilitated recovery of behavioural performance in rats with neurotoxin damage to the hippocampus or brainstem.[57] Exercise also blocked neuronal impairment or loss in other types of brain injury.[57] Additionally, subcutaneous administration of a blocking anti-IGF-I antibody to exercising animals to inhibit exercise-induced uptake of IGF abolished the neuroprotective effects of exercise in various models of neurodegeneration.[57] Trejo and colleagues[58] observed that blocking circulating IGF to the brain was paralleled by a lack of exercise-induced increases in the number of new hippocampal neurons after exercise. These results suggest that exercise supports brain health through IGF-I-mediated mechanisms.[56-58]

2. Brain-Derived Neurotrophic Factor (BDNF)

The nerve growth polypeptide BDNF has been shown to play a role in CNS neurogenesis,[60] neuroprotection[61] and may also mediate exercise benefits in brain disease,[62] neuroregeneration,[63,64] learning and memory[65-67] and cell survival.[68,69] BDNF is also thought to play a role in synaptic plasticity[70-72] through diverse roles that include regulation of axonal and dendritic branching and modelling,[73,74] synaptogenesis in arborizing axon terminals[75] and synaptic transmission efficiency.[76,77]

2.1 Exercise and BDNF

Findings from animal studies support the notion that exercise may induce BDNF-mediated mechanisms that promote neuroplasticity.[78,79] For example, exercise increased BDNF mRNA concentration in the hippocampus,[80,81] BDNF protein in the hippocampus following traumatic brain injury[82] and BDNF mRNA in the spinal cord.[78,83,84] Berchtold et al.[85] found that both regular daily exercise and intermittent exercise induced hippocampal BDNF protein, which not only remained elevated for several days after exercise cessation, but also could be reinduced to peak levels with a single bout of subthreshold exercise for as long as 14 days. These data suggest that an exercise programme may contribute to BDNF-related neuroprotection and neuronal plasticity and thus could conceivably play a role in attenuating degenerative changes associated with MS and other degenerative CNS diseases.

Exercise has also been shown to elevate skeletal muscle BDNF in rodents.[78,86] Although the role of BDNF in muscle remains unclear, it may enhance the survival of injured motor neurons.[87,88] Support for this idea comes from evidence showing that BDNF is a trophic factor for motor neurons,[89] BDNF mRNA is expressed in skeletal muscle[90] and evidence for retrograde transport of exogenously

applied BDNF to motor neuron cell bodies.[89,91] Although muscle BDNF may be a survival factor, its role remains controversial.[92,93]

Serum BDNF has been shown to increase immediately following a single bout of light aerobic exercise in individuals with MS and controls.[94] Considering that BDNF expression has been observed in immune, endothelial and vascular smooth muscle cells[95] makes interpretatation of potential exercise-mediated changes in circulation challenging at this time. Further study is needed to understand the relationship between physical activity, circulating BDNF levels and brain health.

3. Nerve Growth Factor

The neurotrophin, NGF and its receptors are expressed in many cell types and are implicated in a spectrum of biological functions[96,97] including neuronal protection, activity dependent plasticity[97-100] and repair.[97,99,101] NGF may also be important in MS because of its positive influence on memory,[102,103] which can be compromised in MS. Further support for augmenting NGF in MS comes from a study showing that intracerebroventricular injection of NGF prior to EAE reduced cell death, infiltration and demyelination in spinal cord specimens and generally reduced progression of EAE.[104] Radak et al.[105] found that increased BDNF and NGF production with regular swim training improved memory and decreased oxidative stress in the brain of rats. These exercise-related effects did not persist after the cessation of training.[105] Research that examines whether exercise-mediated changes in NGF alter disease activity or symptoms of MS is warranted.

4. Exercise and Mood States

Exercise is associated with salutary effects on depression and anxiety in health and disease.[106-109] Complex psychophysical mechanisms likely contribute to such benefits. One possible link between exercise and amelioration of stressful events could be through BDNF-mediated mechanisms.[110] For example, habituation to wheel running before forced swimming prevented downregulation of hippocampal BDNF mRNA and improved behavioural measures of stress in rats.[111] Exercise, antidepressants and their combination have been shown to increase hippocampal BDNF mRNA in rats.[112] Furthermore, exercise combined with antidepressant therapy, has been shown to reduce the time required for therapeutic efficacy.[111] For a review on the neurotrophin hypothesis of antidepressant action see Russo-Neustadt and Chen.[113] Depression affects upwards of 60% of the MS population,[114] with suicidal ideation reported in as many as 25%.[115] Exercise for adjunctive therapy in depression could enhance positive mood outcomes. Furthermore, some reports suggest that the relationship between depression and neurological disorders may be bidirectional.[116,117]

