**BDNF: The link between beta-amyloid and memory loss**

Margaret Fahnestock, PhD

Department of Psychiatry and Behavioural Neurosciences

McMaster University

1280 Main Street West

Hamilton, ON, L8S 4K1, Canada

Tel. 1-905-525-9140, ext 23344

Fax 1-905-522-8804

Email: [fahnest@mcmaster.ca](mailto:fahnest@mcmaster.ca)

**Summary:**

Brain-derived neurotrophic factor (BDNF) is a critical molecule for learning and memory. Brain BDNF levels correlate with cognitive status. BDNF is down-regulated in Alzheimer’s disease (AD), in age-related cognitive impairment and in a variety of other neurodegenerative and psychiatric disorders exhibiting cognitive deficits. BDNF is down-regulated in the AD brain by soluble, aggregated amyloid-beta, acting via a pathway involving the transcription factor CREB, which activates BDNF transcript IV. The complete pathway by which BDNF is down-regulated is still unclear, and the diagnostic and therapeutic use of BDNF in neurodegenerative disease has not yet been exploited.

**Keywords**: Alzheimer’s disease, amyloid-beta, oligomers, tau, neurotrophin, brain-derived neurotrophic factor, mRNA, exon, CREB

**Abbreviations:**

Aβ, amyloid-beta

AD, Alzheimer’s disease

APP, amyloid precursor protein

BDNF, brain-derived neurotrophic factor

CREB, cyclic-AMP response element binding protein

ELISA, enzyme-linked immunosorbent assay

FAD, familial Alzheimer’s disease

MCI, mild cognitive impairment

**Pathology of Alzheimer’s disease.** Alzheimer’s disease (AD) is the predominant form of dementia in the elderly. AD is characterized behaviourally by memory loss, loss of cognitive function and personality changes. Pathological features of AD include extracellular deposition of aggregated amyloid-beta (Aβ) in the form of senile or amyloid plaques, hyperphosphorylated, aggregated tau protein which accumulates intracellularly as neurofibrillary tangles, neuritic dystrophy, synaptic loss, and neurodegeneration[1,2]. The AD brain undergoes progressive dysfunction and degeneration of synapses, and later neurons, in selective areas of the brain [3,4]. This disrupts communications between brain areas including hippocampus, neocortex, entorhinal cortex and basal forebrain [5], resulting in the behavioral impairments characteristic of AD. The degree of synaptic loss in these areas correlates strongly with the severity of dementia [6].

Human genetic and transgenic mouse data support the theory that overproduction of Aβ is the precipitating insult in AD, at the top of a cascade with neurofibrillary tangle formation a downstream contributor [7]. Aβis formed by sequential action of β- and γ-secretases on the amyloid precursor protein (APP). Mutations in the *APP* gene or in the protease component of the γ-secretase complex, presenilin 1 and 2 (*PS-1*and *PS-2*) genes cause early-onset, familial AD (FAD). Mutations in the *SorL1*gene are associated with late-onset AD [8,9]. All identified pathogenetic mutations in these FAD genes lead to overproduction of Aβ or its most fibrillogenic form, Aβ42 [10].

Only a small fraction of AD cases are familial, whereas the remainder are termed sporadic and are also characterized by accumulation of aggregated Aβ. Age is the strongest risk factor for late-onset AD, followed by the presence of the ApoE4 allele [11]. Other environmental risk factors include stroke, head trauma, cardiovascular disease/metabolic syndrome, and chronic stress, whereas ameliorating factors may include exercise, social and cognitive stimulation, and a Mediterranean or antioxidant-rich diet [12,13]. AD risk factors favour Aβ accumulation through mechanisms which are still unclear. They may promote increased Aβ synthesis or deficits in pathways responsible for clearance of Aβ which can lead to pathological accumulation of this peptide in the absence of known FAD mutations [14,15].

