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The role of BDNF in Alzheimer's disease

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The role of Brain-derived neurotrophic factor in Alzheimer's disease

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Abstract

Brain-derived neurotrophic factor (BDNF) a key neurotrophin and important for synaptic growth and plasticity. Since these are compromised already at an early stage of Alzheimer's disease (AD), the role of BDNF in the disease pathology has gained a lot of interest. Impaired BDNF signaling is well documented in AD brains and to some extent also in amyloid plaque producing AD mouse models. In in cell culture models amyloid-β peptide negatively interacts with BDNF signaling. In AD mouse models, pertubation of BDNF signaling aggravates age-related memory impairment, whereas attemps to increase brain BDNF or its active receptor levels have produced beneficial effects on learning and memory. Notably, experimental manipulation of brain BDNF levels have had no effect on brain amyloid plaque load or levels of hyperphosphorylated tau, suggesting that it acts downstream of the core pathological event in AD. BDNF holds promise as a treatment approach for AD, but itself has unfavorable pharmacokinetic properties. There are some promising new attemps to increase BDNF signaling with peptidomimetics or by indirectly influencing brain BDNF levels.

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., 2000b; 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.

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; Connor et al., 1997; Ferrer et al., 1999). 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 at the University of Eastern Finland: BDNF levels in temporal cortex decline linearly as a function of Braak staging (M. Hiltunen, personal communication). Besides declined levels of the ligand, also the mRNA and protein protein levels for the full-length TrkB receptor are decreased in AD brains (Connor and Dragunow, 1996; Ferrer et al., 1999). In contrast, levels of the truncated TrkB.T1 receptor have been found to be increased (Connor et al., 1996; Ferrer et al., 1999). 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).

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 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).

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, Jeronimo-

Santos, 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 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.

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 levels in two lines (one APPswe,ind, one APPswe/PS1) but no changed in another APPswe/PS1 line (Peng et al., 2009). In contrast, three studies, including our own, found increased BDNF levels, one in an APPswe line (Burbach et al., 2004) and two in 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. Neither do the BDNF levels correlate with amyloid plaques, but the presence of large Aβ oligomers appears to associate with decreases BDNF levels (Peng et al., 2009). The discrepancy 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 and coworkers (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 (Masliah et al., 2001). 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 crossbred 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 positive) around amyloid plaques (Rantamäki et al., 2013). These findings are fully consistent with a recent study that cross-bred a mouse line expressing three APP and two PS1 mutations (so-called 5xFAD mouse) with partially TrkB-deficient mice. TrkB haploinsufficiency did not affect brain amyloid load, but aggravated impaired sponataneous alteration in a Y-maze, a task considered to assess spatial working memory (Devi and Ohno, 2015).

The question whether genetically induced tau pathology in mouse disease models leads to decline in brain BDNF signaling has received little attention so far. The only published study to daet did not find alterations in hippocampal BDNF levels in a transgenic mouse carrying a mutated human tau gene (Burnouf et al., 2012).

Some BDNF polymorphisms increase the risk for AD

Several polymorphisms have been described in the BDNF gene. A single nucleotide polymorphism (C-270T) within the BDNF gene has been associated with late onset AD in a Japanese and German population (Riemenschneider et al., 2002). In contrast, no single nucleotide polymorphism (SNP) in the BDNF gene showed a significant association with AD in a Finnish study (Vepsäläinen et al., 2005). However, a recent American study on almost 700 AD patients found several SNPs to play a role in

AD-related brain neurodegeneration, although not directly increasing the likelihood of obtaining the AD diagnosis (Honea et al., 2013).

The BDNF Val66Met polymorphism has been associated with many psychiatric diseases and its association with AD has also been subject of several studies. However, the results have been mixed. While some studies have linked the met allele with small hippocampal volume and poor memory (Hariri et al., 2003; Peng et al., 2005), other studies have found a similar association with the val allele (Harris et al., 2006; Voineskos et al., 2011). One plausible explanation to this discrepancy is that the BDNF val/met polymorphism plays a disease modifying role which depends on the stage of the disease. Indeed, an age-dependent relationship to cortical thickness, white matter integrity and episodic memory was reported in one study, such that in all studied parameters val/val individuals in late life were susceptible, while in early adult life, met allele carriers demonstrated susceptibility (Voineskos et al., 2011). Another recent study found a faster cognitive decline in healthy elderly subjects carrying the met allele, but only if they were found to be amyloid-positive in a PET scan (Lim et al., 2013). Further, a recent PET imaging study reported the met allele to associate with increased brain amyloid load, but only in ApoE ε4 carriers (Adamczuk et al., 2013). Apart from the extensively studied Val66Met polymorphism also other BDNF polymorphisms may influence the risk of dementia. A recent imaging/-genetics study on more than 600 patients suggests that while BDNF genetic variation is not specifically associated with a diagnosis of AD, it appears to play a role in AD-related brain neurodegeneration Honea et al., 2013).

