BDNF and Alzheimer's Disease—What's the Connection?

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Why Is BDNF interesting?

The protein brain-derived neurotrophic factor (BDNF) has been the focus of intense interest in the Alzheimer's field for a number of years. BDNF belongs to the neurotrophin family of growth factors and affects the survival and function of neurons in the central nervous system, particularly in brain regions susceptible to degeneration in AD. BDNF improves survival of cholinergic neurons of the basal forebrain, as well as neurons in the hippocampus and cortex. This discovery kindled hope in the early 1990s that Alzheimer's could be slowed or halted if brain levels of BDNF could be increased. The idea gained support with the observation that BDNF gene activity and protein levels are reduced in AD brains.

Further research on BDNF in the mid-90s revealed additional exciting functions of this molecule in the brain. Beyond promoting neuronal survival and resilience to injury, BDNF also has a powerful role in facilitating activity-dependent plasticity, which underlies the capacity for learning and memory. Brain regions where plasticity is particularly important include the hippocampus and cortex, critical centers for learning and memory. The hippocampus is a central component for encoding new information, and damage there severely impairs learning. Hippocampal function is compromised early on in the course of AD, and this is considered the principal cause of the memory problems that characterize this disease. The reduction of BDNF seen in AD could cripple the hippocampus in two ways: From a plasticity point of view, insufficient BDNF would weaken synaptic encoding strength or capacity, while from the neurotrophic angle, reduced BDNF makes hippocampal neurons more vulnerable to insult and degeneration.

BDNF is an unusual neurotrophic factor. Its widespread functions in the brain go beyond the traditional role of a growth factor to promote growth, survival., and maintenance of cells. Recently, a third role for BDNF has emerged, in that it appears to be an important factor in psychiatric conditions such as epilepsy, depression, obsessive compulsive disorder, and possibly bipolar disorder. While unlikely to be causally related to Alzheimer's, these mood disorders, particularly depression, often coexist with Alzheimer's and may have a common link through BDNF.

Below, we discuss evidence supporting a role for BDNF in learning and memory, followed by recent genetic data demonstrating a link between BDNF and AD.

BDNF in Learning and Memory

What we've learned from animal models

BDNF is produced by neurons, particularly in the hippocampus and cortex. Neuronal activity, i.e., during encoding of information, stimulates BDNF gene transcription, transport of BDNF mRNA into dendritic spines, and BDNF protein release into the synaptic cleft (Hartmann et al., 2001). BDNF can be transported into the dendrite and may also be synthesized locally in the spine. It has been speculated that one or both of these mechanisms may be able to target active synapses within dendrites. BDNF acts on neurons at both presynaptic and postsynaptic sites by binding to its tyrosine kinase receptor TrkB, and internalization of the BDNF-TrkB complex. Interestingly, internalization does not lead to termination of the BDNF signal., such as occurs for most other growth factor receptors. Rather, the internalized TrkB receptor remains phosphorylated and activated. It becomes a specialized compartment called a "signaling endosome," which seems to be critical for downstream signaling effects of BDNF on the cell body. (For an excellent review on BDNF regulation and plasticity, see Lu, 2003).

By enhancing synaptic transmission and neuronal excitability (Figurov et al., 1996; Griesbeck et al., 1996), BDNF modulates synaptic change, including hippocampal long-term potentiation (LTP), a neural mechanism associated with learning and adaptive behaviors in adult animals (Poo, 2001; Tyler et al., 2002). A critical role for BDNF/TrkB signaling in plasticity mechanisms is evidenced by in-vivo studies where BDNF/TrkB signaling has been impaired by genetic or immunopharmacological means. Mice deficient in BDNF/TrkB signaling have impaired learning and LTP and, importantly, restoring BDNF reverses both the electrophysiological and learning deficits (Levine et al., 1995; Korte et al., 1996; Patterson et al., 1996). In addition, BDNF-deficient mice show decreased synaptic innervation and reduced levels of synaptic vesicle proteins (Martinez et al., 1998; Pozzo-Miller et al., 1999), demonstrating that BDNF is important for normal synaptic signaling (Martinez et al., 1998).