The γ-secretase cleavage site in APP is variable, and therefore Aβ can be found as a peptide of varying lengths [16]. The most common form of Aβ is a 40-amino-acid-long peptide (Aβ40), although the forty-two-amino-acid form (Aβ42) is dramatically increased in AD. Aβ42 aggregates readily to form dimers, trimers, oligomers of various sizes, and protofibrils. These aggregates may initially form intracellularly [17,18], but they eventually accumulate and precipitate extracellularly as amyloid plaques. Aggregates of Aβ are neurotoxic *in vitro* [19,20], cause synaptic degeneration [21,22], and interfere with long term potentiation, a form of memory consolidation [23,24]. However, the mechanism of Aβ toxicity *in vivo* remains unclear.

**Amyoid cascade and tau.** Amyloid plaques do not correlate well with neurodegeneration or clinical dementia [25]. In part, this dilemma may be explained by the observation that distinct aggregation states of Aβ display differential toxic properties. Soluble, aggregated Aβ is now thought to be the toxic species and is implicated as the cause of memory loss in transgenic mice [7,26,27]. Soluble Aβ aggregates exhibit a broad range of sizes [28,29], and specifically which soluble oligomeric aggregates of Aβ, from dimers to high-molecular-weight oligomers and protofibrils, could be the most toxic forms, and what is the downstream mechanism of their neurotoxicity, are still under debate [30-33]. Some popular theories of downstream mechanisms include, but are not limited to, increased reactive oxygen species, mitochondrial dysfunction, disruption of calcium homeostasis and excitotoxicity, autophagy, inflammation, or loss of trophic support [34-40**] (Figure 1)**. It is possible that different species of aggregated Aβ could induce different pathways of neurotoxicity. Increasingly, research is focusing on these soluble aggregates, whereas Aβ deposition as insoluble plaques may actually be protective [41].

Neurofibrillary tangles correlate better with neurodegeneration and dementia than amyloid plaques [42]. Soluble, aggregated Aβ42 is thought to be the primary insult leading to degeneration and may do so, at least in part, via its downstream effect of inducing tau hyperphosphorylation and neurofibrillary tangle formation [26,43]. Aβ induces neurofibrillary tangle formation in animal models [44-49] and in neuroblastoma cells in culture [50]. Furthermore, tau knockout blocks Aβ-induced cognitive impairment in a transgenic AD mouse model [51], and Aβ-induced neurodegeneration is reversed in primary neuronal cultures from tau knockout mice [52]. Tau hyperphosphorylation results in a reduced ability of tau to promote microtubule polymerization [53] and increases aggregation of tau into toxic, soluble oligomers and insoluble filaments and tau inclusions [54]. In addition to altered tau phosphorylation profiles, AD also exhibits changes in tau isoform ratios and a truncated form of the tau protein [55]. Tau truncation results in increased tau hyperphosphorylation, neurofibrillary tangle formation and behavioral impairment in transgenic animals [56].

A crucial pathway for learning and memory and AD is the transcription factor cyclic AMP response element binding protein (CREB) [57]. CREB is regulated by phosphorylation and by transcriptional coactivators which regulate its binding to promoter sites upstream of genes involved in learning and memory (**Figure 2**). Phosphorylated CREB is reduced in AD brain [58] and *in vitro* in neurons treated with Aβ [59,60]. In transgenic AD mice, Aβ decreases the CREB coactivator CRTC1 which is regulated by calcium [61], supporting the model that disruption of calcium homeostasis is a major contributor to Aβ toxicity. Restoring CREB activity in Alzheimer transgenic mice by expression of CREB-binding protein (CBP) rescues learning and memory deficits [62]. The molecule implicated as a major target important in learning and memory and downstream of CREB in these studies is brain-derived neurotrophic factor (BDNF).

**Brain-derived neurotrophic factor as a downstream mediator of Aβ toxicity.** Recent evidence suggests Aβ-associated neurotoxicity may be a consequence of BDNF deficiency. BDNF is widely distributed in the brain but is found in particularly high amounts in regions of the brain affected by Alzheimer’s disease [63]. BDNF maintains survival and function of the specific neurons and their connections that are compromised in AD [64-66]; it regulates growth and complexity of dendrites, neurogenesis, spine maturation and synaptic density, synaptic transmission and plasticity, neuronal excitability, and learning and memory [67-74], which are decreased in AD **(Figure 3)**. A polymorphism in the prodomain of proBDNF which interferes with proBDNF processing and secretion of mature BDNF has been implicated in episodic memory deficits [75,76]. Despite the clear biological effects of this polymorphism, most genetic studies of the BDNF gene in AD have not found any association [77]. Recent studies, however, suggest the BDNF Val66Met polymorphism may interact with age or gender to increase vulnerability to AD [77,78].

