Chapter 7

Brain Reserve Regulators in Alzheimer's Disease

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1. Introduction

Brain reserve refers to the ability of the brain to tolerate pathological changes such as those seen in AD before manifesting clinical signs and symptoms [1-3]. Neurotrophic factors (NTFs), most notably Brain Derived Neurotrophic Factor (BDNF) and its receptor Tyrosine kinase B (TrkB), regulate synaptic plasticity and functional efficiency in adulthood [4-6] and thus may influence brain reserve. BDNF/TrkB signaling affects memory formation and retention [7,8], determines neurite length [9,10], and governs regeneration upon neuronal injury [11,12] by modifying neuronal cytoskeleton. Abnormalities in the neuronal cytoskeleton are well documented in AD. However, how these abnormalities affect AD progression remains unclear. In *Drosophila*, neurodegeneration stems directly from mutations in alpha and beta subunits of the actin capping protein (CP), demonstrating that a mutation in a gene encoding an actin cytoskeleton regulator can lead to demise of neurons [13]. Further, a causative role for actin cytoskeleton abnormalities in neurotoxicity has been documented in a *Drosophila* tauopathy model [14].

Important evidence that cytoskeletal abnormalities are critically involved in the pathogenesis of neurodegeneration stems from the studies demonstrating the effect of apolipoprotein E isoform ε4 (ApoE ε4), the well-documented genetic risk factor for the most common form of AD, late-onset AD [15], on neuronal cytoskeleton. In the United States, the ApoE ε4 allele occurs in 60% of AD patients. ApoE ε4 inhibits neurite outgrowth in cultured neuronal cells [16] and correlates with the simplification of dendritic branching patterns in the brains of AD patients [17]. ApoE ε4 dose inversely correlates with dendritic spine density in dentate gyrus neurons of both AD and aged normal controls [18]. Overexpression and neuron-specific proteolytic cleavage of ApoE ε4 result in tau hyperphosphorylation in neurons of transgenic mice, suggesting a role of ApoE ε4 in cytoskeletal destabilization and the development of AD-related neuronal deficits [19,20]. Humanized ApoE ε4 knock-in homozygous transgenic mice

exhibit cognitive deficits before the onset of age-dependent neuropathology including AD-associated neurofibrillary tangles and neuritic plaques [21,22].

While the relationships between BDNF gene polymorphisms and AD are not yet fully understood [23-25], there is compelling evidence that epigenetic regulation connects BDNF/TrkB signaling with learning and memory. Exercise restored TrkB in ApoE ε4 mice to the level observed in ε3 mice and increased synaptophysin (a marker of synaptic function) in ε4 mice; hippocampal BDNF levels were similarly increased in both ε3 and ε4 mice after exercise [26]. Exposure to an enriched environment for three to four weeks also caused dramatic increase in BDNF mRNA in mouse hippocampus [27]. Understanding the regulation of BDNF/TrkB signaling in AD pathogenesis, particularly in individuals carrying ApoE ε4, could be of great clinical and public health importance because BDNF is inducible and may be one of the key molecules mediating the beneficial effect of certain lifestyle measures (environmental enrichment, increased aerobic physical activity, lower caloric intake) [28-30] on the risk of developing dementia.

2. Neuronal cytoskeleton regulator actin capping protein ß2 (Capzb2) and BDNF/TrkB signaling

As hyperphosphorylated tau gives rise to neurofibrillary tangles in AD, dystrophic neurites, marked by reduced length and poor branching, become apparent. In parallel, perisomatic proliferation of dendrites and sprouting of distal dystrophic neurites take place[31]. These morphological changes in neurons during AD progression indicate major cytoskeletal reorganization raising the possibility that microtubules and microfilaments may represent a target for pathobiological mechanisms underlying AD. The presence of growth cone-like structures on distal ends of dystrophic neurites suggests that regenerative response accompanies cytoskeleton degeneration in AD [31].