5. Exercise and Cognitive Function

Participation in regular exercise preserves white and grey matter brain volume in aging humans[118,119] and predicts better cognitive function in both humans and animals.[120-123] BDNF may be involved with signalling the effects of exercise on synaptic plasticity and cognitive function.[81,122,124] Vaynman et al.[122] found that wheel running enhanced learning in rats and that the fastest learners showed the highest expression of hippocampal BDNF mRNA. Conversely, blocking BDNF action diminished exercise-induced learning and memory enhancement and the increases in BDNF mRNA.[122] Others have reported impaired learning in BDNF knockout mice.[125]

Compromised cognitive function has been shown in 45–84% of MS patients.[126-128] Cognitive deficits include executive function, information processing speed, memory, visuo-spatial abilities and attention.[126] These deficits coincide with declines in brain structure (reduced white and grey matter vol-

ume) and function.[128] Neuroimaging studies suggest evidence for the existence of cortical plasticity in people with MS.[129,130] Prakash et al.[131] recently showed that MS subjects with higher cardiorespiratory fitness had faster behavioural performance tests and exhibited greater recruitment of a specific area of cerebral cortex thought to compensate for cognitive deficits in MS. This finding suggests that maintaining fitness may counteract cognitive decline in MS. Continued research to understand the relationship between exercise and cognitive function is warranted.

6. Oxidative Stress and Exercise

Some evidence suggests that reactive oxygen species are associated with a variety of brain diseases,[132] including MS.[133] Multiple factors such as proteolytic enzymes, reactive nitrogen and reactive oxygen species may be involved in neurodegeneration. Data suggest that antioxidant defences may be reduced in MS.[134] Accumulation of oxidative damage in the brain is also associated with impaired brain function.[135] Accordingly, strategies that minimize excessive oxidative stress may help prevent neurodegeneration and cognitive perturbations.

Neurotrophic factors have been found to protect neurons in cell culture and *in vivo* against oxidative stress.[136-138] For example, intraventricular administration of NGF significantly increases, especially in old animals, the activity of key enzymes involved in the metabolic degradation of superoxide radicals and hydrogen peroxide.[139]

Exercise training has been shown to decrease reactive oxygen species and increase production of BDNF and NGF in the brain of rats,[105] which could help to counteract damages from neuronal degeneration processes. Exercise also increases antioxidant enzyme activities in the brain.[140] Inactivity is associated with increased vulnerability to oxidative stress and a potential cascade of events resulting in neuronal degradation.[140]

7. Adaptive Cellular Stress Response

The term 'hormesis' (preconditioning) refers to the idea that cells exposed to low-dose stressors become resistant to the harmful effects of a more severe stressor in order to avoid injury or death.[141,142] Evidence suggests that exercise may act through hormesis-based mechanisms to improve health and retard aging and age-related degenerative diseases.[141] Hormesis is a potentially important

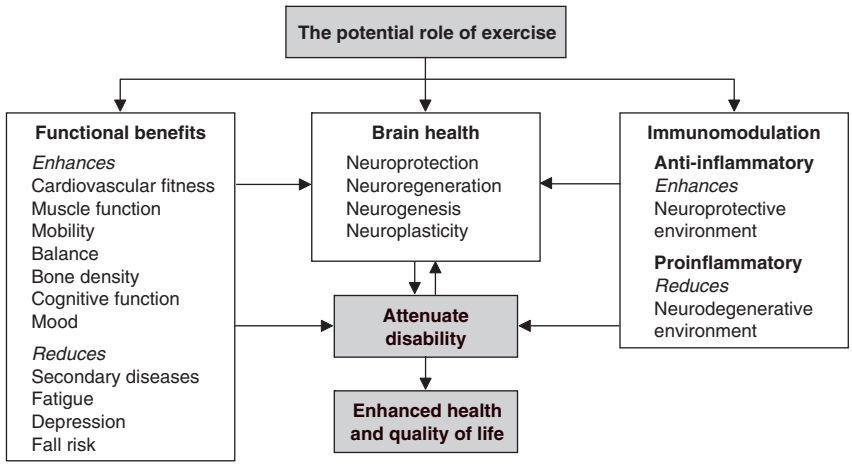

Fig. 1. A conceptual model highlighting the hypothetical effects of exercise in improving health, mobility and modulating disease activity in multiple sclerosis.