In AD, BDNF mRNA and protein are decreased by half in entorhinal cortex, frontal, temporal and parietal cortex and hippocampus [79-84], areas of the brain associated with learning and memory and severely affected in AD. Heterozygous BDNF knockout mice with similarly decreased levels of BDNF exhibit defects in long-term potentiation and cognitive deficits which are rescued by BDNF administration; exogenous BDNF increases synaptic density and reverses cognitive deficits in animal models of AD and dementia [85-89]. Importantly, cortical BDNF protein levels are significantly decreased in preclinical (MCI, mild cognitive impairment) and early stages of AD, suggesting BDNF loss is an early event, and this reduction correlates with clinical neuropsychological scores [83]. Many animal studies have demonstrated that diet, physical activity, and environmental enrichment increase brain BDNF levels and cognitive performance [13,90]. Thus, ample evidence now supports the role of reduced BDNF in the cognitive impairments and memory deficits typical of MCI and AD, and the beneficial effects of increasing BDNF levels on cognitive performance.

The human BDNF gene is complex. It consists of 10 unique 5’-untranslated exons that are individually spliced to a common 3’ exon (exon IX)encoding the preproBDNF protein (**Fig. 4**) [91]. Alternative splicing results in at least 17 different transcripts governed by 9 promoters. These transcripts are differentially regulated during development and in a tissue-, subcellular compartment- and environment-specific manner [92-96], providing exquisitely sensitive and tissue-specific control over BDNF levels. Thus, although all transcripts contain exon IX and therefore encode the BDNF precursor protein proBDNF, differential transcript expression can result in different BDNF levels in distinct brain areas. Our studies have shown that transcript-specific changes in BDNF expression occur in AD. Four of the transcripts expressed in human cortex are down-regulated in AD, specifically transcripts I, II, IV (formerly transcript III) and VI (formerly transcript IV, then V) [97]. These decreases in BDNF transcripts result in significant drops in both proBDNF and BDNF protein levels; BDNF protein is decreased to one-half of normal levels in MCI and AD [81,83].

The pathway responsible for down-regulation of BDNF in AD has been partially determined. Soluble, oligomeric Aβ, but not the fibrillar Aβ found in plaques, down-regulates BDNF *in vitro* [60]. These results add support to a growing literature implicating soluble, oligomeric Aβ in AD neurotoxicity. In transgenic mouse models of AD, increased amounts of soluble, high-molecular-weight, aggregated Aβ, possibly protofibrils, correlate with low BDNF levels [98]. Oligomeric, aggregated Aβ may disrupt calcium influx, reducing CRTC1 activation of CREB [61]; reduced CREB phosphorylation reduces BDNF transcript IV expression [60,99]. Transcript IV, one of the transcripts down-regulated in AD, is the most abundantly expressed BDNF transcript in human cortical tissue, accounting for approximately half of the BDNF mRNA present in this region (**Figure 4**). Therefore, this pathway represents the major contributor to loss of BDNF in AD.

Human BDNF transcripts I and IV are decreased in AD and are increased by activity [97,99,100]. Human transcript IV, but not transcript I, is up-regulated by phosphorylated CREB [99]. Interestingly, *in vitro* and in transgenic AD mouse models, Aβ down-regulates BDNF largely by affecting transcript IV [60,98] but does not decreasetranscript I, suggesting that another pathway, perhaps affecting different transcription factors or epigenetic modifications, is involved in transcript I regulation in AD brain. Our recent analyses of post mortem cortical tissue from subjects with tauopathies (dementias with tau but not amyloid pathology) show that BDNF is down-regulated in Pick’s disease and corticobasal degeneration, and that transcript IV is the major target [101]. This suggests that pathological tau is downstream of Aβ but upstream of BDNF in the toxic amyloid cascade (**Figure 1**). Thus, the mechanisms by which Aβ or its cascade might cause cellular and synaptic loss and learning and memory deficits have been partially, but not fully, elucidated.