Changes in growth cone morphology, motility, and direction of growth are controlled by interactions between F-actin and microtubules and their associated proteins [32]. The growth cone morphology is characterized by lamellipodia, which are the veil-like extensions at the periphery, and filopodia, which are narrow, spiky extensions coming from the periphery of the growth cone. Interestingly, APP concentrates in lamellipodia where it is proposed to play a role in growth cone motility and neurite outgrowth [33]. Upon acute neuronal injury, the first critical steps that initiate regenerative response are microtubule polymerization and F-actin cytoskeleton rearrangement leading to the formation of a motile growth cone [34]. Actin cytoskeleton regulator CP (F-actin capping protein, CapZ) is an α/β heterodimer that binds the barbed end of F-actin thus blocking the access of actin monomers to the fast growing end. Both mammalian and *Drosophila* CP subunits play a critical role in the organization and dynamics of lamellipodia and filopodia in non-neuronal cells [35]. One of the mammalian β-subunit isoforms, Capzb2, is predominantly expressed in the brain [36]. Capzb2 not only caps F-actin barbed end but also binds βIII-tubulin directly, affecting the rate and the extent of microtubule polymerization in the presence of tau [37]. Moreover,

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Capzb2 - βIII-tubulin interaction is indispensable for normal growth cone morphology and neurite length (Figure 1) [37].

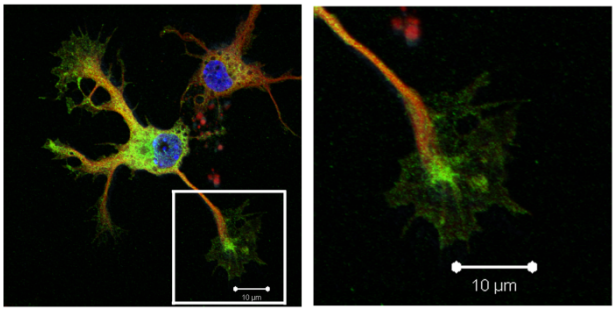

Figure 1. [37]: Capzb2-EGFP (green) expression in mouse hippocampal neurons. In addition to soma and processes, Capzb2 is expressed in growth cones (red- ß-tubulin, blue- nuclei).

Interestingly, the interaction between actin capping protein and ß-tubulin has been uncovered in a mass spectrometry screen for the alterations in protein-target binding *in vivo* in response to spatial learning [38], a process that requires BDNF [39].

In line with the previously documented increased cytoskeletal reorganization including dendritic proliferation and sprouting in neurons of AD patients [40,41,31], we recently demonstrated increased expression of Capzb2 (Figure 2) and TrkB in mid-stages (Braak and Braak III-IV, BBIII-IV) AD pathology[42].

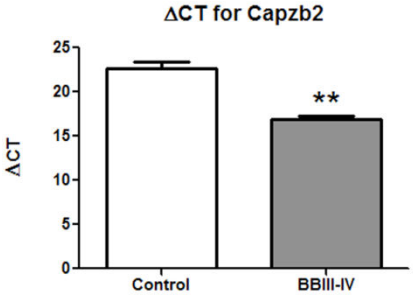

Figure 2. [42]: Hippocampal pyramidal neurons from a control case contain less Capzb2 mRNA (higher ΔCT) than the neurons from Braak and Braak III-IV AD cases (**p<0.01, Student's t test).

BDNF binding to the TrkB receptor initiates intracellular cascades involving cell survival, growth, and differentiation via mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), and phospholipase C-g (PLCγ) signaling pathways, as recently reviewed [43]. PI3K and MAPK simultaneous triggering alters both actin and microtubule dynamics needed for dendrite branching [43]. BDNF has been shown to promote growth of undifferen-

tiated dendrites and axons in cultured hippocampal pyramidal neurons [44], a process that requires Capzb2 [37]. Thus, the expression of Capzb2 may represent one of the likely downstream read-outs for BDNF-TrkB neuronal signaling. In a rat model of dementia there is activity-dependent, synapse-specific regulation of CapZ redistribution possibly important in both maintenance and remodeling of synaptic connections receiving spatial and temporal patterns of inputs [45].

