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Review

The role of BDNF in Alzheimer's disease

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1. Introduction

Brain-derived neurotrophic factor (BDNF) is an important member of the classic neurotrophin family of growth factors, along with nerve growth factor, and neurotrophins 3, 4/5 and 6. It regulates neuronal survival, differentiation and plasticity by activating the receptor tyrosine kinase TrkB and p75 low-affinity neurotrophin receptor (Huang and Reichardt, 2001; Poo, 2001). Reduced BDNF signaling through TrkB leads to impaired spatial memory (Minichiello et al., 1999; Saarelainen et al., 2000; Minichiello, 2009), while overexpression of TrkB enhances memory (Koponen et al., 2004). Further, when signaling through TrkB BDNF enhances long-term potentiation (LTP) of hippocampal synapses (Minichiello, 2009) while through p75 it promotes long-term depression (LTD) (Rosch et al., 2005). These properties of BDNF have led to speculations about its role in Alzheimer's disease (AD) where synaptic and neuronal loss and impaired memory constitute an essential part of the pathology.

2. Altered BDNF signaling in AD brains

BDNF mRNA and protein levels have been found to be reduced in postmortem brain samples of AD patients (Phillips et al., 1991; Narisawa-Saito et al., 1996; Connor et al., 1997; Ferrer et al., 1999; Holsinger et al., 2000; Hock et al., 2000; Garzon et al., 2002; Fahnestock et al., 2002). Importantly, reduced BDNF levels were reported already at the mild cognitive impairment (MCI) stage of the disease in one study and were shown to correlate with cognitive function (Peng et al., 2005). This is consistent with findings in our brain bank

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at the University of Eastern Finland: BDNF levels in temporal cortex decline linearly as a function of Braak staging (M. Hiltunen, personal communication). As Braak staging of AD is entirely based on neurofibrillary tangles (i.e. tau pathology), it is of note that a recent study reported decreased BDNF mRNA levels in also brains of patients with non-Alzheimer tauopathies (Belrose et al., 2014).

Besides declined levels of the ligand, also the mRNA and protein levels for the full-length TrkB receptor have been found to be decreased in AD brains in some reports (Ferrer et al., 1999; Allen et al., 1999; Ginsberg et al., 2006) but unchanged in others (Savaskan et al., 2000; Wong et al., 2012). In contrast, levels of the truncated TrkB.T1 receptor have been found to be increased (Connor et al., 1996; Ferrer et al., 1999; Wong et al., 2012). The TrkB.T1 receptor has a dominant negative action on both TrkB (Eide et al., 1996) and p75 (Michaelsen et al., 2010) signaling, and prevents both LTP and LTD in experimental models (Michaelsen et al., 2010).

2.1. Direct interactions between Aβ and BDNF/TrkB in vitro

There is some evidence that amyloid-β (Aβ) protein can directly inhibit the proteolytic conversion of BDNF from pro-BDNF thus reducing its levels (Zheng et al., 2010). In addition, Aβ indirectly affects BDNF levels at the synapses by interfering with its axonal transport. This seems to occur independently of Aβ induced hyperphosphorylation of the microtubulus-associated protein tau via calcineurin activation (Ramser et al., 2013). Aβ also inhibits retrograde axonal transport of the BDNF-TrkB complex via a mechanism involving the deubiquitinating enzyme, ubiquitin C-terminal hydrolase L1 (Poon et al., 2013). There is also direct evidence that administration of oligomeric Aβ significantly downregulates BDNF expression in vitro (Garzon and Fahnestock, 2007; DaRocha-Souto et al., 2012; Rosa and Fahnestock, 2015). One possible mechanism is via downregulation of CREB phosphorylation, which may result from interaction of Aβ with PKA activation (Vitolo et al., 2002; Rosa and Fahnestock, 2015).

Recent evidence suggests that the change in the balance between full-length and truncated TrkB receptors in AD brains may also derive from direct action of Aβ protein. Aβ (depending on its aggregation state) increases mRNA levels of truncated TrkB forms (Wong et al., 2012; Jerónimo-Santos et al., 2015). In addition, Aβ induces a calpain-mediated cleavage on TrkB-FL receptors, thus reducing their levels. BDNF binding to the TrkB receptor activates three intracellular signaling cascades: Ras–mitogen activated protein kinase (MAPK) pathway, the phosphatidylinositol 3-kinase (PI3K)–Akt pathway and the PLCγ–$Ca2^{+}$ pathway (Minichiello, 2009). Phosphorylation at the tyrosine 515 of TrkB leads to activation of specific adaptor molecules, Shc for the Ras-MAPK pathway, and GAB1 and IRS1 for the PI3K–Akt pathway, while phosphorylation of the tyrosine 816 directly phosphorylates and activates the PLCγ (Minichiello, 2009). In primary cortical neurons, administration of oligomeric Aβ interferes with BDNF-induced activation of Ras-MAPK and PI3K–Akt pathways, but not with PLCγ activation. The interaction takes places at the Shc and IRS-1 adaptor proteins (Tong et al., 2004). Aβ can thus impair TrkB-mediated signaling at multiple levels.

