Delta Secretase and BDNF Signalling in Alzheimer's Disease

Buse Unlu[1] ⓘ **, Sumeyra Ildiz[1]** ⓘ **, Duygu Gezen Ak[1]** ⓘ **, Erdinc Dursun[1]** ⓘ

[1]Department of Neuroscience, Institute of Neurological Sciences, Istanbul University-Cerrahpasa, Istanbul, Turkiye

ORCID ID: B.U. 0000-0003-0078-0951; S.I. 0000-0003-3364-3216; D.G. 0000-0001-7611-2111; E.D. 0000-0003-3701-6674

Cite this article as: Unlu B, Ildiz S, Gezen Ak D, Dursun E. Delta secretase and BDNF signalling in Alzheimer's disease. Experimed 2023; 13(1): 1-7.

ABSTRACT

As one of the major contributors of the central nervous system, neurons require neurotrophic factors, which are synthesized from neighbouring cells, for several cellular processes, such as neuronal survival, growth, and differentiation. Neurotrophic factors are categorized into the neurotrophin family, the neuropoietic cytokines, and the glial cell-derived neurotrophic factor. The neurotrophin family comprises four growth factors: nerve growth factor (NGF), neurotrophin-3 (NT3), neurotrophin-4 (NT4), and brain-derived neurotrophic factor (BDNF). One of the best-known neurotrophic factors is BDNF. Its importance is based on its central role in neuronal survival. Entry of the BDNF into the neurons occurs via TrkB receptors, and it is transported to the cell body along microtubules in axons. As it is known in the brains of Alzheimer's patients, the axonal transport of BDNF is destructed via the hyperphosphorylated tau. There are several causes for the hyperphosphorylation of tau. Among them, delta secretase (δ-secretase), a lysosomal cysteine protease, cleaves both amyloid precursor protein (APP) and tau. It is supposed to play an essential role in tau hyperphosphorylation, particularly in the aging brain. In this review, we focus on the activity of δ-secretase, how it leads to tau hyperphosphorylation, and how it disrupts the axonal transport of BDNF in Alzheimer's disease.

Keywords: BDNF, axonal transport, delta secretase, Alzheimer's disease, APP, tau protein

INTRODUCTION

Secretases Participate in Pathological Mechanisms of Alzheimer's Disease

Alzheimer's Disease is a degenerative brain disease and is one of the most common forms of dementia, causing 60-80% of all cases in the world (1). Dementia is a decline in cognitive ability that interferes with daily life activities (2). This decline occurs because of neuronal damage and destruction in the parts of the brain involved in cognitive functions (1). Studies to reveal the etiopathogenesis of Alzheimer's disease are continuing intensively, both in terms of the negative effects on the individual and his/her relatives and the socioeconomic effects of the disease. The incidence of age-related neurological diseases has increased due to the aging of the world population, and this disease has turned into a direct public health problem today.

As it is well-known, there are two possible hallmark pathologies for Alzheimer's Disease; extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT). Firstly, amyloid plaques are pleated sheets of ss-amyloid peptide (3). Ss-amyloid is generated from the amyloid precursor protein (APP). In the physiological process, APP is cleaved by α and γ secretases. However, cleavage of APP due to the proteolytic action of β and γ secretases creates Ss-amyloid which is known mostly for its pathologic functions (4). Having been recently identified, the role of delta secretase (δ-secretase) on the molecular mechanism is still elusive (5). On the other hand, NFTs are composed of hyperphosphorylated tau protein (4). Tau is a cytoskeletal microtubule-associated protein that is regarded as a microtubule stabilizer (6). When hyperphosphorylated, tau proteins that normally bind to the microtubules leave the microtubule and form neurofibrillary tangles via clumping together (7). In 2014, Zhang et al. found that δ-secretase

Experimed 2023; 13(1): 1-7.

