REVIEW ARTICLE

The role of TrkB receptor signaling in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders among the elderly. However, there is no reliable drug for the treatment of AD, which is largely due to the unknown mechanisms and the lack of credible drug targets. Some studies demonstrated the hat the brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB) signaling pathway may be a potential therapeutic target for AD. As the most widely studied neurotrophin in the brain, BDNF has a high affinity for TrkB receptor and plays an important role in the regulation of neuronal survival, growth, and synaptic plasticity. Mechanistically, TrkB signaling cascade is considered to be the most important way in which BDNF exerts neuroprotective effects. The expression of TrkB receptor was also found to be significantly decreased in AD patients and AD animals compared with the control, suggesting the involvement of TrkB receptor and TrkB-dependent signal in AD pathogenesis. In this review, we aim to discuss the possible role of TrkB-dependent signal in AD pathogenesis, focusing on three major downstream pathways including phosphatidylinositol-3 kinase/protein kinase B (PI3K/AKT), extracellular regulated kinase (ERK), and phospholipase C-γ1 (PLC-γ1) pathways.

Keywords: Tropomyosin receptor kinase B, Alzheimer's disease, Phosphatidylinositol-3 kinase, Extracellular regulated kinase, Phospholipase C-γ1.

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1. INTRODUCTION

The tropomyosin receptor kinase (TRK) family of receptors is encoded by the neurotrophic tyrosine receptor kinase (NTRK) genes. A subset of NTRK genes encodes tropomyosin receptor kinase proteins (TrkA, TrkB, and TrkC) that play a critical role in neural development and homeostasis (Nakagawara *et al.*, 1995; Valent *et al.*, 1997; Wang *et al.*, 2022; Weier *et al.*, 1995). Each TRK receptor comprises an extracellular domain, a transmembrane region, and an intracellular region containing tyrosine kinase activity (Amatu *et al.*, 2019). In vivo, TRK receptors mediated signaling triggers are usually activated by neurotrophins which mainly include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4) (Bothwell, 2019). It is worth noting that TrkB receptor has a higher affinity in binding to BDNF, NT-3, and NT-4 (Klein *et al.*, 1991; Strohmaier *et al.*, 1996). Although the role of TRK signaling is still to be fully understood, BDNF, a high-affinity ligand for TrkB, has been shown to play an important role in preserving

neurons and preventing or delaying neurodegeneration (Zhao *et al.*, 2019). In the central nervous system, TrkB receptor was found in two isoforms: a truncated non-functional variant called TrkB-Tc and a full-length isoform called TrkB-Fl (Valle-Leija *et al.*, 2017). Functionally, the TrkB-Fl isoform included the catalytic domain of the tyrosine kinase and could autophosphorylate to activate intracellular signals, while the TrkB-Tc was the most richly expressed isoform of TrkB in adult rodent brains and could antagonize the effect of TrkB-Fl (Saba *et al.*, 2020). Overall, neuroprotective therapy is required to account for the balance of TrkB-Fl and TrkB-Tc. In this review, we review the role of TrkB signaling in AD and its possible downstream pathways.

2. INVOLVEMENT OF TrkB RECEPTOR SIGNALING IN AD

TRK signaling plays an important role in the central nervous system as mentioned in previous studies, while one of the most investigated is the TrkB-dependent signaling pathways (Bartkowska *et al.*, 2007; Gupta *et al.*, 2013; Stoleru *et al.*, 2013). Alzheimer's disease (AD) is the most common age-related neurodegenerative disease that seriously threatens the health of the elderly. The expression of BDNF and TrkB receptor were significantly decreased in AD patients (Ferrer *et al.*, 1999; Peng *et al.*, 2005), suggesting the involvement of TrkB signaling in AD. In vivo studies show that BDNF deficiency triggers tau proteolytic cleavage, resulting in the resultant tau N368 fragment that binds to TrkB receptors, blocking its neurotrophic signals and inducing neuronal cell death (Xiang *et al.*, 2019). Apart from that, excessive δ-secretase blocks the interaction of TrkB receptor and amyloid precursor protein (APP), thereby leading to increasing Aβ production in AD (Xia *et al.*, 2021). Thus, up-regulated BDNF expression activating TrkB signaling is thought as a promising therapeutic strategy for AD (Zhang, J. *et al.*, 2019). Although BDNF-TrkB signaling is critical for neuronal growth, morphogenesis and synaptic plasticity in the brain (Minichiello, 2009; Pang and Lu, 2004), Supplementing BDNF alone is not a good therapeutic option for AD due to the short in vivo half-life of BDNF (Chen *et al.*, 2018). Therefore, the idea of finding a chemical compound to mimic the effect of BDNF remains an attractive option for AD therapy. As these previous studies mentioned, 7, 8-Dihydroxyflavone (7, 8-DHF), a mimetic of BDNF, was widely used to treat various neuropsychiatric disorders such as AD, anxiety and depression (Chen *et al.*, 2018; Wang *et al.*, 2021; Yang *et al.*, 2021). However, 7, 8-DHF has the limitation of poor oral bioavailability in vivo, so researchers are focusing on another TrkB receptor agonist named R13 (a prodrug of 7, 8-DHF). It has been reported to have better oral bioavailability and a longer duration of action (Chen *et al.*, 2018). Moreover, our previous study showed that R13 treatment could significantly improve learning and memory in 5xFAD mice by activating TrkB receptor (Li *et al.*, 2022). In addition, R13 was also reported to significantly attenuate abnormal motor performance and reduce the advance of spinal motor neuron pathology and gastrocnemius muscle atrophy in $SOD1^{G93A}$ mice (Li *et al.*, 2021). Therefore, it is reasonable to speculate that activation of TrkB signaling may be the core of AD therapy.