BDNF as a biomarker for AD

Findings of decreased brain BDNF levels rise the question whether corresponding decline in serum BDNF levels would serve as a biomarker for AD. An early study in patients with severe AD reported decreased serum BDNF levels compared to elderly controls (Yasutake et al., 2006). However, such a difference could not be verified in a large study group of patients with mild to moderate AD (O'Bryant et al., 2009), and one study even reported increased serum BDNF in MCI/AD patients independent of disease severity (Angelucci et al., 2010). Nevertheless, a later study reported that increased serum BDNF levels were associated with poorer visual and verbal memory among AD cases but not among elderly controls (O'Bryant et al., 2011). Although the above-mentioned studies comparing diagnosed MCI/AD patients with healthy controls failed to find consistent differences in serum BDNF levels between the groups, studies on healthy elderly subjects found increased serum BDNF to protect against later AD, especially among college-educated women over 80 (Weinstein et al., 2014). Thus, serum BDNF may provide some value in predicting the risk of AD, but alone lacks sufficient power as a biomarker.

BDNF as treatment for AD

If BDNF levels decrease in the AD brain already at an early stage of the disease, measures to restore brain BDNF levels appear as a natural treatment strategy. One study attempted this by lentiviral gene transfer of BDNF into the entorhinal cortex. The gene transfer led to increased BDNF protein levels in the hippocampus and improved hippocampal dependent memory in APP transgenic mice and aged rats (Nagahara et al., 2009). It also reversed reduced entorhinal neuron number and synaptophysin immunoreactivity in APP transgenic mice, but consistent with studies with genetic manipulation on brain BDNF levels, did not influence brain Aβ levels (Nagahara et al., 2013). There are also numerous ways to influence brain BDNF levels indirectly. One study transplanted neuronal stem cells into the hippocampi of aged APP/PS1/tau transgenic mice and found improved spatial learning after the treatment. However, transplanted neural stem cells with inactivated BDNF expression were ineffective suggesting that the beneficial effect of cell transplantation was mediated by their BDNF production (Blurton-Jones et al., 2009).

BDNF itself does not have pharmacokinetics suitable for systemic administrations due to its short plasma half-life and poor BBB penetration. Therefore, several attempts have been made to develop small molecule BDNF mimetics with more suitable pharmacokinetics. One study reported that intranasal administration of a BDNF mimetic (LM22A) in mice bound selectively to the TrkB receptor and activated the PI3K-Akt and Ras-MAPK pathways. The compound also improved motor learning after traumatic brain injury in rats (Massa et al., 2010). Another approach to increase brain BDNF levels has been the use of BDNF modulating peptides. One these, a tripeptide Neuropep-1, after intraperitoneal injection increased brain BDNF levels in APP/PS1/tau transgenic mice, improved their spatial learning and memory, and also reduced brain amyloid plaque load (Shin et al., 2014). In addition, many nonspecific treatments have been reported to increase brain BDNF levels, which at least partially, also mediate the observed beneficial effect on memory. For instance, a recent study demonstrated that social interaction increases hippocampal neurogenesis and spatial memory in APP/PS1 mice, and increased hippocampal BDNF mRNA levels. However, inactivation of BDNF expression blocked the memory enhancing effect of social interaction (Hsiao et al., 2014). There are several reports that physical exercise increases circulating BDNF levels. One study in healthy elderly showed that six months of aerobic exercise increased serum BDNF levels, which was associated with hippocampal volume increase and spatial memory improvement (Erickson et al., 2011). A recent study demonstrated that aerobic exercise increases plasma BNDF levels also in AD patients (Coelho et al., 2014).

Conclusions

Substantial evidence indicates that brain BDNF signaling through the TrkB receptor deteriorates in the AD brain already at an early stage of the disease. Human genetic and experimental animal studies suggest that declined BDNF levels associate with synaptic and neuronal loss and cognitive impairment

with aging and AD, but there is little evidence that BDNF signaling would play a major role in the disease specific amyloid or tau pathology. Several approaches to increase brain BDNF levels in experimental animal models have yielded encouraging results but there are still numerous unsolved issues before BDNF-based treatments will become available in the clinics.

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