Unlu et al.
Molecular pathogenesis of Alzheimer's Disease

participates in the proteolysis of tau, as well (8). Furthermore, imbalanced distribution and abnormal regulation of the neurotrophic factors refer to one of the pathophysiological mechanisms underlying Alzheimer's disease. Neurotrophic factors have a feedback mechanism with δ-secretase, in which disorganisation destructs the balance and gives rise to the neurodegenerative disease (9).

Brain-Derived Neurotrophic Factor (BDNF) Takes Essential Neural Processes

Neurotrophic factors play an essential role in the proliferation, differentiation, growth, and survival of nerve cells as endogenous proteins and act as crucial ligands. In this way, they perform the functions throughout the developmental stages (10). Besides their role in neurodevelopment and several other neural processes, they are also involved in maintaining neural plasticity in the central and peripheral nervous system (11). According to the structure, target, and signalling pathways, neurotrophic factors are categorized into the neurotrophin family, the neuropoietic cytokines, and the glial cell-derived neurotrophic factor (12). The neurotrophin family comprises four growth factors: Nerve growth factor (NGF), neurotrophin-3 (NT3), neurotrophin-4 (NT4), and BDNF (10). Following the discovery of the nerve growth factor in the early 1950s by Rita Levi-Montalcini,

BDNF was first purified from a pig brain in 1982 (13). Proteolytic cleavage of neurotrophins is required to transform them from an immature synthesized form to a mature form (14). The distinct neurotrophins act via two receptors: Tyrosine-related kinase (Trk) receptors and p75 neurotrophin receptor (p75NTR) (11). BDNF and TrkB receptors were the main focus of studies on neurodegenerative and neuropsychiatric disorders in the last decades. BDNF activity is present in the basal forebrain, cortex, and hippocampus. The localisation also implicates the roles of BDNF in thinking, memory formation, learning, and synaptic plasticity (15). Alterations in expression and the activity of BDNF are reported in many neurodegenerative and neuropsychiatric disorders (16). Studies based on animal models have revealed the alteration of expression levels of BDNF in neuropsychiatric and neurodegenerative disorders (17).

Regulation of BDNF and its Ligand Binding Required for Normal Processing of Nervous Systems

The human *BDNF* gene is located on chromosome 11p14.1, and encodes the BDNF protein (11). Synthesis of BDNF occurs in the soma of neurons and glia and is transported to nerve terminals (18). Precursor protein BDNF (pre-pro-BDNF) is the first synthesized form of BDNF in the endoplasmic reticulum (ER), where the pre-pro-BDNF is folded, and its proteolytic
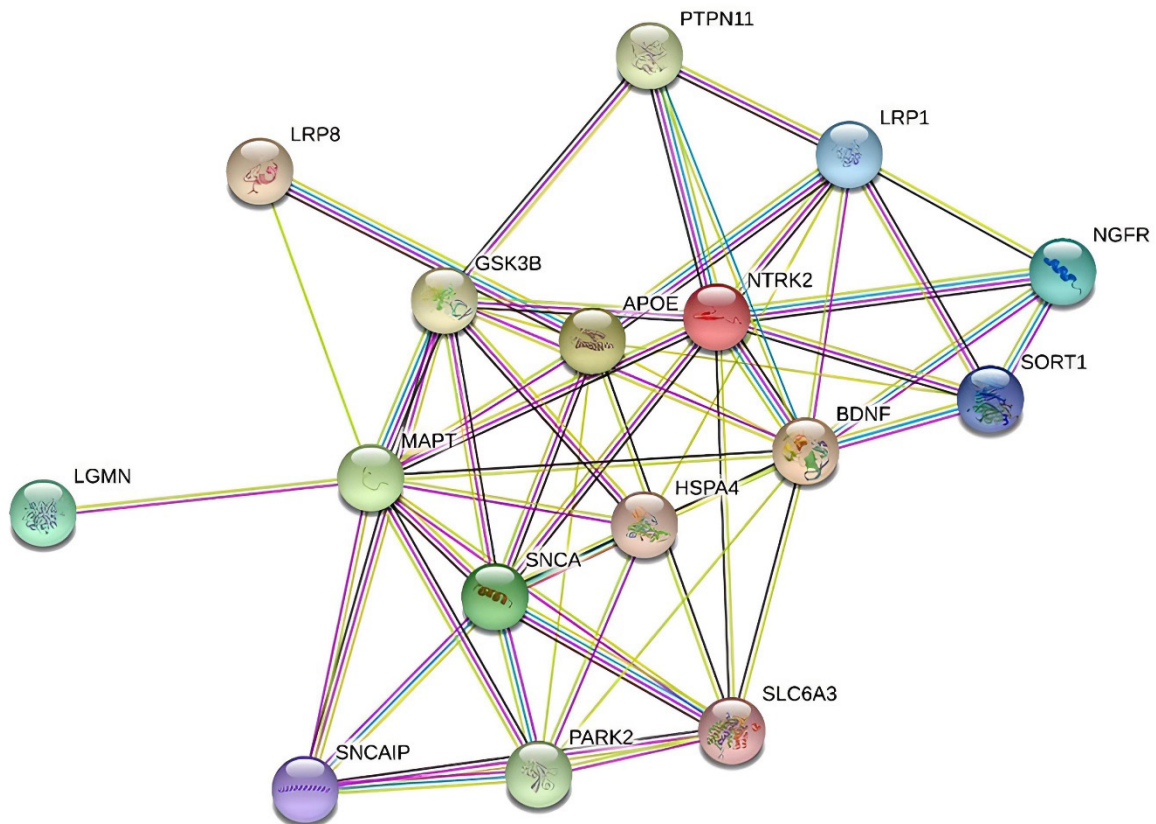

