Brain-Derived Neurotrophic Factor: *The Neurotrophin Hypothesis of Psychopathology*

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ABSTRACT

While monoaminergic hypotheses of psychopathology remain popular, there has been growing interest in the role of neurotrophins in neuropsychiatric disorders. Basic laboratory work has documented the importance of neurotrophins in neuronal survival and synaptic plasticity, and a range of clinical studies has provided analogous evidence of their role in neuropathology. Work on gene variants in brain-derived neurotrophic factor, and associated changes in structural and function brain imaging, have further contributed to our understanding of this area. Much remains to be done to delineate fully the relevant mechanisms by which brain-derived neurotrophic factor and other neurotrophins contribute to psychopathology, and to develop targeted therapeutic interventions. Nevertheless, the neurotrophin hypothesis has already given impetus to a range of valuable research.

CASE REPORT

Steven is a 62-year-old man who presented for treatment for depression. His symptoms included anhedonia, low energy, lack of concentration, and poor memory. He had difficulty recalling important conversations and meetings. He was particularly concerned about the latter symptoms because his work as an accountant required him to be mentally focused and well organized. A thorough neuropsychiatric workup revealed no evidence of any general medical disorders accounting for these symptoms. He was treated with a selective serotonin reuptake inhibitor for several months. Although his overall mood improved, he was particularly grateful for the effects of pharmacotherapy on his concentration and memory, and the consequent improvement in his functioning at work.

COGNITIVE-AFFECTIVE NEUROSCIENCE

Neurotrophins are secreted peptides that are essential for the differentiation and survival of neurons, and play a key role in synaptic plasticity.[1] After the early discovery of nerve growth factor, a range of mammalian neurotrophic factors were identified, including brain-derived neurotrophic factor (BDNF). They share a similar structure, are synthesized as precursor proteins

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(proneurotrophins), and once secreted in mature form act to facilitate receptor dimerization and consequent receptor phosphorylation.[2,3]

BDNF is an activity-dependent neurotrophin that is densely distributed throughout the brain. Proneurotrophins bind to the p75 neurotrophin receptor p75NTR, while mature neurotrophins bind to the tropomyosin-related kinase family of receptor tyrosine kinases, with BDNF predominantly activating tropomyosin-related kinase B. The yin-yang hypothesis[4] states that proneurotrophins elicit apoptosis, while neurotrophins promote dendritic spine growth. Similarly, in the adult brain, proneurotrophins elicit long-term depression, while neurotrophins lead to long-term potentiation.[5]

Neuroanatomy/Neurochemistry

BDNF promotes neuronal survival and plasticity via activation of transcription factors, such as cyclic adenosine monophosphate-response element binding protein (which in turn drives expression of the prosurvival gene Bcl-2), and early growth transcription factors, such as Egr1 and Egr3 (which in turn regulate synthesis of the activity-regulated cytoskeletal-related gene).[3] BDNF moderates the expression of a range of other genes, interacting with the glutamate,[6] dopamine,[7,8] serotonin,[9,10] and other excitatory and inhibitory neurotransmitter[11] systems. There is also neurotrophic cross-talk between the nervous and immune systems.[12]

BNDF plays a role in a range of neurodegenerative, neuroinflammatory, and neurodevelopmental disorders, as well as in some psychiatric and substance use disorders.[3] Decreased hippocampal BDNF mRNA and cell atrophy are, for example, seen in several animal models of depression, depression is associated with decreased hippocampal volume, and at postmortem depressed patients have decreased hippocampal BDNF.[3] Hippocampal neurogenesis appears necessary for antidepressant effects,[13] down-regulation of BDNF can be prevented by antidepressants in animals,[14] and BDNF increases during the treatment of depressed patients.[15] Nevertheless, there are inconsistencies and complexities in the literature on BDNF and depression.[16-19] Furthermore, BDNF may act differently on the stress and reward systems.[20]

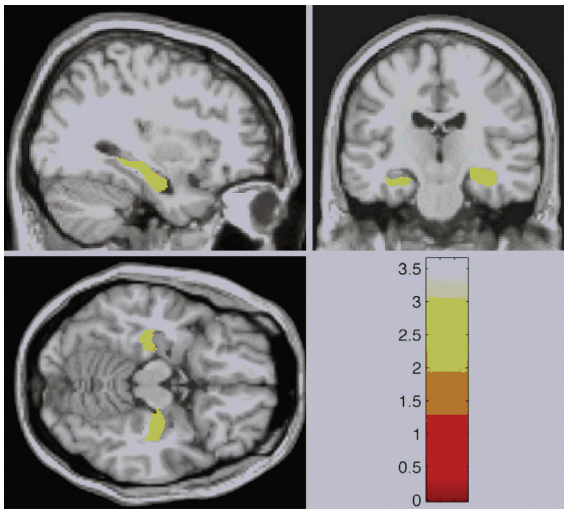
A single nucleotide polymorphism in the 5′ pro-domain of the BDNF gene on chromosome 11p13 results in an amino-acid substitution of valine (val) with methionine (met) at codon 66 (Val66Met), in a region that plays a key role in activity-dependent BDNF secretion.[21,22] Interaction of this region of BDNF with the receptor sortilin is markedly reduced by the met allele, leading to reduced intracellular trafficking and activity-dependent BDNF secretion.[23] Furthermore, BDNF met/met mice demonstrate increased anxiety.[24]

Clinical studies in humans have demonstrated that subjects with the Val66Met allele have impaired temporal lobe-related cognitive performance[21,25-28]; smaller volumes of hippocampus, amygdala, or temporal regions[28-34]; abnormal hippocampal[21,35] and amygdala[36] activation; and lower hippocampal *N*-acetylaspartate[21,37] (Figures 1–3). The impact of the met allele is found not only in healthy subjects but also in patients with depression,[38,39] bipolar disorder,[34,40] and schizophrenia,[28,30,33,41,42] and the variant also impacts on age-related changes of the brain.[38,43]

Gene/Environment

Genetic studies of BDNF in psychiatric disorders remain somewhat inconsistent. There is some evidence, for example, that the Val66Met allele is

FIGURE 1.
Voxel-based morphometry of hippocampal volume shows significantly reduced hippocampal volume in BDNF-met carriers[29]



Pezawas L, Verchinski BA, Mattay VS, et al. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci.* 2004;24:10099-10102. Reprinted with permission, copyright 2004.