In reverse, BDNF appears to have protective effects on neuronal toxicity induced by Aβ peptides both in vitro and in vivo (Arancibia et al., 2008; Kitiyanant et al., 2012). BDNF co-incubation in hippocampal (Zeng et al., 2010) or entorhinal cortical slices (Criscuolo et al., 2015) also prevents Aβ1–42 induced impairment in LTP induction. Less is known about possible effects of BDNF on Aβ production. One study suggests that BDNF shifts APP processing towards the α-secretase pathway in a neuronal cell line (Holback et al., 2005) but there are no data on BDNF effects on APP processing in primary neurons. Even less is known about interactions between BDNF and tau protein. Theoretically, BDNF signaling via TrkB receptor and activation of the PI3K-Akt pathway should dampen the activity of the most important tau kinase, glycogen synthetase kinase 3β (GSK3β) by its inhibitory phosphorylation. Indeed, one study reported tau dephosphorylation at several sites, including the common AD-associated AT8 site, in neuronal cells after BDNF stimulation. The effect was shown to be mediated by the PI3K-Akt pathway (Elliott et al., 2005). However, there are no data whether the same effect can be found in primary neurons.

2.2. Impaired BDNF-TrkB signaling associates with mild cognitive decline in APP transgenic mice

Several studies have addressed possible changes in brain BDNF levels in amyloid plaque forming transgenic mouse lines with mixed results. One study reported decreased BDNF mRNA levels in two lines (APPswe,ind and APPswe/PS1-P264L) but no change in another APPswe/PS1-M146V line (Peng et al., 2009). Decreased BDNF protein levels were also reported in a triple transgenic APPswe/PS1/tau line (Castello et al., 2012). In contrast, three studies, including our own, found increased BDNF protein levels, one in an APPswe line (Burbach et al., 2004) and two in an APPswe/PS1(dE9) line (Szapacs et al., 2004; Rantamäki et al., 2013). Thus the BDNF levels do not seem to depend on whether the mice carry only APP mutation or both APP and PS1 mutations. However, independent of the particular mutation, brain BDNF levels may depend on the resulting Aβ aggregation state. In particular, Peng and coworkers (2009) comparing three amyloid producing mouse lines found an association between reduced BDNF levels and increased levels of large Aβ oligomers. The findings that amyloid plaque forming mice do not show consistent decline in brain BDNF levels as human AD brains do, may reflect the fact that these mice do not show significant neuronal loss. Interestingly, similar to Burbach et al. (2004) we found that BDNF immunoreactivity concentrates around amyloid plaques (Rantamäki et al., 2013). A similar plaque-associated strong BDNF immunoreactivity has also been reported in AD brains (Murer et al., 1999). These findings suggest that BDNF may get 'trapped' to amyloid plaques without being available as neuronal growth support. This also implies that the functional brain BDNF levels in plaque loaded brain region may be actually lower than the total BDNF levels. A common finding in amyloid plaque forming transgenic mice is the presence of dystrophic neurites around the plaques (Bell et al., 2006). Whether concentration of BDNF in amyloid plaques is actually related to these dystrophic changes remains an intriguing possibility that warrants further studies. Consistent with findings in AD brains and Aβ administration in neuronal cultures, we have found increased ratio of the truncated TrkB.T1 to the full-length TrkB.TK receptor in the cortex of plaque bearing APPswe/PS1dE9 mice (Kemppainen et al., 2012). This was largely due to increased levels of TrkB.T1 receptor.

To assess the functional role of the increased TrkB.T1 to TrkB.TK ratio, we cross-bred APP/PS1 mice with either TrkB.T1 or TrkB.TK overexpressing mice and assessed their spatial memory with Morris swim task at middle age. We found that overexpression of TrkB.T1 vs. TrkB.TK in APP/PS1 mice has opposite, albeit moderate, effects on spatial learning, so that TrkB.T1 overexpression impaired while TrkB.TK overexpression augmented learning (Kemppainen et al., 2012). These cognitive effects were independent of amyloid load, which was unaffected by the TrkB manipulations (Kemppainen et al., 2012). Further, to assess the functional role of BDNF deficient in the AD brain, we cross-bred APPswe/PS1dE9 mice with BDNF + / - mice (homozygous BDNF −/− mice do not survive till adult age) and similarly tested their spatial learning and memory. As expected, BDNF haploinsufficiency resulted in impaired spatial learning (Rantamäki et al., 2013). Consistent with the data on TrkB manipulation, BDNF haploinsufficiency did not influence brain amyloid load, nor did it alter accumulation of phospho-tau (AT8 site) around amyloid plaques (Rantamäki et al., 2013). Similarly, partial knockdown of BDNF did not affect brain amyloid or tau pathology in triple transgenic mice (Castello et al., 2012). Collectively, these findings suggest that decline in brain BDNF levels unlikely drives amyloid or tau pathology but appears to

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