**BDNF as an indicator of cognitive status.** Decreased BDNF is characteristic of a variety of neurodegenerative and psychiatric disorders in addition to AD, including Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, Pick’s disease, schizophrenia, depression, and others [102-105]. Although the constellation of affected transcripts may differ among different disorders, it is unlikely that particular transcripts are specific to different diseases. For example, transcripts I, II, IV and VI are decreased in AD cortex (97), while transcripts II, IV and VI are also decreased in cortex of subjects with schizophrenia [106]. Whether BDNF transcript IV-specific changes reported for AD, schizophrenia and tauopathies also occur in other neurodegenerative disorders has not been investigated. Rodent models of Parkinson’s and Huntington’s diseases exhibit transcript-specific changes in BDNF expression which suggest that transcript IV regulation may not be specific for Alzheimer’s disease [107,108]. Further investigation into the specific pathways mediating BDNF down-regulation in each disease is warranted. What is clear is that decreased BDNF in various regions of the CNS is associated with the cognitive symptoms of these disorders.

In normal brain, BDNF mRNA levels peak during young adulthood and remain constant from adulthood through aging in human cortex and hippocampus [109,110]. However, BDNF levels decrease with age in cognitively impaired human parietal cortex [83], in the aged primate brain [111] and in the aged, cognitively impaired canine brain [13]. Loss of BDNF is an early event in neurodegeneration. In a transgenic mouse model of AD, BDNF levels decline along with object recognition memory long before spatial memory deficits or plaque deposition become apparent [112]. Similarly, in humans, decreased BDNF is already evident in MCI. MCI is considered a predementia stage of AD [113], as approximately 8% per year of MCI patients convert to AD [114]. This patient group consists of those who will convert as well as those with age-related cognitive decline who will not convert. Nevertheless, BDNF protein is decreased by over 30% in cortical tissue from this group compared to age-matched, cognitively normal controls [83]. Importantly, the amount of BDNF decrease in MCI and AD correlates with the degree of cognitive decline. Thus, BDNF levels may serve as an indicator of cognitive status in neurological disorders. An assay for BDNF levels could be a useful diagnostic tool, in combination with other behavioral and biological assays, for tracking cognitive decline in aging and in neurodegenerative and psychiatric conditions.

BDNF mRNA and protein levels are not currently directly measurable in brain except postmortem. Several groups have used commercial enzyme-linked immunosorbent assays (ELISAs) to measure BDNF protein levels in serum of MCI and AD subjects, but the results are conflicting. BDNF protein levels in most studies are decreased in serum of AD subjects compared to controls, consistent with results in the brain [115-119]. However, two studies reported elevated BDNF protein in MCI and/or AD serum [120,121], and one study reported no difference between controls and AD [122]. There are many potential reasons for these discrepancies, including differences in sample collection, BDNF antibodies and assay methods used. BDNF is subject to substantial inter-subject and diurnal variations, so repeated measures and time of sample collection are important. Evidence suggests that BDNF protein may cross the blood-brain barrier [123-125]. However, the source of the BDNF protein in whole serum is not entirely clear, since BDNF is also synthesized in vascular endothelial cells [126], BDNF protein is stored and released by platelets [127], and BDNF may be taken up by binding proteins in blood [128]. Currently available antibodies are subject to substantial non-specific cross-reactivity with other blood proteins, further complicating the analysis. Nevertheless, in some studies, BDNF protein levels in serum and cerebrospinal fluid as measured by ELISA are correlated with cognitive status in both age-related cognitive decline and in AD [115-119,129, 130].

Another potential approach is the measurement of BDNF mRNA from peripheral blood leukocytes, which has been demonstrated to distinguish changes in BDNF levels in depressed patients from levels after antidepressant treatment [131]. We have shown that this approach may also be useful for distinguishing AD from control subjects [132]. There is significant evidence in rodent models that BDNF mRNA or protein levels in blood can reflect those in brain [133,134]. This suggests that a reliable assay for BDNF in blood could be a valuable diagnostic tool, along with other measures, for monitoring changes in cognitive impairment with disease or therapy.