3. Increased expression of TrkB and Capzb2 accompanies preserved cognitive status in early AD pathology

Recent study compared mRNA (Figure 3) and protein (Figure 4) expression of BDNF, TrkB and Capzb2 in samples of neuropathologically normal and cognitively intact subjects (controls), with samples of persons with AD-related pathological changes who were cognitively intact prior to death (Clinical Dementia Rating zero, CDR0), and samples of persons with AD-related pathological changes as well as early clinical dementia (CDR0.5 – 1) [46]. This approach was possible due to the existence of a unique sample of Framingham Heart Study (FHS) participants who have undergone repeated antemortem cognitive testing and brain imaging [47,48]. All FHS participants in the FHS have undergone screening cognitive tests (an MMSE) once in two years and have also had a more detailed cognitive assessment examining multiple cognitive domains once in 1974-75, once in 1999-2004 and at least twice thereafter. The presence or absence of dementia in all FHS participants is defined using DSM-IV criteria that require impairment in memory and in at least one other area of cognitive function, as well as documented functional disability. AD is defined using NINCDS-ADRDA criteria for definite, probable or possible AD[49]. All FHS participants are invited to become brain donors and the nearly 700 persons who have accepted this invitation undergo a detailed neuropsychological testing [50,51], at least once every 2 years beyond age 75 years. Persons who screen positive or are otherwise referred (by self, family or treating physicians) undergo detailed neurological and neuropsychological assessment, informant interview (with a physician administered CDR) and a review of hospital records, nursing home notes, brain imaging and laboratory tests. A structured family interview (including Blessed Dementia and Hachinski scales) [52,53] is conducted with the next-of-kin based on which a retrospective CDR score is assigned after the participant dies. The retrospective CDR is very similar to the retrospective collateral dementia interview validated by Davis and colleagues (1991)[54]. A final clinical decision regarding the presence or absence of dementia, diagnosis of dementia type and date of onset/diagnosis is made by a clinical consensus panel including behavioral neurologists and neuropsychologists who review all available records including records at the time of death. All deaths are reviewed to assign a cause of death and to determine if dementia was present or absent at the time of death. The neuropathological report is generated prior to a final clinicopathological conference during which the clinical diagnoses and pathological findings are discussed.

Hippocampi from selected FHS cases were used to determine whether specifically vulnerable population of CA1 neurons shows a compensatory response to the neuropathological changes

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of Alzheimer Disease (AD) and whether that response depends on an up-regulation of the BDNF pathway. The expression of TrkB and Capzb2 in CA1 hippocampal neurons of individuals with preserved cognitive status (CDR 0) and initial neurofibrillary tangle formation was increased in comparison to cognitively intact individuals without any neurofibrillary tangles (Figure 3) [46]. In contrast, BDNF expression remained unchanged, raising the possibility that the up-regulated TrkB expression in CDR0 individuals is responsible for the increase in BDNF/TrkB signaling tapping the brain reserve (Figure 3) [46]. In the group of individuals with more advanced tangle formation and early to mild dementia (CDR 0.5-1), the increase in TrkB expression and the unchanged expression of BDNF might have been insufficient to provide adequate brain reserve (Figure 3) [46].