mechanism whereby neurons may be protected and resist apoptosis.[141-143] When exposed to stress, a variety of stress-responsive signalling pathways may induce biochemical events that enhance stress resistance, including neurotrophic factor signalling, antioxidant systems and antiapoptotic proteins.[141,143] Emerging evidence suggests that exercise may enhance pathways that support stress resistance.[144,145] In nerve injury and neurodegenerative disease, exercise could impose a mild stress on neurons resulting in activation of transcription factors that induce the expression of BDNF and other stress-resistant proteins,[143-147] and thus has the potential to impact cellular adaptive responses that promote neuronal survival under stress.

8. Conclusions

Exercise-induced neuronal activity contributes to the production of different neurotrophic factors that in turn modulate neuronal survival and plasticity. Emerging findings suggest that exercise and exercise training may favourably promote neural health, improve neuronal survival, resistance to brain injury[57] and stimulate neurogenesis,[7] while contributing to the preservation of cognitive function[120] and reduced risk of depression. Based on a growing body of evidence, we propose that there is a promising link between exercise, initiated with appropriate timing,[82] and promotion of brain health in MS and other diseases.[148] The theoretical considerations proposed in this article are shown as a conceptual model in figure 1. Part II of this review presents some evidence for exercise-related modulation of immune function and its implications for MS. Further research is needed to connect the exercise stimulus with subsequent molecular events that may attenuate neurodegeneration. The promising link between exercise and brain health in MS deserves further investigation. While we have presented the hypothetical benefits of exercise neuromodulation, not all studies are positive[82] and whether exercise protects tissue at risk in neurodegenerative conditions such as MS remains speculative at this time.

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References

1. White L, Dressendorfer R. Exercise and multiple sclerosis. Sports Med 2004; 34: 1077-100
2. White L, McCoy S, Castellano V, et al. Effect of resistance training on risk of coronary artery disease in women with multiple sclerosis. Scand J Clin Lab Invest 2006; 66: 351-5
3. Kempermann G, van Praag H, Gage FH. Activity-dependent regulation of neuronal plasticity and self repair. Prog Brain Res 2000; 127: 35-48
4. Kramer A, Hahn S, Cohen N, et al. Ageing, fitness and neurocognitive function. Nature 1999; 4000: 418-9
5. Rogers R, Meyer J, Mortel K. After reaching retirement age physical activity sustains cerebral perfusion and cognition. J Am Geriatr Soc 1990; 38: 123-8
6. Fordyce D, Farrar R. Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. Behav Brain Res 1991; 46: 123-33
7. van Praag H, Christie BR, Sejnowski TJ, et al. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 1999; 96: 13427-31
8. van Praag H, Kempermann G, Gage F. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 1999; 2: 266-70
9. Smith AD, Zigmond MJ. Can the brain be protected through exercise? Lessons from an animal model of parkinsonism. Exp Neurol 2003; 184: 31-9
10. Stummer W, Weber K, Tranmer B, et al. Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. Stroke 1994; 25: 1862-7
11. Adlard P, Perreau V, Pop V, et al. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci 2005; 25: 4217-22
12. Lyngberg K, Danneskiold-Samsoe B, Halskov O. The effect of physical training on patients with rheumatoid arthritis: changes in disease activity, muscle strength and aerobic capacity: a clinically controlled minimized cross-over study. Clin Exp Rheumatol 1988; 6: 253-60
13. Le Page C, Ferry A, Rieu M. Effect of muscular exercise on chronic relapsing experimental autoimmune encephalomyelitis. J Appl Physiol 1994; 77: 2341-7