**BDNF as a potential therapeutic.** Increasing BDNF levels in the brain is a focus of interest as a means of preventing or treating cognitive impairment due to neurodegenerative disease. Gene therapy by viral administration of BDNF or CREB activators and implantation of BDNF-secreting stem cells have been successful in reversing learning and memory deficits in animal models of AD [61,62,86,88]. Although the results in rodent models have been encouraging, safety and efficacy must be extensively tested in higher animals including non-human primates [88] prior to initiating clinical trials. Lentivirus is the vector of choice at the present time, as it infects postmitotic cells and has a longer expression profile than some other popular viral vectors. Lentivirus expressing BDNF rescued impaired visuospatial learning in an aged monkey model of cognitive impairment one month after injection into entorhinal cortex [88]. Long-term expression was not tested. NGF expression for up to one year with no adverse effects has been demonstrated for lentivirus implanted into monkey basal forebrain [135], suggesting that safe, long-term expression of BDNF is possible. Another problem which must be overcome is limited distribution of the virus in the brain. This may be solved by judicious choice of injection site. Viral injection into the entorhinal cortex provides BDNF to entorhinal cortex as well as to hippocampus via BDNF anterograde transport [88]. BDNF in entorhinal cortex may also provide support to widespread regions of the brain, including basal forebrain cholinergic neurons [136,137], although distribution of BDNF to sites other than hippocampus was not examined in the viral gene therapy studies. The advantage of BDNF-secreting stem cells is that they have the potential to migrate to areas suffering neurodegeneration in AD, PD and HD [138], but cells suitable for implantation in humans and expressing BDNF long-term must be developed and tested.

BDNF protein administered peripherally does not readily enter the brain. Therefore, delivery of exogenous BDNF protein in many studies has been by direct intraparenchymal administration. This method suffers from an undesirable level of invasiveness and lack of BDNF diffusion within the brain tissue. A less invasive approach, peripheral administration of BDNF linked to a monoclonal antibody to the transferrin receptor which crosses the blood-brain barrier, has been shown to ameliorate neurodegeneration in a stroke model (139-142). A similar BDNF fusion protein with an antibody to the insulin receptor was shown to cross the blood-brain barrier and elevate BDNF levels in a non-human primate, although efficacy in a monkey disease model remains to be tested. Nanoparticles may, in future, provide another method of crossing the blood-brain barrier, although the technology is still young [143].

BDNF levels are very tightly regulated in the brain; BDNF is released by activity in a synapse-specific manner, and too much BDNF can have as severe adverse effects as too little [74,144]. Delivery of exogenous BDNF may not provide appropriate levels of the protein or the fine spatial and temporal control of expression present in the normal brain. Therefore, methods of elevating endogenous BDNF, which is more likely to be expressed and controlled appropriately, also constitute an important line of research. Several BDNF-enhancing molecules are under investigation, including the phosphodiesterase and CREB activator rolipram, the kinase inhibitor CEP-1347, and the BDNF receptor (TrkB) agonists 7,8-dihydroxyflavone and LM22A [134,145-148]. Lifestyle modifications including exercise, enrichment and diet [13,90] hold promise for significantly elevating endogenous brain BDNF levels. Many studies in rodents have demonstrated that physical activity promotes neurogenesis and synaptic plasticity [149,150], modulates transcript-specific BDNF mRNA and protein levels [151-153], and improves cognitive function [90]. Rodents housed in enriched environments display increased hippocampal BDNF mRNA [154] and CREB immunoreactivity [155]. Similarly, a flavonoid-rich diet improves spatial working memory in aged rats by activating CREB and BDNF in the hippocampus [156]. In a recent study, we showed that the combined treatment of diet and enrichment, but not either intervention alone, significantly increases BDNF mRNA in the aged, cognitively impaired canine brain [13]. In humans, findings with regard to the effect of diet on cognition are less conclusive [157]. However, there is significant literature in humans demonstrating that enrichment, which includes exercise, social engagement and intellectual stimulation, reduces the risk of cognitive decline [158,159]. To date, there have been no long-term randomized control trials studying the effects of exercise or enrichment on cognitive decline in MCI or AD patients. Performance of long-term trials on MCI subjects, along with optimization of duration, intensity and interval of exercise required for prevention, is a pressing need.

