

## BDNF Signaling Ameliorates Neurodegenerative Disorders Trevor Archer

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Brain-derived neurotrophic factor (BDNF) is associated with neuroplasticity changes promoting health and well-being whereas these influences may be opposed by pro-inflammatory cytokines, key factors in neurodegenerative processes [1]. For example, BDNF-enhancing interventions, such as acute, intense physical exercise [2,3], increase hippocampal and other brain regional integrity [4] thereby preventing cell death and instead supporting neuronal proliferation and maturation with enhanced repair, growth and function of neurons in neurodegenerative disorders [5,6]. Sampaio, *et al.* [7], in a review of the therapeutic applications of neurotrophic factors, particularly BDNF, postulate that they are essential for survival, development and maintenance of neurons of necessity for impeding neurodegenerative progress in Alzheimer's disease (AD) and Parkinson's disease (PD). In this regard, Parkinsonian symptoms may be exacerbated through depressive symptoms [8-10]; depression in PD is associated with reduced BDNF [11]. Under conditions of repetitive stress, cognitive decline is related to reduced BDNF a dysregulated hypothalamic-pituitary-adrenal axis and DNA-hypomethylation [12]. Similarly, Individuals presenting schizophrenia spectrum disorders demonstrate defined patterns of elevated overall mortality, metabolic abnormalities, and cognitive-functioning deterioration that is observed normally later in the life-cycle among healthy populations [13]. Disturbance of the BDNF gene, e.g. Val66Met single nucleotide polymorphism, exacerbate AD symptoms and biomarkers and other brain disorders [14]. Thus, among a middle-aged cohort presenting risk-for-AD, it was observed that the carriage of the *BDNF* Met allele was related to a steeper decline in the performance of episodic memory and executive function and this deterioration was exacerbated by a greater burden of beta-amyloid (*ibid*). Also, decreased levels of BDNF have been detected in AD patients in comparison with healthy controls [15].

Metabolic syndrome, implicated in AD, Huntington's disease (HD) and other neurodegenerative disorders, is affected by the status of BDNF, its prophylactic or therapeutic uses, BDNF gene therapy and BDNF administration [16]. Both in human HD patients and animal models of HD, BDNF gene transcription factors are reduced [17-19], implying the necessity of the neurotrophic factor for therapies against HD [20].

Mesenchymal stem/stromal cells and BDNF treatment reduced striatal atrophy in the YAC128 mouse model of HD, promoting neurogenesis-like activity and augmenting lifespan [21]. Furthermore, BDNF is a major factor deciding the integrity of the hippocampal formation and cortico-striatal pathway both of which are compromised in HD [22]. Amyotrophic lateral sclerosis (ALS) presents an ethnically heterogeneous motor neuron disorder arising from the selective loss of motor neurons in the brain and CNS [23]. Links between ALS-related metabolic changes and neurodegeneration by examination of ALS-causing mutations interfere with the peripheral and brain-specific expression and signaling of the metabolic master regulator PGC-1A which when deficient alters the BDNF genes [24]. In a large Chinese cohort, the relationships between ALS and BDNF polymorphisms, G192A and C270T, were established [25]. In this context, B cell leukemia 11b (*Bcl11b*), a zinc finger protein transcription factor that regulates BDNF, has been targeted as a novel therapeutic approach for treatment of several neurodegenerative diseases including AD, HD, ALS and NeuroHIV [26,27]. Fingolimod (FTY720), a compound developed for treatment of multiple sclerosis, gave protection against 6-hydroxydopamine-induced cytotoxicity and apoptosis in SH-SY5Y cells linked with activation of AKT and ERK1/2 pro-survival pathways and an increase in brain derived neurotrophic factor expression *in vitro* and *in vivo* [28]. There is accumulating evidence also that amongst its other effects, BDNF renders an anti-apoptosis, anti-oxidation and p62/sequestosome-1-mediated suppression of heightened autophagy [29]. Among healthy adults, a meta-analysis showed greater

duration of exercise was associated with greater increases in BDNF in plasma than in serum and among male participants rather than female [30]. Further, neurotrophin-supplementation induced the activation of compensatory and regenerative processes in an Alzheimer-like animal model, the senescence-accelerated OXYS rats [31]. Alcohol-administration chronically was shown to induce both behavioral disturbance and neurodegenerative markers, including elevated lipid peroxidation, mitochondrial oxidized glutathione, interleukin-1 beta, tumor necrosis factor-alpha and Bax levels in isolated hippocampal tissues concomitant with reduced glutathione, superoxide dismutase, glutathione peroxidase and glutathione reductase levels as well as reductions in CREB, BDNF and Bcl-2 while curcumin induced the re-activation of the CREB-BDNF signaling pathway [32]. Additionally, it was found too, in mice, that four weeks of combined treadmill and running wheel exercise induced: (i) a marked augmentation of the synaptic load in the dentate gyrus, (ii) promoted alterations in astrocytic morphology, and (iii) altered orientation of astrocytic projections towards dentate granule cells which were all changes associated elevated TrkB receptor levels in astrocytes [33]. In summary, it is increasingly evident that in the search for prophylactic and therapeutic strategies for treating the above neurodegenerative conditions the role of physical exercise and other factors, e.g. exercise plus Milmed, that enhance BDNF signaling must receive greater focus [34,35].

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