14. Le Page C, Bourdoulous S, Beraud E, et al. Effect of physical exercise on adoptive experimental auto-immune encephalomyelitis in rats. Eur J Appl Physiol Occup Physiol 1996; 73: 130-5
15. Larsen J, Skalicky M, Viidik A. Does long-term physical exercise counteract age-related Purkinje cell loss? A stereological study of rat cerebellum. J Comp Neurol 2000; 428: 213-22
16. Mattson M. Neuroprotective signaling and the aging brain: take away my food and let me run. Brain Res 2000; 866: 47-53
17. Neeper S, Gomez-Pinilla F, Choi J, et al. Exercise and brain neurotrophins. Nature 1995; 373: 109
18. Neeper SA, Gomez-Pinilla F, Choi J, et al. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. Brain Res 1996; 726: 49-56
19. Oliff H, Berchtold N, Isackson P, et al. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. Brain Res Mol Brain Res 1998; 61: 147-53
20. Widenfalk J, Olson L, Thoren P. Deprived of habitual running, rats downregulate BDNF and TrkB messages in the brain. Neurosci Res 1999; 34: 125-32
21. Ang ET, Wong PTH, Moochhala S, et al. Neuroprotection associated with running: is it a result of increased endogenous neurotrophic factors? Neuroscience 2003; 118: 335-45
22. Carro E, Trejo J, Nunez A, et al. Brain repair and neuroprotection by serum insulin-like growth factor I. Mol Neurobiol 2003; 27: 153-6
23. Mattson MP, Maudsley S, Martin B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci 2004; 27: 589-94
24. Maisonpierre P, Belluscio L, Squinto S, et al. Neurotrophin-3: a neurotrophic factor related to NGF and BDNF. Science 1990; 247: 1446-51
25. Hallbook F, Ibanez CF, Persson H. Evolutionary studies of the nerve growth factor family reveal a novel member abundantly expressed in xenopus ovary. Neuron 1991; 6: 845-58
26. Ip N, Ibanez C, Nye S, et al. Mammalian neurotrophin-4: structure, chromosomal localization, tissue distribution, and receptor specificity. Proc Natl Acad Sci U S A 1992; 89: 3060-4
27. Cao L, Jiao X, Zuzga D, et al. VEGF links hippocampal activity with neurogenesis, learning and memory. Nat Genet 2004; 36: 827-35
28. Zhou L, Shine H. Neurotrophic factors expressed in both cortex and spinal cord induce axonal plasticity after spinal cord injury. J Neurosci Res 2003; 74: 221-6
29. Anlar B, Sullivan K, Feldman E. Insulin-like growth factor-I and central nervous system development. Horm Metab Res 1999; 31: 120-5
30. Anderson MF, Aberg MAI, Nilsson M, et al. Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. Brain Res Dev Brain Res 2002; 134: 115-22
31. Russo VC, Gluckman PD, Feldman EL, et al. The insulin-like growth factor system and its pleiotropic functions in brain. Endocr Rev 2005; 26: 916-43
32. Fernandez S, Fernandez AM, Lopez-Lopez C, et al. Emerging roles of insulin-like growth factor-I in the adult brain. Growth Horm IGF Res 2007; 17: 89-95