What we've learned from human genetics

Recent genetic studies have established a decisive role for BDNF in human cognition. Polymorphisms in the DNA sequence of a gene can result in seemingly subtle differences in the final protein product, which nevertheless can profoundly change the functionality of the product protein. One polymorphism in the BDNF gene that does just that is caused by a single amino acid substitution in the coding region of the BDNF gene (val/met substitution at codon 66). This substitution derails trafficking of the BDNF protein within the cell such that it is no longer released in response to appropriate cellular cues. The effect of this is seen at the level of hippocampal function, as the polymorphism is associated with impaired memory and abnormal hippocampal activation. Remarkably, these cognitive decrements were revealed in a cohort of 641 cognitively intact adults aged 25-45 (Egan et al., 2003; see ARF related news story; Hariri et al., 2003). Having made it clear that deficiencies in BDNF function has serious cognitive consequences even in young people, these studies prompt the question of what the relationship is between abnormal BDNF and AD.

BDNF polymorphisms are risk factors for AD

Three different BDNF polymorphisms have been proposed as possible risk factors for AD based on genetic linkage studies. The val/met polymorphism (position 196, codon 66) described above conferred increased susceptibility to AD that appeared to be independent of ApoE genotype (Ventriglia et al., 2002). The single nucleotide polymorphism C270T has been associated with late-onset but not early-onset AD in a Japanese population (51 early onset; 119 late onset; 498 controls, Kunugi et al., 2001). Another study of the C-270T polymorphism in a German population (210 AD cases, 188 controls) found its frequency increased in AD, and risk appeared to be higher in AD patients lacking the ApoE4 allele (Riemenschneider et al., 2002). Except for the met-BDNF polymorphism, little is known about how the polymorphisms affect BDNF function. These questions are currently under study, and are likely to expand our understanding of the role of BDNF in AD, as well as in learning, memory, and cognitive function throughout life.

Can BDNF levels in the brain be increased?

Animal studies demonstrate that brain levels of BDNF are modified in response to certain types of stimulation that occur normally in our daily lives. Remarkably, two potent stimuli that rapidly increase BDNF levels in the hippocampus are exercise and learning. In rodents, voluntary daily wheel running consistently increases BDNF mRNA and protein levels in the hippocampus and other brain regions, including parts of the cortex (for review on exercise and BDNF, see Cotman and Berchtold, 2002; also see ARF related news story). In addition, learning itself increases brain BDNF levels, particularly in the hippocampus. Interestingly, in humans, regular exercise is associated with benefits to brain health and cognitive function, which may in part be due to increased availability of BDNF. Indeed, physically active adults not only have a lower risk of cognitive impairment, but also a lower risk of depression and of developing AD or dementia of any type (Friedland et al., 2001; Laurin et al., 2001). Furthermore, exercise improves depression not only in normal adults, but also in people with moderate to severe AD, demonstrating that exercise can be an effective intervention when the course of neurodegeneration/neuropathology has already progressed. Just this week, JAMA published results of a randomized intervention trial of 153 AD patients, in which exercise training (and caregiver education) improved physical health and depression (Teri et al., 2003). In addition, there is evidence that mental activity/learning may also be somewhat protective against AD. An association between BDNF and these positive effects of exercise (and learning) on depression and dementia has not yet been definitely established; however, BDNF may serve as a common molecular mechanism. Increasing BDNF availability in the brain (stimulated, for example, by exercise or learning) is rapidly gaining strength as an important approach to improving cognitive function throughout life and offsetting depression and dementia. We believe that future studies will find BDNF to be a critical molecule in AD.

Let's discuss these questions (and more)

- What molecular pathways underlie BDNF regulation?
- What experimental models exist to study this? What new models should be created?
- How much exercise is necessary to keep BDNF levels elevated?
- Can exercise really stem the disease? How powerful an effect does it have?
- When would one have to start regulating BDNF levels to affect the course of AD? Would it work only prior to overt AD in mild cases, or also when the disease has progressed?
- How do diet (e.g., blueberries) or environmental factors (e.g., stress) affect BDNF levels?
- Do estrogen and androgens affect BDNF levels?
- Are there other types of environmental enrichment that increase BDNF?
- Can drugs be developed to boost BDNF levels?
- Could a BDNF therapeutic be nasally delivered?
- Why does BDNF expression diminish with age?
- How does BDNF function overlap with that of other growth factors implicated in AD, such as NGF or GDNF?
- Can BDNF ever act like a proinflammatory cytokine?

In-text references and further reading

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