with isoelectric points of 9.6 and 5.2[20], which suggests that they may bind in an electrostatic manner. We sought to investigate this putative interaction using surface plasmon resonance and biochemical methods[20]. Surprisingly, the BDNF pro-peptide binds to mature BDNF with high affinity, but not to other NTs. More interestingly, this interaction was enhanced at acidic pH compared with neutral pH. Thus, it is conceivable that stronger binding between BDNF and its pro-peptide may occur in acidic intracellular compartments such as trafficking vesicles, rather than in the extracellular space. To explore the physiological role of this interaction, we performed electrophysiological studies. Interestingly, when pre-incubated with BDNF, the BDNF pro-peptide completely attenuated the ability of BDNF to inhibit hippocampal LTD[6]. Thus, these results suggest that the BDNF pro-peptide, when co-released with BDNF, might modulate the availability of BDNF via a stable interaction in the extracellular space.

Novel insights: The Role of BDNF in the PNS and Brain-Body Integrity

Recently, numerous reports have revealed the roles and functions of BDNF in the PNS and the brain-body interface. BDNF expression is up-regulated in models of neuropathic pain, and BDNF enhances the ventral root potential induced by C-fiber stimulation, demonstrating the mechanical role of BDNF in the development of neuropathic pain[21]. However, injury to the sural nerve, which almost innervates skin, does not induce neuropathic pain. Recently, Zhou et al. (2010) indicated that sural nerve injury fails to produce neuropathic pain due to a limited amount of BDNF contained in the nerve[22]. Furthermore, in another recent study, Liu et al. (2017) demonstrated that TNF-alpha differentially regulates synaptic plasticity in the hippocampus and spinal cord via microglia-dependent mechanisms after peripheral nerve injury[23], suggesting a mechanical difference between chronic pain and memory deficit.

Exercise provides many beneficial effects to the human brain, including improving cognitive function, reducing the risk of Alzheimer's disease, and alleviating depression[24]. Recently, Ogborn et al. (2010) showed that 5 days of treadmill exercise elevated BDNF expression in the soleus more than in the medial gastrocnemius[25]. More recently, it was demonstrated that up-regulation of BDNF expression in the hippocampus after exercise is mediated by activation of the important metabolic mediator, peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1a (PGC-1a) and the previously identified muscle protein fibronectin type III domain containing 5 (FNDC5)[26], suggesting that the regulation of BDNF expression linking the brain and body after exercise is distinct from the neuronal activity-dependent up-regulation of BDNF expression that enhances synaptic function in the brain.

These findings provide new insight into the development of neuropathic pain and brain-body connections after exercise. Since both the BDNF pro-peptide and BDNF are derived from the same precursor, exactly how the BDNF pro-peptide contributes to the PNS and brain-body connections remains to be determined in future studies.

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References

1. Bibel M, Barde YA. Neurotrophins: key regulators of cell fate and cell shape in the vertebrate nervous system. Genes Dev. 2000; 14: 2919-2937.
2. Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci. 2003; 4: 299-309.
3. Reichardt LF. Neurotrophin-regulated signalling pathways. Philos Trans R Soc Lond B Biol Sci. 2006; 361: 1545-1564.
4. Waterhouse EG, Xu B. New insights into the role of brain-derived neurotrophic factor in synaptic plasticity. Mol Cell Neurosci. 2009; 42: 81-89.
5. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci. 2013; 14: 7-23.
6. Mizui T, Ishikawa Y, Kumanogoh H, et al. BDNF pro-peptide actions facilitate hippocampal LTD and are altered by the common BDNF polymorphism Val66Met. Proc Natl Acad Sci U S A. 2015; 112: E3067-3074.
7. Poo MM. Neurotrophins as synaptic modulators. Nat Rev Neurosci. 2001; 2: 24-32.
8. Lessmann V, Brigadski T. Mechanisms, locations, and kinetics of synaptic BDNF secretion: an update. Neurosci Res. 2009; 65: 11-22.
9. Seidah NG, Benjannet S, Pareek S, et al Cellular processing of the neurotrophin precursors of NT3 and BDNF by the mammalian proprotein convertases. FEBS Lett. 1996; 379: 247-250.
10. Mowla SJ, Pareek S, Farhadi HF, et al. Differential sorting of nerve growth factor and brain-derived neurotrophic factor in hippocampal neurons. J Neurosci. 1999; 19: 2069-2080.
11. Leibrock J, Lottspeich F, Hohn A, et al. Molecular cloning and expression of brain-derived neurotrophic factor. Nature. 1989; 341: 149-152.
12. Dieni S, Matsumoto T, Dekkers M, et al. BDNF and its pro-peptide are stored in presynaptic dense core vesicles in brain neurons. J Cell Biol. 2012; 196: 775-788.
13. Lessmann V, Gottmann K, Heumann R. BDNF and NT-4/5 enhance glutamatergic synaptic transmission in cultured hippocampal neurones. Neuroreport. 1994; 6: 21-25.
14. Figurov A, Pozzo-Miller LD, Olafsson P, et al. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature. 1996; 381: 706-709.
15. Patterson SL, Abel T, Deuel TA, et al. Recombinant BDNF rescues

deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron. 1996; 16: 1137-1145.

16. Xu B, Gottschalk W, Chow A, et al. The role of brain-derived neurotrophic factor receptors in the mature hippocampus: modulation of long-term potentiation through a presynaptic mechanism involving TrkB. J Neurosci. 2000; 20: 6888-6897.
17. Minichiello L, Calella AM, Medina DL, et al. Mechanism of TrkB-mediated hippocampal long-term potentiation. Neuron. 2002; 36: 121-137.
18. Kolbeck R, Jungbluth S, Barde YA. Characterisation of neurotrophin dimers and monomers. Eur J Biochem. 1994; 225: 995-1003.
19. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112: 257-269.
20. Uegaki K, Kumanogoh H, Mizui T, et al. BDNF Binds Its Pro-Peptide with High Affinity and the Common Val66Met Polymorphism Attenuates the Interaction. International journal of molecular sciences. 2017; 18: 1042-1031.
21. Pezet S, Malcangio M, McMahon SB. BDNF: a neuromodulator in nociceptive pathways? Brain research. Brain research reviews. 2002; 40: 240-249.
22. Zhou LJ, Ren WJ, Zhong Y, et al. Limited BDNF contributes to the failure of injury to skin afferents to produce a neuropathic pain condition. Pain. 2010; 148: 148-157.
23. Liu Y, Zhou LJ, Wang J, et al. TNF-alpha Differentially Regulates Synaptic Plasticity in the Hippocampus and Spinal Cord by Microglia-Dependent Mechanisms after Peripheral Nerve Injury. J Neurosci. 2017; 37: 871-881.
24. Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell metabolism. 2012; 16: 706-722.
25. Ogborn DI, Gardiner PF. Effects of exercise and muscle type on BDNF, NT-4/5, and TrKB expression in skeletal muscle. Muscle & nerve. 2010; 41: 385-391.
26. Wrann CD, White JP, Salogiannnis J, et al. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. Cell metabolism. 2013; 18: 649-659.