There is also significant evidence that acute, aerobic exercise temporarily elevates BDNF levels in the periphery [160]. Two studies indicate that this elevation in peripheral BDNF reflects increased expression in human brain [124,125]. Thus it is imperative that reliable methods for assaying BDNF in human peripheral blood are developed. This would enable further research on how exercise and other changes in lifestyle modulate BDNF levels and cognitive function in the elderly and would lead to advancement of guidelines for prevention of cognitive decline.

**Conclusion:**

Recent evidence supports soluble, aggregated Aβ as a precipitating insult in Alzheimer’s disease, with abnormally phosphorylated, aggregated tau downstream. The pathways and mechanisms by which Aβ and tau might cause synaptic and neuronal degeneration resulting in impaired cognition and memory are unclear. Different sizes and conformations of soluble amyloid aggregates may induce deficits via multiple pathways. One important downstream mediator of these pathways is BDNF. BDNF maintains survival and function of AD-vulnerable neurons and the connections between them. BDNF expression is severely decreased in hippocampus, entorhinal cortex, neocortex, and basal forebrain in AD. This loss occurs early in AD and is correlated with cognitive impairment. Similar decreases in BDNF cause learning and memory deficits in animal models which are rescued by exogenous BDNF, supporting the theory that degeneration and memory loss are due to insufficient amounts of this trophic factor. One of the pathways by which soluble, oligomeric Aβ down-regulates BDNF is via decreased CREB phosphorylation and reduced BDNF transcript IV expression. How tau contributes to that pathway, and the mechanisms governing down-regulation of BDNF transcripts I, II and VI in AD, remain to be determined. Decreased BDNF mediates the effects of Aβ on synaptic degeneration and cognitive deficits in AD and may serve as a marker for cognitive decline in AD, age-related cognitive impairment and other neurological conditions exhibiting memory deficits. Methods of raising BDNF levels in the brain by delivery of exogenous BDNF or induction of endogenous BDNF hold promise for combatting cognitive impairment. However, much work needs to be done to demonstrate the specificity and accuracy of BDNF as a biomarker for cognitive decline and to determine the best methods for increasing brain BDNF levels as a therapeutic for MCI and AD.

**Future perspective:**

It is now clear that decreased BDNF mediates many of the toxic effects of Aβ onsynaptic loss and learning and memory deficits in Alzheimer’s disease. The pathway(s) by which Aβ decreases BDNF expression include transcriptional down-regulation via calcium influx, decreased CREB phosphorylation and reduced BDNF transcript IV expression. The pathways by which BDNF transcripts I, II and VI are down-regulated in AD have not been elucidated and may provide additional targets for therapy in future. Aggregated, hyperphosphorylated tau may also contribute to Aβ-induced BDNF down-regulation. However, tau cannot account for all the effects of Aβ on BDNF expression, since tauopathies do not exhibit the same pattern of transcript regulation as AD. Therefore, some of the effects of AD pathology on BDNF expression are liable to be mediated by Aβ acting via tau, while others are likely mediated by Aβ and tau pathways independent of each other. Sorting out which downstream effects on multiple endpoints are mediated by Aβ, tau or both is crucial for designing appropriate interventions. Basic research to elucidate these pathways and a better understanding of how AD pathology reduces BDNF and results in cognitive impairment are essential to interrupting this cascade, informing drug discovery and rescuing synaptic and neuronal degeneration and dysfunction.

BDNF serum protein levels are decreased in Alzheimer’s disease, age-related cognitive impairment and in other neurological and psychiatric disorders exhibiting cognitive impairment. The reagents for quantifying BDNF protein levels are imperfect and the source of BDNF protein in the blood cannot yet be pinpointed with certainty. The use of peripheral blood leukocyte mRNA to monitor BDNF levels shows promise. In view of the many neurodegenerative and psychiatric disorders characterized by changes in BDNF levels, both blood and brain markers may be used to determine whether specific BDNF transcripts are specific for certain diseases. In future, improvement of reagents and methods for assaying BDNF in peripheral blood, as well as further validation of blood measures as a reflection of brain BDNF levels and cognitive function, is a priority. These advances will enable BDNF to be used as a diagnostic tool, in conjunction with psychological tests, imaging or other methods, for tracking changes in cognition associated with age, disease or treatment.