However, targeting TrkB signaling in AD still has some limitations and challenges. Firstly, one of the main limitations is related to the complexity of the signaling pathway. The signaling pathways downstream of TrkB are highly interconnected and dynamic, making it difficult to specifically target TrkB signaling without affecting other signaling pathways. This lack of specificity may result in off-target effects and unwanted side effects. Secondly, another challenge in targeting TrkB signaling is related to the limited delivery of therapeutic agents to the brain. TrkB signaling is primarily involved in the central nervous system, and any therapeutic intervention targeting TrkB signaling needs to effectively cross the blood-brain barrier (BBB) to reach the brain. The BBB is a highly selective barrier that restricts the entry of most drugs into the brain (Wu *et al.*, 2023). Therefore, developing effective strategies to bypass or overcome the BBB is crucial for the successful targeting of TrkB signaling in AD. Thirdly, the heterogeneity of AD pathology poses a challenge in targeting TrkB signaling. AD is a complex neurodegenerative disease characterized by the accumulation of Aβ plaques and neurofibrillary tangles in the brain (Scheltens *et al.*, 2021). However, the underlying mechanisms and pathways involved in AD pathology can vary among individuals. This heterogeneity makes it challenging to identify specific patient populations that would benefit the most from targeting TrkB signaling. Moreover, the stage of the disease and the extent of neuronal damage may also influence the efficacy of targeting TrkB signaling. Additionally, another

limitation of targeting TrkB signaling in AD is the potential for adverse effects on other cognitive impairments. TrkB signaling is not only involved in neuronal functions but also plays important roles in other tissues and organs, such as the cardiovascular system and immune system (Cortese *et al.*, 2011; Hang *et al.*, 2021). Therefore, interfering with TrkB signaling may have unintended consequences on these physiological processes, leading to unwanted side effects. Overall, while targeting TrkB signaling holds promise as a therapeutic approach for AD, some several limitations and challenges need to be addressed. The complexity of the signaling pathway, limited delivery to the brain, heterogeneity of AD pathology, and potential adverse effects on other cognitive impairments are important considerations in the development of TrkB-targeted therapies for AD. Further research and innovation are needed to overcome these challenges and maximize the potential benefits of targeting TrkB signaling in the treatment of AD. Even so, more encouragingly, as shown in Table 1, scientists have also discovered a variety of potential therapeutic agents for AD via regulating TrkB signaling during the past decades.

Agent	Class	Target site	Ref.
7,8-dihydroxyflavone	Flavanoid	TrkB agonist	(Chen *et al.*, 2018)
R13	Small molecule	TrkB agonist	(Li *et al.*, 2022)
benzimidazole derivative (CF3CN)	Small molecule	TrkB agonist	(Chen *et al.*, 2021)
Ginsenoside Rg1	Panaxtriol	Regulating PI3K/AKT/ GSK-3 pathway	(Wu *et al.*, 2022)
Cerebrosides	Glycosphingolipids	Activation PI3K/AKT pathway	(Li *et al.*, 2019)
Angelica sinensis polysaccharides (ASP)	Polysaccharide	Activating BDNF/TrkB/ CREB pathway	(Du *et al.*, 2020)
8-[2-(2-Pentylcyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA)	Small molecule	Activating TrkB/LC-γ1/ PKC pathway	(Kanno *et al.*, 2016)
Alendronate	Small molecule	Activating BDNF/TrkB	(Olloquequi *et al.*, 2022)
TLQP-21/62	Peptide	Regulating BDNF/TrkB pathway	(Beckmann *et al.*, 2020; El Gaamouch *et al.*, 2020)
LMDS-1	Small molecule	TrkB agonist	(Fan *et al.*, 2020)
Cycloastragenol	Saponin	Activating TrkB/MAPK pathway	(Ikram *et al.*, 2021)
LM-031	Small molecule	Regulating CREB/ BDNF/BCL2 pathway	(Chiu *et al.*, 2022)

Table 1. Potential therapeutic agents for AD via regulating TrkB signaling.