Figure 1. The direct interaction between LGMN (δ-secretase) and MAPT (microtubule associated protein tau), and its indirect interactivity with synuclein alpha (SNCA), apolipoprotein E (ApoE) as shown on the network (STRING).

Unlu et al.
Molecular pathogenesis of Alzheimer's Disease

Experimed 2023; 13(1): 1-7.

cleavage takes place to give rise to the protein precursor form of BDNF (pro-BDNF) (32 kDa) (19). Further proteolytic cleavage of the pro-BDNF consists of either intracellular or extracellular cleavage. The constitutive pathway of the trans-Golgi network involves the intracellular proteolytic cleavage of pro-BDNF, the liberation of furin, the packaging of mature BDNF (mBDNF) into vesicles, and the fusing of the vesicles with plasma membrane (11). On the other hand, the plasmin system and matrix metalloproteases 2 and 9 (MMP2 and MMP9) are involved in the extracellular processing of pro-BDNF, which can act as endogenous ligands directly (20). Influx of Ca^{2+} via N-Methyl-D-aspartate (NMDA) receptors, which is permeable to Ca^{2+}, and voltage-gated Ca^{2+} channels take part in the neural activity based on the regulation of transcription of BDNF (21).

Extracellular pro-BDNF and mBDNF exert distinct physiological responses (19). So, maintaining the proper ratio of pro-BDNF to mBDNF is critical during different neurodevelopmental stages. BDNF binds to two different types of receptors with a distinct affinity. The first receptor is p75NTR, a transmembrane-spanning protein called nerve growth factor receptor (NGFR). It is a member of the tumour necrosis factor receptor (TNFR) superfamily (22). It possesses structurally various domains, including a carboxy-terminal intracellular domain with a flexible juxta membrane adaptor protein-binding region, amino-terminal extracellular domain, and globular death domain (22). Regulation of receptor conformation and ligand binding is mediated by four cysteine-rich domains in the p75 amino-terminal extracellular domain (23).