33. Aberg N, Brywe K, Isgaard J. Aspects of growth hormone and insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. Sci World J 2006; 18: 53-80
34. Dudek H, Datta SR, Franke TF, et al. Regulation of neuronal survival by the serine-threonine protein kinase Akt. Science 1997; 275: 661-5
35. Beck K, Powell-Braxton L, Widmer H, et al. Igf1 gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumin-containing neurons. Neuron 1995; 14: 717-30
36. Carson M, Behringer R, Brinster R, et al. Insulin-like growth factor I increases brain growth and central nervous system myelination in transgenic mice. Neuron 1993; 10: 729-40
37. Ye P, Li L, Richards RG, et al. Myelination is altered in insulin-like growth factor-I null mutant mice. J Neurosci 2002 Jul 15; 22 (14): 6041-51
38. Ding Q, Vaynman S, Akhavan M, et al. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. Neuroscience 2006; 140: 823-33
39. Fernandez A, de la Vega A, Torres-Aleman A. Insulin-like growth factor I restores motor coordination in a rat model of cerebellar ataxia. Proc Natl Acad Sci USA 1998; 95: 1253-8
40. Leinninger GM, Backus C, Uhler MD, et al. Phosphatidylinositol 3-kinase and Akt effectors mediate insulin-like growth factor-I neuroprotection in dorsal root ganglia neurons. FASEB J 2004; 18: 1544-6
41. Kaspar BK, Llado J, Sherkat N, et al. Retrograde viral delivery of IGF-I prolongs survival in a mouse ALS model. Science 2003; 301: 839-42
42. Vincent A, Mobley B, Hiller A, et al. IGF-I prevents glutamate-induced motor neuron programmed cell death. Neurol Dis 2004; 16: 407-16
43. Carro E, Trejo J, Gomez-Isla T, et al. Serum insulin-like growth factor I regulates brain amyloid- levels. Nat Med 2002; 8: 1390-7
44. Kermer P, Klocker N, Labes M, et al. Insulin-like growth factor-I protects axotomized rat retinal ganglion cells from secondary death via PI3-K-dependent Akt phosphorylation and inhibition of caspase-3 in vivo. J Neurosci 2000; 20: 2-8
45. Svensson J, Diez M, Engel J, et al. Endocrine, liver-derived IGF-I is of importance for spatial learning and memory in old mice. J Endocrinol 2006; 189: 617-27
46. Lupien S, Bluhm E, Ishii D. Systemic insulin-like growth factor-I administration prevents cognitive impairment in diabetic rats, and brain IGF regulates learning/memory in normal adult rats. J Neurosci Res 2003; 74: 512-23
47. Hoshaw B, Malberg J, Lucki I. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. Brain Res 2005; 1037: 204-8
48. Yao D-L, Xia L, Hudson LD, et al. Insulin-like growth factor-I given subcutaneously reduces clinical deficits, decreases lesion severity and upregulates synthesis of myelin proteins in experimental autoimmune encephalomyelitis. Life Sci 1996; 58: 1301-6
49. Yao D, Liu X, Hudson L, et al. Insulin-like growth factor I treatment reduces demyelination and up-regulates gene ex-