In AD, Aβ accumulation was deemed to inhibit TrkB signaling, which consequently resulted in synaptic and cognitive damage associated with AD (Minichiello, 2009; Pang and Lu, 2004). Consistently, activated TrkB receptor signaling was reported to modulate some AD-related pathology and behavior such as Aβ deposition, synapse loss, and memory deficit in AD model mice (Arancibia *et al.*, 2008; Nagahara *et al.*, 2009). Beyond that, BDNF administration activating TrkB receptor signaling has also been shown to improve learning and memory in a rat dementia model with cognitive deficits (Ando *et al.*, 2002). Mechanistically, a recently study elaborated on the crucial role of TrkB signaling in ameliorating cognitive impairment. On the one hand, the knockout of TrkB receptor activated the δ-secretase by inhibiting T322 phosphorylation, which triggered the hydrolysis of the total Tau to Tau N368 fragment (Xiang *et al.*, 2019). The resultant Tau N368 fragment could bind TrkB receptor and block its neuroprotective effects, leading to AD-like pathology and cognitive

deficits (Xiang *et al.*, 2019). On the other hand, R13 treatment activating TrkB signaling significantly increased ATP levels by enhancing oxidative phosphorylation and promoting mitochondrial biogenesis in 5xFAD mice, and finally improved AD pathology and cognitive impairment (Li *et al.*, 2022). Interestingly, the activation of TrkB signaling induced by R13 treatment also affected several biological processes associated with mitochondria, including oxidative phosphorylation, oxidation-reduction process, aerobic respiration, fatty acid metabolism, mitochondrial fragmentation, etc (Li *et al.*, 2022). Though the exact mechanism of TrkB signaling remains unclear, the above studies strongly suggest the involvement of TrkB signaling from multiple perspectives in AD. Together, TrkB receptor may play a key role in the pathogenesis of AD.

3. THE MAIN PATHWAYS ASSOCIATED WITH TrkB SIGNALING IN AD

Given the important role of TrkB signaling in alleviating AD pathology and cognitive impairments and the fact that there are no effective treatment options for AD, some researchers focus on targeting TrkB-dependent signaling in the drug development of AD. As described above, BDNF, a member of the neurotrophin family, was by far the best-known "synaptogenic" molecule and perhaps the only one that had been shown to promote synaptic function in humans (Lu *et al.*, 2014), and TrkB receptor was the most important way that BDNF displayed neuroprotective effects in vivo (Numakawa and Odaka, 2021). Numerous studies suggested that the activation of TrkB signaling pathway may be the target for AD therapy (Arancibia *et al.*, 2008; Wang *et al.*, 2020; Wu *et al.*, 2015). For instance, TrkB agonists such as 7, 8-DHF and LMDS-1 treatment could improve synaptic function and ameliorate AD-like pathology and cognitive deficits in an Aβ mouse model (Fan *et al.*, 2020). Mechanistically, it is widely believed that TrkB agonists bind to TrkB receptor promotes TrkB phosphorylation, thereby activating several important intracellular downstream signaling cascades, including phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT), extracellular regulated kinase (ERK), and phospholipase C-γ1 (PLC-γ1) pathways, which were the basis of the TrkB signaling cascades. Next, we will focus on the roles of these three TrkB-dependent pathways in the treatment of AD.