Another receptor of BDNF is tropomyosin-related kinase B (TrkB), which is one of the Trk receptor families responsible for regulating synaptic strength and plasticity in the adult nervous system (13). The BDNF-TrkB signalling pathway plays a role in various neuronal diseases. The overexpression of BDNF is also suggested to be related to pathological conditions (24). BDNF/TrkB signalling is critical for neural development, survival, differentiation, and plasticity; it is involved in transcription, translation, and protein trafficking, which occur during phases of synaptic development (25). The binding of BDNF to TrkB triggers activation of the downstream mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K) and phospholipase Cγ (PLCγ) pathways (26). The MAPK and PI3K play a critical role in the translation and trafficking of proteins induced by synaptic activity. The PLCγ is responsible for the regulation of intracellular Ca^{2+} that is
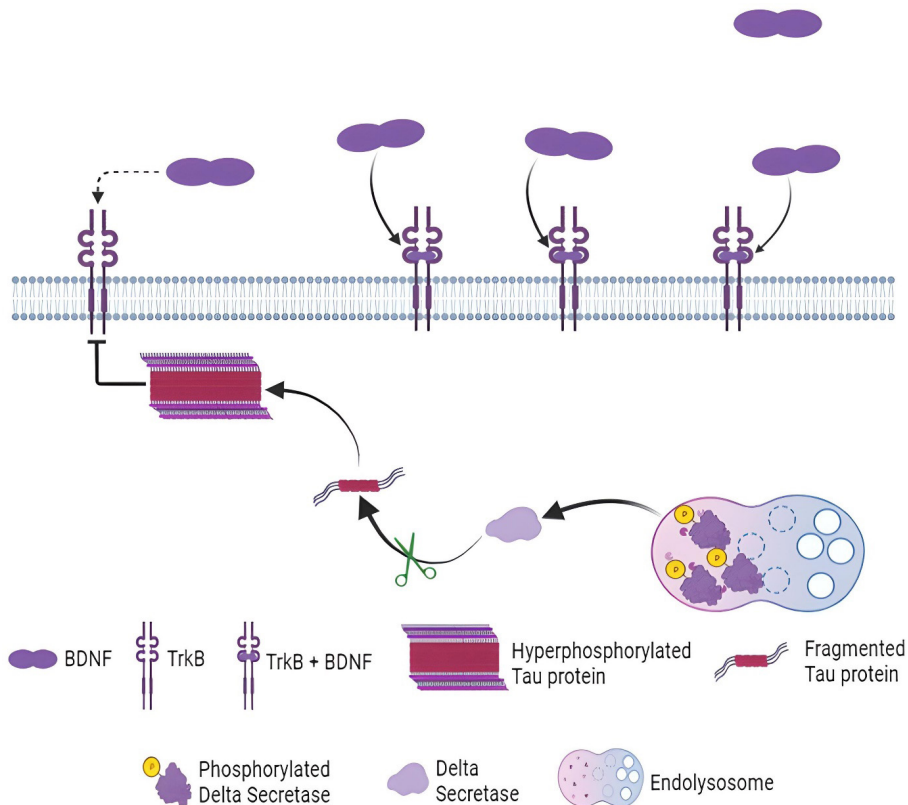

Figure 2. Blockage of the TrkB receptor by hyperphosphorylation of tau via the action of activated delta secretase. Delta secretase is located in the endolysosome as an inactive form. Decreasing the BDNF level lowered the phosphorylation of delta secretase and resulted in the activation of delta secretase. Activated delta secretase cleaves the tau protein. The specific tau fragment is sensitive for phosphorylation. The formed tau fragment tends to bind the TrkB receptor and gives rise to blockage of BDNF binding to the TrkB receptor. BDNF: Brain-derived neurotrophic factor, TrkB: Tyrosine kinase B (drawn by using BioRender).

Experimed 2023; 13(1): 1-7.