pression of myelin-related proteins in experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A 1995; 92: 6190-4
50. Liu X, Yao D, Webster H. Insulin-like growth factor I treatment reduces clinical deficits and lesion severity in acute demyelinating experimental autoimmune encephalomyelitis. Mult Scler 1995; 1: 2-9
51. Ye P, D'Ercole AJ. Insulin-like growth factor I protects oligodendrocytes from tumor necrosis factor-alpha-induced injury. Endocrinology 1999; 140: 3063-72
52. Leinninger G, Feldman E. Insulin-like growth factors in the treatment of neurological disease. Endocr Rev 2005; 9: 135-9
53. Probert L, Akassoglou K, Pasparakis M, et al. Spontaneous inflammatory demyelinating disease in transgenic mice showing central nervous system-specific expression of tumor necrosis factor. Proc Natl Acad Sci U S A 1995; 92: 11294-8
54. Akassoglou K, Probert L, Kontogeorgos G, et al. Astrocyte-specific but not neuron-specific transmembrane TNF triggers inflammation and degeneration in the central nervous system of transgenic mice. J Immunol 1997; 158: 438-45
55. Ye P, Kollias G, D'Ercole A. Insulin-like growth factor-I ameliorates demyelination induced by tumor necrosis factor-α in transgenic mice. J Neurosci Res 2007; 85: 712-22
56. Carro E, Nunez A, Busiguina S, et al. Circulating insulin-like growth factor I mediates effects of exercise on the brain. J Neurosci 2000; 20: 2926-33
57. Carro E, Trejo J, Busiguina S, et al. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci 2001; 21: 5678-84
58. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci 2001; 21: 1628-34
59. Carro E, Torres-Aleman I. Serum insulin-like growth factor I in brain function. Keio J Med 2006; 55: 59-63
60. Rossi C, Angelucci A, Costantin L, et al. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. Eur J Neurosci 2006; 24: 1850-6
61. Schabitz W, Schwab S, Spranger M, et al. Intraventricular brain-derived neurotrophic factor reduces infarct size after focal cerebral ischemia in rats. J Cereb Blood Flow Metab 1997; 17: 500-6
62. Hubka P. Neural network plasticity, BDNF and behavioral interventions in Alzheimer's disease. Bratisl Lek Listy 2006; 107: 395-401
63. Xu X, Guenard V, Klritman N, et al. A combination of BDNF and NT-3 promotes supraspinal axonal regeneration into Schwann cell grafts in adult rat thoracic spinal cord. Exp Neurol 1995; 134: 261-72
64. Ye J, Houle J. Treatment of the chronically injured spinal cord with neurotrophic factors can promote axonal regeneration from supraspinal neurons. Exp Neurol 1997; 143: 70-81
65. Mizuno M, Yamada K, Olariu A, et al. Involvement of brain-derived neurotrophic factor in spatial memory formation and maintenance in a radial arm maze test in rats. J Neurosci 2000; 20: 7116-21
66. Alonso M, Monica RMV, Ivan I, et al. Signaling mechanisms mediating BDNF modulation of memory formation in vivo in the hippocampus. Cell Mol Neurobiol 2002; 22: 663-74
67. Alonso M, Vianna R, Depino A, et al. BDNF-triggered events in the rat hippocampus are required for both short- and long-term memory formation. Hippocampus 2002; 12: 551-60
68. Yan Q, Elliott J, Snider WD. Brain-derived neurotrophic factor rescues spinal motor neurons from axotomy-induced cell death. Nature 1992; 360: 753-5
69. Kishino A, Ishige Y, Tatsuno T, et al. BDNF prevents and reverses adult rat motor neuron degeneration and induces axonal outgrowth. Exp Neurol 1997; 144: 273-86
70. McAllister A, Katz L, Lo D. Neurotrophins and synaptic plasticity. Annu Rev Neurosci 1999; 22: 295-318
71. Lu B. BDNF and activity dependent synaptic plasticity. Learn Mem 2003; 10: 86-98
72. Lu B. Acute and long-term synaptic modulation by neurotrophins. Prog Brain Res 2004; 146: 137-50
73. Lom B, Cohen-Cory S. Brain derived neurotrophic factor differentially regulates retinal ganglion cell dendritic and axonal aborization in vivo. J Neurosci 1999; 19: 9928-38
74. Yacoubian T, Lo D. Truncated and full length Trk B receptors regulate distinct modes of dendritic outgrowth. Nat Neurosci 2000; 3: 342-9
75. Alsina B, Vu T, Cohen-Cory S. Visualizing synapse formation in arborizing optic axons in vivo: dynamics and modulation by BDNF. Nat Neurosci 2001; 4: 1093-101
76. Lohof A, Ip N, Poo M. Potentiation of developing neuromuscular synapses by the neurotrophins NT-3 and BDNF. Nature 1993; 27: 350-3
77. Kafitz K, Ross C, Thoenen H, et al. Neurotrophin-evoked rapid excitation through TrkB receptors. Nature 1999; 28: 918-21
78. Gomez-Pinilla F, Ying Z, Roy R, et al. Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. J Neurophysiol 2002; 88: 2187-95
79. Vaynman S, Gomez-Pinilla F. License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. Neurorehabil Neural Repair 2005; 19: 283-95
80. Chen MJ, Russo-Neustadt AA. Exercise activates the phosphatidylinositol 3-kinase pathway. Mol Brain Res 2005; 135: 181-93
81. Vaynman S, Ying Z, Gomez-Pinilla F. Interplay between brain-derived neurotrophic factor and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. Neuroscience 2003; 122: 647-57
82. Griesbach GS, Hovda DA, Molteni R, et al. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. Neuroscience 2004; 125: 129-39
83. Macias M, Fehr S, Dwornik A, et al. Exercise increases mRNA levels for adhesion molecules N-CAM and L1 correlating with BDNF response. Neuroreport 2002; 13: 2527-30
84. Perreau V, Adlard P, Anderson A, et al. Exercise-induced gene expression changes in the rat spinal cord. Gene Expr 2005; 12: 107-21
85. Berchtold NC, Chinn G, Chou M, et al. Exercise primes a molecular memory for brain-derived neurotrophic factor pro-