3.1. PI3K/AKT signaling

PI3K/AKT signaling pathway is mainly involved in the regulation of signal transduction and biological processes including cell proliferation, apoptosis and metabolism (Long *et al.*, 2021). Accumulating pieces of evidence suggested that TrkB/PI3K/AKT signaling pathway regulated the formation of AD characteristic pathology and cognitive function. For instance, Cerebrosides, a class of neutral glycosphingolipids, were reported to improve $A\beta_{1\text{-}42}$-induced cognitive deficiency in a rat model of AD via activating TrkB/PI3K/AKT pathway (Li *et al.*, 2019). Another study consistently demonstrated that TrkB-dependent AKT activation could protect Aβ-GFP SH-SY5Y cells against Aβ toxicity (Chiu *et al.*, 2022). As the main downstream signal after TrkB activation, PI3K/AKT induces diverse biological action including neurotoxicity and neuronal survival via regulating downstream molecules such as glycogen synthetase kinase 3β (GSK-3β), mTOR and caspase-9. The phosphorylation of AKT could suppress the activity of GSK-3β via phosphorylating the Ser9 site of GSK-3β, which then decreases the phosphorylation of Tau and alleviates Tau pathology (Fan *et al.*, 2020). The phosporylated formation of mTOR, a downstream member of AKT, was reported to promote the growth and development of dendrites, which was essential for maintaining normal synaptic plasticity (O'Mara and Aggleton, 2019). The activation of PI3K/AKT/mTOR signaling pathway could inhibit autophagy and reduce the degradation of some important synaptic proteins such as PSD-95 (Nikoletopoulou *et al.*, 2017). Meanwhile, when PI3K/AKT signaling pathway was activated, it could induce the activation of α-secretase promoting the nonamyloid production of APP (Gabbouj *et al.*, 2019). In addition, cell death in AD is correlated with the expression of pro-apoptotic protein. A previous study showed that caspase-9 mediated pro-apoptotic pathway was inhibited via preventing the release of mitochondrial cytochrome *c* (Avrutsky and Troy, 2021), suggesting that PI3K/AKT/caspase-9 signal played an important role in improving mitochondria and promoting cell survival. Mitochondrial dysfunction has long been considered a key factor in the initiation and development of AD. Accordingly, TrkB receptor-mediated activation of PI3K/AKT may be of great significance in alleviating AD-related neuron loss and cognitive deficits.

3.2. ERK signaling

As mentioned above, ERK pathway is another downstream signaling of TrkB activation. Its role is mainly focused on neuronal survival and synaptic function. In vivo, the expression of phosphorylated TrkB and ERK was significantly down-regulated in the Aβ-injected mice brains, while these markers were up-regulated in the Aβ+Cycloastragenol (an anti-AD compound) co-treated mice brains (Ikram *et al.*, 2021), Consistently, the activation of ERK signaling could promote the APP cleaves in α-secretases-dependent manner and thus reduce the production of toxic Aβ (Zhang, T. *et al.*, 2019). These studies strongly indicated that TrkB/ERK signal had a better correlation with Aβ. Considering the important role of Tau pathology in AD, LM-031, a coumarin derivative has demonstrated the potential to improve BDNF signaling and promote neuronal survival via decreasing the expression of pro-aggregated Tau protein in the TrkB/ERK pathway-dependent manner (Lin *et al.*, 2022). Overexpressed Tau may mediate the toxicity of extrasynaptic N-methyl-D-aspartatic acid (NMDA) receptors by inhibiting ERK phosphorylation (Sun *et al.*, 2016). Beyond that, oxidative stress also plays an important role in the pathogenesis of AD. TrkB inhibitor ANA-12 and ERK inhibitor SCH772984 treatment eliminated the inhibition of DL0410 (a novel acetylcholinesterase inhibitor) on malondialdehyde (MDA) accumulation and mitochondrial membrane potential (MMP) loss in hydrogen peroxide (H_2O_2)-induced oxidative stress model (Zhang *et al.*, 2020). In a recent study, LMDS-1, a potential TrkB agonist, was reported to improve cognitive deficits and AD-like pathology by activating TrkB/ERK pathway (Fan *et al.*, 2020). Furthermore, LMDS-1 treatment also upregulated the expression of CREB and BDNF while down-regulated the GSK3β active formation and Tau phosphorylation (Fan *et al.*, 2020). As the main downstream signal of ERK, CREB phosphorylation is the key to promoting the expression of cAMP-responsive element-mediated genes such as BDNF (Wang *et al.*, 2018), which displays beneficial neuroprotective effects. On the one hand, increasing BDNF further binds to TrkB receptor, and thus activates ERK signaling pathway. On the other hand, the activation of TrkB-mediated ERK signaling could upregulate CREB and its downstream antiapoptotic regulator B-cell lymphoma 2 (BCL2) (Chiang *et al.*, 2021). The above pieces of evidence indicate that targeting TrkB/ERK signaling may provide new treatment strategies for AD. However, we still need to know more precisely the mechanism underlying how TrkB-dependent signal participates in the pathogenesis of AD.