Unlu et al.
Molecular pathogenesis of Alzheimer's Disease

involved in transcription via cAMP and protein kinase C (25). The deficiency of BDNF/TrkB signalling is the underlying reason for the neurodegeneration in AD. The release of BDNF to the extracellular space can be acute and/or gradual, so different cellular mechanisms can be activated. The acute increase of BDNF concentration in extracellular space reveals transient activation of the TrkB receptor, which enables dendritic growth and spine morphogenesis. A gradual increase of BDNF concentration in extracellular space reveals sustained activation of the TrkB receptor, which initiates dendritic arborization and spinogenesis (26).

δ-secretase Cleaves APP and Tau

δ-secretase is called asparagine endopeptidase (AEP, also known as Legumain - LGMN), a cysteine proteinase, and plays an important role in cleavage after specific asparagine residue (5). In humans, the *LGMN* gene, which is located on chromosome 14q32.12, encodes δ-secretase (27). The primary location of δ-secretase is endolysosomes (28). Synthesis of δ-secretase occurs as an inactive proenzyme, so it is cleaved in its N- and C-terminal propeptides to be activated under acidic conditions (28). Autocatalytic cleavage of δ-secretase is necessary to transform zymogen pro-δ-secretase, 56 kDa, into its active form (29). Post-translational modifications at distinct pH values drive catalytic activity of δ-secretase. So, the regulation of enzymatic activity of δ-secretase is based on pH. Aging leads to upregulation of δ-secretase in the brain and causes simultaneous cleavage of APP, specifically at N373 and N585 residues and tau (5). Aging also raises the activity of δ-secretase and tau cleavage (8). Furthermore, the S226 residue of the δ-secretase is phosphorylated by a cell cycle kinase called SRPK2 by which phosphorylation of δ-secretase at S226 residue takes place and in turn leads to its translocation into cytoplasm (30). Cleavage of BACE at N294 is carried out by δ-secretase, which accelerates its proteolytic activity and elevates amyloid pathology (31). The BACE N294 fragment that is formed raises the δ-secretase activity (31).

The specific cleavage of APP increases Aβ production and enables senile plaque formation. Cleavage of APP by δ-secretase after N585 residue gives rise to the formation of 586-695 APP fragments, and β- and γ-secretase easily cleaves the fragments to yield Aβ (27). As the cleavage of APP by δ-secretase occurs after N373, it yields the toxic 1-373 APP fragment (27). When the AEP cleavage of APP is blocked, amyloid deposition and production are reduced (5). In addition, hyperphosphorylation of tau arises in Alzheimer's disease (32). 1-368 tau fragment arises from cleavage of tau after N368 by δ-secretase (27). The tau fragment is more susceptible to phosphorylation in comparison with full-length tau (27). Formation of tau fragment leads to disturbance of microtubule assembly activity of tau (8). NFT formation by hyperphosphorylated tau results in Alzheimer's disease pathology. The brain of human wild-type APP/tau transgenic mice was injected by δ-secretase, which facilitates the process of senile plaques and NFT formation in both genders, results in both synaptic and cognitive defects (33). Absence of the δ-secretase activity resulted in the sharp

decrease of NFT pathology and recovery of cognitive functions, as shown by P301S mice (33). Moreover, binding 1-368 tau fragment to TrkB causes blockage of neurotrophic signals and induction of neuronal cell death (9).

BDNF Phosphorylates δ-secretase

Phosphorylation of δ-secretase by BDNF-activated Akt on T322 residues regulates its lysosomal translocation and inactivation (34). A decrease in BDNF levels causes weakened δ-secretase phosphorylation, which activates it, and its translocation into cytoplasm arises (35). On the other hand, tau, especially the δ-secretase–truncated tau N368 fragment, specifically binds to TrkB receptors, an interaction that BDNF antagonizes. Tau N368 strongly interacts with the TrkB receptor C-terminal tail, a site of PLC-γ1 binding. This action is down-regulated by the presence of BDNF (36). Binding of tau N368 fragment to TrkB receptors evokes blockage of neurotrophic signals, which triggers cell death (34). BDNF or TrkB receptors knockout gives rise to declined phosphorylation of δ-secretase on T322 residue, contributes to cleavage of tau 368 residue, occurrence of Alzheimer's disease pathology and cognitive abnormalities (9).