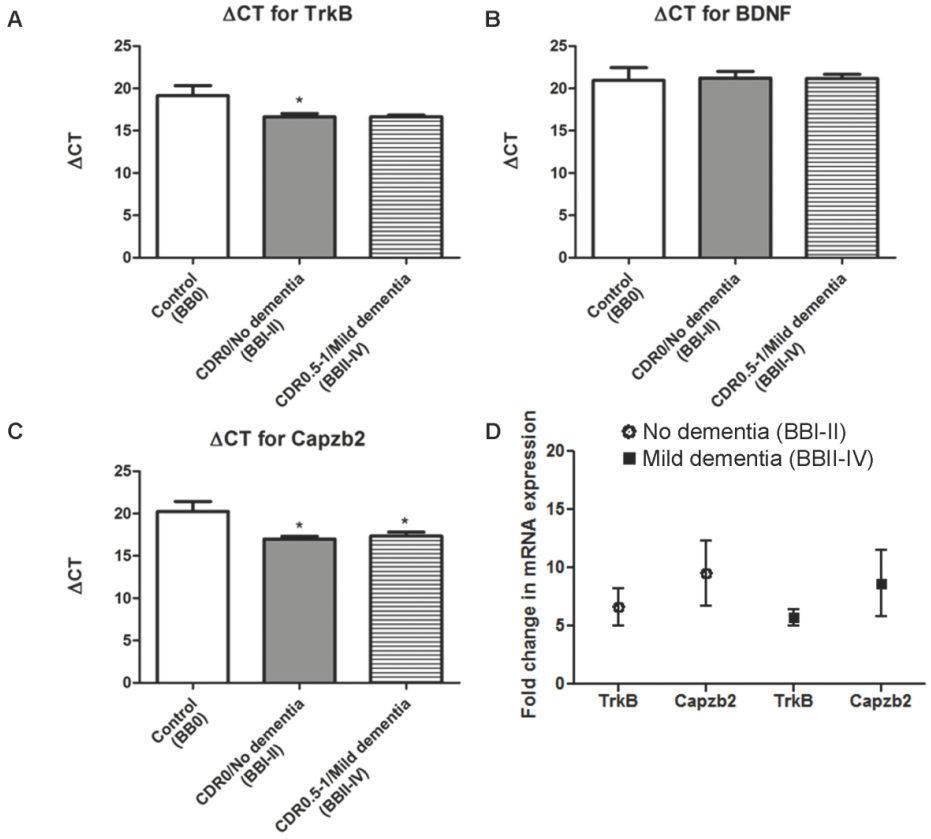

Figure 3. [46]: TrkB, BDNF, and Capzb2 mRNAs expression in control, CDR 0 (no dementia) and CDR 0.5-1 (mild dementia) subjects. TrkB mRNA expression is significantly increased (lower ΔCT) in subjects with early AD pathology (BBI-II) but no dementia (A). BDNF mRNA expression is similar in all groups examined (B). Capzb2 mRNA is significantly increased (lower ΔCT) in cases with AD pathology (C). Fold-increases of mean mRNA expression of TrkB and Capzb2 in cases with AD pathology in comparison to controls (D).