3.3. PLC-γ1 signaling

PLC-γ1 is a member of PLC family, and is highly expressed in the brain. Its function is closely correlated with neurite growth and synaptic plasticity, which is mainly dependent on activation of TrkB signaling. The activation of TrkB could recruit PLC-γ1 to generate two-second messengers such as inositol trisphosphate (IP3) and diacylglycerol (DAG) that are crucial for BDNF-TrkB signaling mediated synaptic plasticity. IP3 promoted the release of Ca^{2+} from internal stores resulting in the activation of Ca^{2+}/calmodulin-dependent protein kinase, which caused CREB-mediated transcription of long-term potentiation (LTP)-related proteins (Colucci-D'Amato *et al.*, 2020). DAG stimulated DAG-regulated PKC isoforms that had a wide range of functions for memory, blood-brain barrier maintenance, and damage repair that change as the body ages. Interestingly, the mutant PKC formation can cause neurodegeneration and cognitive decline. In some cases, the absence of appropriate PKC translocation exacerbated Aβ toxicity and stroke outcomes (Lucke-Wold *et al.*, 2015). AD and stroke share several known vascular risk factors including infection defense, blood-brain barrier repair, and recovery from traumatic brain injury. And Aβ has also been shown to be a predisposing factor to stroke (Sriram *et al.*, 2022). Besides, repetitive brain injury such as stroke could cause acetylation of Tau at lysine 280 leading to hyperphosporylation of Tau (Lucke-Wold *et al.*, 2017). Meanwhile, recent studies indicated that PKC dysfunction was closely associated with tau phosphorylation and the activation of GSK3β (Alonso *et al.*, 2013). While the restoration of PKC translocation and activity could reduce tau phosphorylation and Aβ accumulation (Sun and Alkon, 2012).

Many studies showed that PLC-γ1 was associated with AD pathogenesis (Jang *et al.*, 2013; Yang *et al.*, 2017). For instance, the binding of Tau N368 and TrkB receptor was found to be able to inhibit PLC-γ1 activation and thus induced synaptic dysfunction in vivo (Xiang *et al.*, 2019). Another study showed that Tau could directly bind to the src homology 3 (SH3) domain of PLC-γ1, which further activated PLC-γ1-mediated downstream signaling.

While phosphorylated Tau weakened the interaction of Tau-SH3 and inhibited PLC-γ1 signaling (Sinsky *et al.*, 2021). These studies strongly indicate that the PLC-γ1 signaling pathway plays an important role in regulating Tau pathology associated with AD. In addition, the expression of PLC-γ1 was remarkably lower in the cortical AD patients than in the normal control (Shimohama *et al.*, 1995). Though there is not enough direct evidence on the effect of PLC-γ1 in the development and progression of AD, several studies associated with TrkB-dependent signaling in AD indicate that PLC-γ1 plays an important role in the regulation of AD pathogenesis.

4. CONCLUSION

The activation of TrkB signaling cascades is involved in the regulation of various physiological and pathological events in the brain. As shown in the Graphical Abstract, the main TrkB-dependent signaling pathways including PI3K/Akt signaling, ERK signaling, and PLC-γ1 signaling individually or collectively regulate neuronal survival, growth, and synaptic plasticity, which thus promote the recovery of cognitive impairment. Pathologically, multiple studies showed that TrkB signaling activation contributed to improvement in reducing Aβ accumulation and tau phosphorylation. Although a large number of research findings indicated the correlation of TrkB-dependent signaling with AD pathogenesis, many questions remain unresolved. Until now, there is no signal drug that has yet been approved based on TrkB signaling, except for some small-molecule TrkB agonists such as 7,8-DHF, R13, LMDS-1, etc, which have shown positive anti-AD effects in preclinical studies. Hence, we still need to know more precisely the mechanism underlying how TrkB-dependent signal participates in the pathogenesis of AD.

Abbreviations

AD, Alzheimer's disease; TRK, tropomyosin receptor kinase; NTRK, neurotrophic tyrosine receptor kinase; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin 3; NT-4, neurotrophin 4; 7, 8-DHF, 7, 8-Dihydroxyflavone; PI3K, phosphatidylinositol-3 kinase; AKT, protein kinase B; ERK, extracellular regulated kinase; PLC-γ1, phospholipase C-γ1; GSK-3β, glycogen synthetase kinase 3β; CREB, cyclic AMP responsive element binding protein; NMDA, N-methyl-D-aspartatic acid; MDA, malondialdehyde; MMP, mitochondrial membrane potential; H_2O_2, hydrogen peroxide; BCL2, B-cell lymphoma 2; SH3, src homology 3; IP3, inositol trisphosphate; DAG, diacylglycerol; long-term potentiation (LTP).

Author contributions

All authors are involved in drafting and revising the manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

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