

BRAIN-DERIVED NEUROTROPHIC FACTOR, NEURONAL REPAIR AND MENTAL HEALTH

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Brain Derived Neurotrophic Factor (BDNF) is initially synthesized as a 247 amino acid pre-proBDNF which is cleaved to form a 228 a.a. pro-BDNF and finally 119 a.a. mature BDNF (14 kDa). BDNF is expressed in fibroblasts, astrocytes, neurons, megakaryocytes, Schwann cells, and smooth muscle cells where, acting via its tyrosine kinase receptor TrkB, it is involved in neuronal differentiation and maturation, synapse formation, neuroprotection and neuronal repair.

Several neurological / psychiatric diseases have been associated with abnormalities of BDNF expression, notably depression, Alzheimer's disease / dementia and learning deficits associated with pre-natal alcohol exposure and early life stress.

In animal models, antidepressant drugs increase expression of brain BDNF and it has been proposed that stress-induced neuronal damage is the aetiological factor in depression, and that antidepressants act by facilitating neuronal repair. Adult depressed patients have been shown to have serum BDNF concentration only 70% of those of healthy controls and in depressed patients, antidepressant therapy increases serum BDNF by 36%.

Alzheimer's disease has also been associated with decreased post-mortem brain BDNF, but studies of serum BDNF in patients with Alzheimer's disease are inconclusive. We are currently investigating the possibility of using antidepressants to treat non-depressed patients with early Alzheimer's disease to investigate potential effects on disease progression.

In children, exposure to alcohol in utero and early life stress are associated with long-term deficits in learning and memory. Using mice, we have shown that prenatal alcohol exposure and early life stress in mice both resulted in deficits of learning and memory at 2-3 months of age, but that there was elevated brain BDNF, suggesting a compensatory increase in response to earlier neuronal insult. Importantly pharmacological interference with the brain renin-angiotensin in these animal models further elevated BDNF expression and also reversed some of the learning deficit.

Collectively, these findings suggest that some currently available antidepressants and antihypertensives are able to increase brain BDNF function resulting in the alleviation of some psychiatric / neurological disorders in adults and children and that the possibility exists that targeted BDNF or other drug delivery may be of value in the treatment of traumatic brain injury.