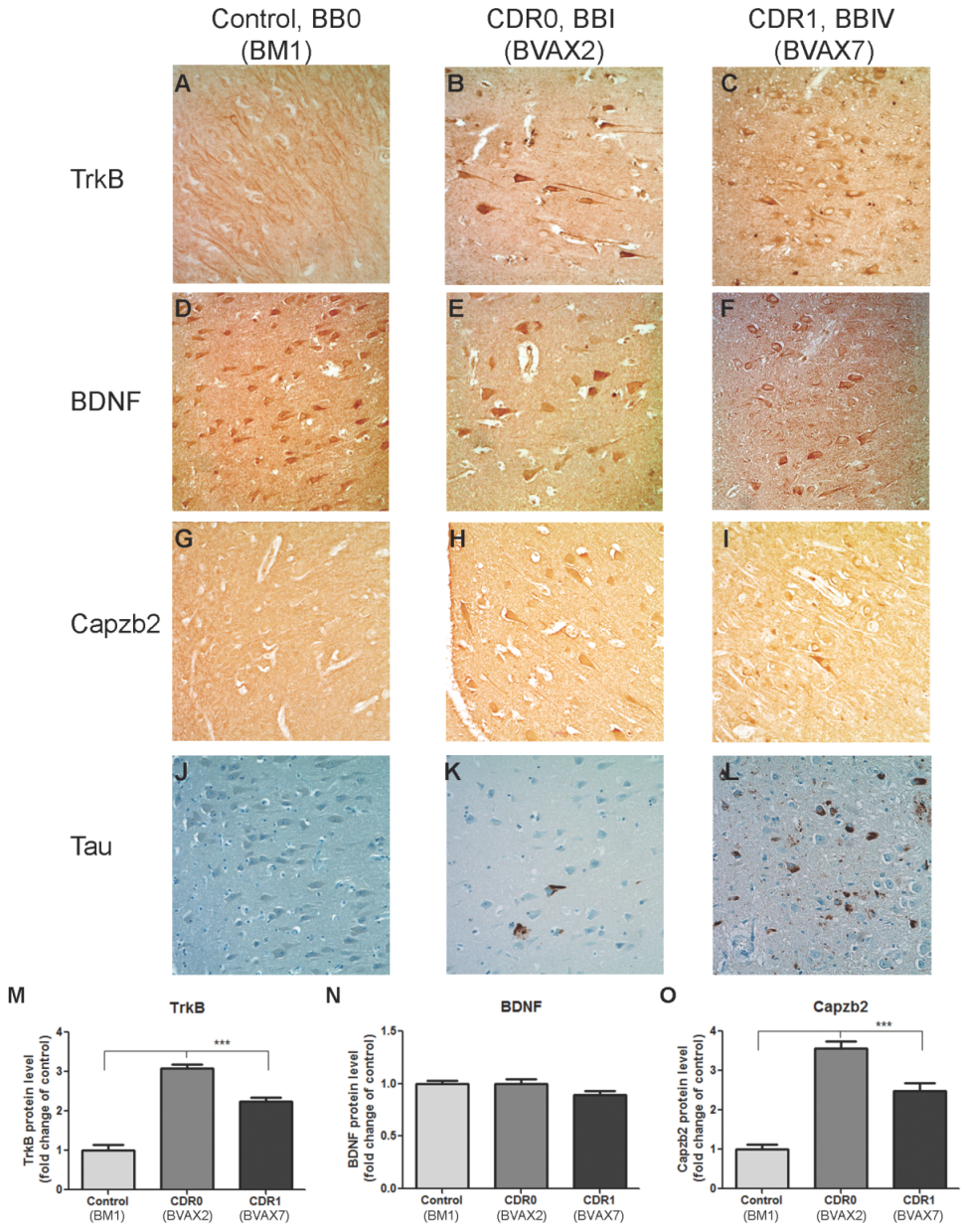

Figure 4. [46]: Immunohistochemistry for TrkB (A-C), BDNF (D-F), and Capzb2 (G-I) in representative individuals from control, CDR0, and CDR1 groups reflects established trends in mRNA expression. Immunohistochemistry for tau highlights intensity of neurofibrillary changes in a CDR0 subject (K) and in a CDR1 subject (L), while the control is free of neuropathology (J).

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In light of the reported restoration of learning and memory functions in AD animal models upon BDNF gene delivery [55], exogenous intervention to boost BDNF/TrkB signaling might appear a compelling therapy in early AD. However, the experiments by Frank et al. (1996) suggest that the exposure of developing and adult rodent hippocampal neurons to BDNF *in vitro* and *in vivo* results in long-term functional desensitization to BDNF and down regulation of TrkB mRNA [56]. It is possible that BDNF/TrkB signaling is differentially regulated in healthy vs. diseased hippocampal neurons. Nevertheless, the reported increase in TrkB mRNA expression in astrocytes occasionally associated with senile plaques in hippocampi of AD brains raises concerns that the administration of neurotrophic factors could promote gliosis and plaque formation [57]. Importantly, if the observed increase in TrkB expression in cognitively intact FHS subjects with initial formation of neurofibrillary tangles constitutes brain reserve, down regulation of TrkB might represent a potentially harmful side-effect of exogenous BDNF delivery.

4. Conclusion

One in five persons currently 65 years old will develop clinical Alzheimer's dementia in their lifetime. However, postponing the onset of clinical disease by as little as five years could halve individual risk and population burden of disease [58,59]. Since the timing of clinical dementia onset is determined not only by the pace of pathological changes but also by brain reserve, that postponement might be possible. The study of CA1 hippocampal neurons in FHS participant brain donors[46] adds to the emerging evidence that the BDNF/TrkB pathway may be involved in the compensatory response to early AD pathology, i.e. it may underlie the biology of cognitive reserve. Consequently, an epigenetic enhancement of BDNF/TrkB signaling in persons with early cognitive changes associated with AD pathology (mild cognitive impairment, MCI, due to AD pathology)[60] and in persons with no clinical symptoms but with biomarker evidence of AD pathology (so-called preMCI due to AD pathology) [61] may be beneficial in delaying the onset of clinical dementia. The lifestyle modifications that are thought to reduce the risk of developing clinical AD, such as intake of docosahexaenoic acid (DHA) and increased exercise, appear to interact with BDNF-related synaptic plasticity[62]. As reviewed by Sananbenesi and Fischer (2009)[63], deregulation of "plasticity genes", in particular synaptic plasticity genes, accompanies aging, a major risk for AD. Histone deacetylase inhibitors (HDACs) and environmental enrichment have been shown to reinstate learning behavior and improve memory in a CK-p25 mouse model of neurodegeneration[64], whereas altered histone acetylation is associated with age-dependent memory impairment in mice[65]. These findings make deciphering of epigenetic signatures in preserved vs. failing human cognitive functions urgent and necessary for the development of rational interventions in the progression of AD [66,67]. The prevention of clinical AD will likely require a multi-dimensional approach and the modulation of the BDNF/TrkB pathway, calibrated to each individual's needs, might be one facet of this multi-dimensional approach.

Summary

During the progression of Alzheimer's disease (AD), hippocampal neurons show degenerative as well as regenerative changes, possibly influenced by genes that may modify brain reserve, the ability of the brain to tolerate pathological changes in AD before manifesting clinical signs and symptoms. Recent data suggest that the expression of these genes in the hippocampal neurons correlates with the cognitive function. Identifying molecules that may promote regenerative potential and/or increase brain reserve provides novel targets for interventions in late-onset AD.

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