Current and future studies are focused on increasing BDNF levels in the brain as a means of preventing or treating cognitive impairment due to neurodegenerative disease, psychiatric disorders or injury. These efforts include viral administration of BDNF or CREB activators and implantation of BDNF-secreting stem cells. Results in rodent and non-human primate models have been encouraging, and following additional demonstrations of safety and efficacy in higher animal disease models, clinical trials will certainly proceed. Pharmacological modulators of endogenous BDNF expression are under investigation and should be tested in higher animal models. Lifestyle modifications including exercise, enrichment and diet also hold promise for significantly elevating endogenous brain BDNF levels. Reliable methods for assaying peripheral BDNF levels as a reflection of brain levels will promote further research into the design of enrichment programs for cognitively impaired subjects, long-term clinical trials and the development of evidence-based guidelines for lifestyle changes for the prevention of AD.

**Executive summary:**

* **Soluble, aggregated Aβ is now thought to be the initial insult in Alzheimer’s disease, but the pathways by which it causes synaptic loss and learning and memory deficits are unclear.**
* **BDNF is a key downstream mediator of Aβ toxicity.**
* **BDNF is down-regulated early in MCI and Alzheimer’s disease, BDNF levels are correlated with cognitive status, and administration of BDNF rescues learning and memory deficits in animal models of Alzheimer’s disease.**
* **Aβ decreases BDNF primarily by reducing phosphorylated CREB which regulates BDNF transcript IV. Pathological tau may also contribute to this pathway. Further research to elucidate these pathways will allow better understanding and identification of therapeutic targets.**
* **Brain or serum BDNF levels may be a useful indicator of cognitive status. Improvements in methods for assaying BDNF in peripheral blood would promote further studies and provide an endpoint, in conjunction with other methods, for monitoring therapeutic approaches. Correlation of peripheral and central BDNF levels is an important goal.**
* **Delivery of exogenous BDNF to the brain by viral vectors or stem cell implantation is promising. Long-term safety and efficacy of viral delivery in higher animal models of cognitive impairment should be demonstrated so that clinical trials may proceed. BDNF-secreting stem cells suitable for human implantation must be developed.**
* **Increasing endogenous BDNF levels by exercise or enrichment can ameliorate learning and memory deficits. Long-term randomized control trials in subjects with MCI are needed.**

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**Reference annotations**

\*Peng S, Wuu J, Mufson EJ, Fahnestock M: Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. *J. Neurochem.* 93, 1412-1421 (2005). **This paper demonstrates that BDNF levels are decreased in MCI and early AD.**

\*\*Garzon DJ, Fahnestock M: Oligomeric amyloid decreases basal levels of brain-derived neurotrophic factor (BDNF) mRNA via specific downregulation of BDNF transcripts IV and V in differentiated human neuroblastoma cells. *J. Neurosci.* 27(10), 2628-2635 (2007). **This paper demonstrates that soluble, aggregated Aβ, but not the fibrillar form found in plaques, decreases CREB phosphorylation and specific BDNF transcript levels.**

\*Nagahara AH, Merrill DA, Coppola G *et al:* Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nat. Med.* 15(3), 331-337 (2009). **This paper demonstrates the beneficial effects of exogenous BDNF administration on learning and memory deficits in AD.**

\*\*Blurton-Jones M, Kitazawa M, Martinez-Coria H *et al:* Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc. Natl. Acad. Sci. U. S. A.* 106(32), 13594-13599 (2009). **This paper demonstrates that the beneficial effects of stem cell implantation on synaptic density and learning and memory deficits in transgenic mouse models of AD are due to secretion of BDNF.**

\*\*Fahnestock M, Marchese M, Head E *et al:* BDNF increases with behavioral enrichment and an antioxidant diet in the aged dog. *Neurobiol. Aging.* May 4 (2010). [Epub ahead of print] **This paper demonstrates the beneficial effects on cognition of raising endogenous BDNF levels by simple changes in lifestyle. It is the first such study to use a higher mammal (dog) rather than a rodent model.**

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