BDNF=brain-derived neurotrophic factor; met=methionine.

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associated with susceptibility to anxiety,[44] depression,[17] and bipolar disorder,[45] but various data are contradictory.[16,17,46] Trait depression may contribute to the susceptibility of met carriers to hippocampal atrophy,[47] consistent with the hypothesis that BDNF plays a key role in activity-dependent networks that are altered in depression.[19]

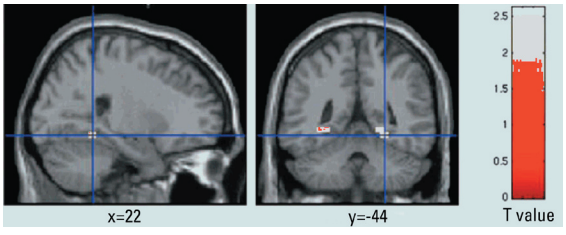
Furthermore, chronic stress leads to hippocampal cell loss and to down-regulation of BDNF.[14] Indeed, in animal models,[48,49] hippocampal BNDF may be altered by variations in maternal care, stress, environmental enrichment, exercise, and diet. Once again, some work is contradictory, with early trauma leading to increased hippocampal BDNF,[50] perhaps consistent with a more complex view of the role of BDNF signaling in psychopathology.[19]

BDNF transcription is controlled by different promotors in different brain regions. Each is regulated by different genetic and environmental factors.[51] Additional work is needed to delineate fully how BDNF gene-environment interactions ultimately impact on psychological function and dysfunction.[52]

Evolutionary Approaches

Gene variants may be useful in particular circumstances. Nevertheless, it is unclear why the BDNF-met missense mutation has persisted, given its association with impairment in temporal lobe-mediated cognitive performance, such as episodic memory. The existence of some data indicating a protective effect of the met allele on psychiatric disorder[16,17] suggest that there may also be certain positive effects, speculatively in particular contexts (eg, under some circumstances, inefficient fear conditioning may be advantageous).

FIGURE 2.
Increased activation of the parahippocampal gyrus on fMRI during a memory task in BDNF-val subjects during retrieval[35]



Hariri AR, Goldberg TE, Mattay VS, et al. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J Neurosci.* 2003;23:6690-6694.

fMRI=functional magnetic resonance imaging; BDNF=brain-derived neurotrophic factor; val=valine.

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CLINICAL IMPLICATIONS

DSM-IV-TR *Diagnosis*

Just as monoaminergic hypotheses of psychopathology have failed to provide a biological basis for our nosological distinctions between psychiatric disorders, so it is unlikely that a neurotrophin hypothesis will be able to do so. Rather, mechanisms involved in neuronal survival and synaptic plasticity are likely to play a role in a broad range of different brain-mind functions and dysfunctions.[53,54]

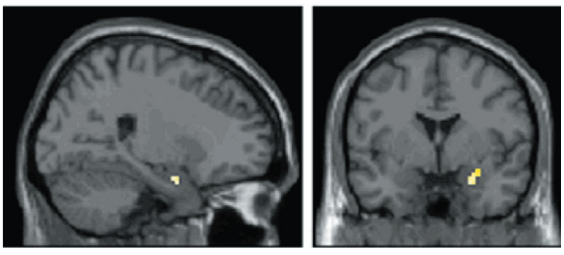
Assessment/Evaluation

A number of psychiatric disorders, including depression, are characterized by decreased levels of BDNF. However, sensitivity and specificity are insufficient to recommend the clinical use of this assay.[55] Similarly, the use of structural and functional brain imaging to assess the central correlations of BDNF gene variants remains solely within the realm of the research laboratory.

Pharmacotherapy/Psychotherapy

Knowledge about the role of neurotrophic factors in neuropsychiatric disorders has led to a number of innovative targets for therapeutic

FIGURE 3.
Increased activation of the amygdala on fMRI in subjects with the BDNF-met allele on exposure to unpleasant versus neutral images[36]



Montag C, Reuter M, Newport B, et al. The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: evidence from a genetic imaging study. *Neuroimage.* 2008;42:1554-1559. Reproduced with permission, copyright 2008.

fMRI=functional magnetic resonance imaging; BDNF=brain-derived neurotrophic factor; met=methionine.

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intervention.[56-58] For example, BDNF has been administered intrathecally in amyotrophic lateral sclerosis.[59] Small molecules that induce synthesis and release of neurotrophins, or that bind to and activate neurotrophin receptors, may have therapeutic relevance in a number of conditions.[57] Decreasing neurogenesis may be beneficial in some disorders, such as epilepsy.[60]

CONCLUSION

Whereas monoaminergic hypotheses often focus on the cybernetics or fine tuning of neuronal function, a neurotrophin hypothesis also addresses the differentiation and survival of particular neurocircuitry. As we continue to investigate the brain-mind and its embodiment in circuits and molecules, it seems certain that a focus on neurotrophins will therefore remain key. At this time, there remains considerable debate about the way in which BDNF contributes to disorders such as depression.[16-19] Nevertheless, there has also been a great deal of progress in a relatively short timespan, and agents for relevant therapeutic targets are under development. ***CNS***

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