tein induction in the rat hippocampus. Neuroscience 2005; 133: 853-61
86. Dupont-Versteegden E, Houlé J, Dennis R, et al. Exercise-induced gene expression in soleus muscle is dependent on time after spinal cord injury in rats. Muscle Nerve 2004; 29: 73-81
87. Sendtner M, Holtmann B, Kolbeck R, et al. Brain-derived neurotrophic factor prevents the death of motoneurons in newborn rats after nerve section. Nature 1992; 360: 757-9
88. Griesbeck O, Parsadanian A, Sendtner M, et al. Expression of neurotrophins in skeletal muscle: quantitative comparison and significance for motoneuron survival and maintenance of function. J Neurosci Res 1995; 42: 21-33
89. Koliatsos V, Clatterbuck R, Winslow J, et al. Evidence that brain-derived neurotrophic factor is a trophic factor for motor neurons in vivo. Neuron 1993; 10: 359-67
90. Funakoshi H, Frisen J, Barbany G, et al. Differential expression of mRNAs for neurotrophins and their receptors after axotomy of the sciatic nerve. J Cell Biol 1993; 123: 455-65
91. Kishino A, Nakayama C. Enhancement of BDNF and activated-ERK immunoreactivity in spinal motor neurons after peripheral administration of BDNF. Brain Res 2003; 964: 56-66
92. Copray S, Liem R, Brouwer N, et al. Contraction-induced muscle fiber damage is increased in soleus muscle of streptozotocin-diabetic rats and is associated with elevated expression of brain-derived neurotrophic factor mRNA in muscle fibers and activated satellite cells. Exp Neurol 2000; 161: 597-608
93. Liem R, Brouwer N, Copray J. Ultrastructural localisation of intramuscular expression of BDNF mRNA by silver-gold intensified non-radioactive in situ hybridisation. Histochem Cell Biol 2001; 116: 545-51
94. Gold SM, Schulz K-H, Hartmann S, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J Neuroimmunol 2003; 138: 99-105
95. Lommatzsch M, Zingler D, Schuhbaeck K, et al. The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiol Aging 2005; 26: 115-23
96. Levi-Montalcini R, Dal Toso R, della Valle F, et al. Update of the NGF saga. J Neurol Sci 1995; 130: 119-27
97. Sofroniew MV, Howe CL, Mobley WC. Nerve growth factor signaling, neuroprotection, and neural repair. Annu Rev Neurosci 2001; 24: 1217-81
98. Castren E, Pitkanen M, Sirvio J, et al. The induction of LTP increases BDNF and NGF mRNA but decreases NT-3 mRNA in the dentate gyrus. Neuroreport 1993; 4: 895-8
99. Hennigan A, O'callaghan RM, Kelly ÃM. Neurotrophins and their receptors: roles in plasticity, neurodegeneration and neuroprotection. Biochem Soc Trans 2007; 35: 424-7
100. Prakash N, Cohen-Cory S, Frostig RD. Rapid and opposite effects of BDNF and NGF on the functional organization of the adult cortex in vivo. Nature 1996; 381: 702-6
101. Ramer MS, Priestley JV, McMahon SB. Functional regeneration of sensory axons into the adult spinal cord. Nature 2000; 403: 312-6
102. Niewiadomska G, Baksalerska-Pazera M, Gasiorowska A, et al. Nerve growth factor differentially affects spatial and recognition memory in aged rats. Neurochem Res 2006; 31: 1481-90
103. Woolf NJ, Milov AM, Schweitzer ES, et al. Elevation of nerve growth factor and antisense knockdown of TrkA receptor during contextual memory consolidation. J Neurosci 2001; 21: 1047-55
104. Tafreshi P. Nerve growth factor prevents demyelination, cell death and progression of the disease in experimental allergic encephalomyelitis. Iran J Allergy Asthma Immunol 2006; 5: 177-81
105. Radak Z, Toldy A, Szabo Z, et al. The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. Neurochem Int 2006; 49: 387-92
106. Byrne A, Byrne DG. The effect of exercise on depression, anxiety and other mood states: a review. J Psychosom Res 1993; 37: 565-74
107. DiLorenzo TM, Bargman EP, Stucky-Ropp R, et al. Long-term effects of aerobic exercise on psychological outcomes. Prev Med 1999; 28: 75-85
108. Knubben K, Reischies FM, Adli M, et al. A randomised, controlled study on the effects of a short-term endurance training programme in patients with major depression. Br J Sports Med 2007; 41: 29-33
109. Paffenbarger R, Lee I, Leung R. Physical activity and personal characteristics associated with depression and suicide in American college men. Acta Psychiatr Scand Suppl 1994; 377: 16-22
110. Duman RS. Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. Neurobiol Aging 2005; 26: 88-93
111. Russo-Neustadt A, Ha T, Ramirez R, et al. Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. Behav Brain Res 2001; 120: 87-95
112. Garza AA, Ha TG, Garcia C, et al. Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain. Pharmacol Biochem Behav 2004; 77: 209-20
113. Russo-Neustadt AA, Chen MJ. Brain-derived neurotrophic factor and antidepressant activity. Curr Pharm Des 2005; 11: 1495-510
114. Bakshi R, Shaikh ZA, Miletich RS, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 2000; 6: 181-5
115. Turner AP, Williams RM, Bowen JD, et al. Suicidal ideation in multiple sclerosis. Arch Phys Med Rehab 2006; 87: 1073-8
116. Hesdorffer D, Hauser W, Annegers J, et al. Major depression is a risk factor for seizures in older adults. Ann Neurol 2000; 47: 246-9
117. Larson SL, Owens PL, Ford D, et al. Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore Epidemiologic Catchment Area study. Stroke 2001; 32: 1979-83
118. Colcombe SJ, Erickson KI, Raz N, et al. Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci 2003; 58: 176-80
119. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006; 61: 1166-70

120. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003; 14 (2): 125-30

121. Colcombe S, Kramer A, Erickson K, et al. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A 2004; 101: 3316-21

122. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 2004; 20: 2580-90

123. Kramer AF, Erickson KI, Colcombe SJ. Exercise, cognition, and the aging brain. J Appl Physiol 2006; 101: 1237-42

124. Tyler WJ, Alonso M, Bramham CR, et al. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem 2002; 9: 224-37

125. Linnarsson S, Bjorklund A, Ernfors P. Learning deficit in BDNF mutant mice. Eur J Neurosci 1997; 9: 2581-7

126. Arango-Lasprilla J, DeLuca J, Chiaravalloti N. Neuropsychological profile of multiple sclerosis. Psicothema 2007; 19: 1-6

127. Rao S, Leo G, Bernardin L, et al. Cognitive dysfunction in multiple sclerosis: I. Frequency, patterns, and prediction. Neurology 1991; 41: 685-91

128. Bobholz JA, Rao SM. Cognitive dysfunction in multiple sclerosis: a review of recent developments. Curr Opin Neurol 2003; 16: 283-8

129. Staffen W, Mair A, Zauner H, et al. Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. Brain 2002; 125: 1275-82

130. Filippi M, Rocca MA, Mezzapesa DM, et al. A functional MRI study of cortical activations associated with object manipulation in patients with MS. Neuroimage 2004; 21: 1147-54

131. Prakash RS, Snook EM, Erickson KI, et al. Cardiorespiratory fitness: a predictor of cortical plasticity in multiple sclerosis. Neuroimage 2007; 34: 1238-44

132. Mattson M, Liu D. Energetics and oxidative stress in synaptic plasticity and neurodegenerative disorders. Neuromolecular Med 2002; 2: 215-31

133. LeVine SM. The role of reactive oxygen species in the pathogenesis of multiple sclerosis. Med Hypotheses 1992; 39: 271-4

134. Ferretti G, Bacchetti T, Principi F, et al. Increased levels of lipid hydroperoxides in plasma of patients with multiple sclerosis: a relationship with paraoxonase activity. Mult Scler 2005; 11: 677-82

135. Radak Z, Taylor A, Ohno H, et al. Adaptation to exercise-induced oxidative stress: from muscle to brain. Exerc Immunol Rev 2001; 7: 90-107

136. Mattson M, Scheff S. Endogenous neuroprotection factors and traumatic brain injury: mechanisms of action and implications for therapy. J Neurotrauma 1994; 11: 3-33

137. Guo ZH, Mattson MP. Neurotrophic factors protect cortical synaptic terminals against amyloid- and oxidative stress-induced impairment of glucose transport, glutamate transport and mitochondrial function. Cereb Cortex 2000; 10: 50-7

138. Wu A, Ying Z, Gomez-Pinilla F. The interplay between oxidative stress and brain-derived neurotrophic factor modulates the outcome of a saturated fat diet on synaptic plasticity and cognition. Eur J Neurosci 2004; 19: 1699-707

139. Nistico G, Ciriolo M, Fiskin K, et al. NGF restores decrease in catalase activity and increases superoxide dismutase and glutathione peroxidase activity in the brain of aged rats. Free Radic Biol Med 1992; 12: 177-81

140. Kiraly M, Kiraly S. The effect of exercise on hippocampal integrity: review of recent research. Int J Psychiatry Med 2005; 35: 75-89

141. Arumugam TV, Gleichmann M, Tang S-C, et al. Hormesis/preconditioning mechanisms, the nervous system and aging. Ageing Res Rev 2006; 5: 165-78

142. Radak Z, Chung H, Goto S. Exercise and hormesis: oxidative stress-related adaptation for successful aging. Biogerontology 2005; 6: 71-5

143. Mattson MP. Neuronal life-and-death signaling, apoptosis, and neurodegenerative disorders. Antioxid Redox Signal 2006; 8: 1997-2006

144. Gomez-Pinilla F. The influences of diet and exercise on mental health through hormesis. Ageing Res Rev. Epub 2007 May 5

145. Radak Z, Chung HY, Koltai E, et al. Exercise, oxidative stress and hormesis. Ageing Res Rev. Epub 2007 Aug 2

146. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002; 25: 295-301

147. Sim YJ, Kim H, Kim JY, et al. Long-term treadmill exercise overcomes ischemia-induced apoptotic neuronal cell death in gerbils. Physiol Behav 2005; 84: 733-8

148. Dishman RK, Berthoud HR, Booth FW, et al. Neurobiology of exercise. Obesity (Silver Spring) 2006; 14: 345-56

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