Transcription factor C/EBPβ plays an important role in the age-dependent augmentation of δ-secretase activity in the brain (37). Upregulation of C/EBPβ is correlated to deficiency of BDNF/TrkB, which exacerbates inflammatory cytokines and triggers the JAK2/STAT3 pathway. Upraised δ-secretase expression and fragmentations of APP and tau take place in return (34). BDNF-provoked Akt phosphorylation of δ-secretase at T322 residue results in its inactivation and it resumes locating in lysosome (35). Blockage of BDNF neurotrophic signals is via cleavage of TrkB receptor at N365 and N486/489 residues on the extracellular and intracellular domain (ICD), respectively, by δ-secretase (38). Depletion of C/EBPβ led to inhibition of the expressions of APP, tau and δ-secretase, and restrained APP and tau cleavage, and resulted in alleviation of Alzheimer's disease pathology from 3xTg mice (33). Alzheimer's disease pathology was diminished in δ-secretase knockout 3xTg mice (33). As has been proven, C/EBPβ manages Alzheimer's disease pathology by affecting the δ-secretase activity. Depletion of BDNF in primary neuronal culture induces BDNF/TrkB signalling and increases inflammatory cytokines, stimulates the JAK2/STAT3 pathway and transcription factor C/EBPβ, and results in high δ-secretase expression (33).

δ-secretase Cleaves Inhibitor-2 Protein Phosphatase-2A (I2PP2A) and Results in Abnormal Hyperphosphorylation of Tau

Under acidic conditions, another protein cleaved by δ-secretase is inhibitor-2 protein phosphatase-2A (I_2^{PP2A}) at Asn-175 neuronal cytoplasm, which produces I_{2NTF} and I_{2CTF} (39, 40). I_2^{PP2A} is a SET protein, is also called template-activating factor (TAF1β), which is found in the neuronal cytoplasm and is also an inhibitor of PP2A (41). The level of I_2^{PP2A} in the brains of Alzheimer's Disease patients is higher than in normal brains (42). PP2A accounts for ~70% of tau protein phosphatase activity in the adult human

Unlu et al.
Molecular pathogenesis of Alzheimer's Disease

Experimed 2023; 13(1): 1-7.

brain (39). Inhibition of PP2A phosphatase can change the balance between phosphorylation and dephosphorylation of tau protein, so results in increasing tau phosphorylation (40). Inhibition of PP2A activity occurs due to the interaction of the N- and C- terminal fragments of I_2^{PP2A}, which are cleavage products I_{2NTF} and I_{2CTF} (39, 40). Translocation of I_2^{PP2A} from the neuronal nucleus to the cytoplasm with the co-localization of PP2A results in abnormal hyperphosphorylation of tau by the inhibiting of PP2A phosphatase in the brains of Alzheimer's disease patients due to δ-secretase (39).

Activity of δ-secretase Might Engage Axonal Degeneration and Prompt Dislocation of BDNF

A variety of substances are shuttled bidirectionally throughout the axon microtubule of neurons. The ATP-dependent process is called axonal transport (43). The kinesin superfamily of motor proteins takes part in transporting substances in anterograde transport (44). In addition, cytoplasmic dynein participates in retrograde transport. Retrograde axonal transport plays a vital role in essential processes such as neurotrophic factor signalling, autophagy, and lysosomal degradation (43). Axonal transport provides intracellular trafficking over a long distance which is highly regulated to supply the normal function of neurons and cell viability (43).

Tau plays an essential role in the function of normal axonal transport (45). The binding capacity of tau and its ability to stabilize microtubules declines with the phosphorylation of tau (46). Glycogen synthase kinase-3 (GSK-3) is considered to be the primary kinase of phosphorylation of tau (32). Augmented tau phosphorylation slows down tau transport in neurons, and impeding tau phosphorylation by GSK-3 decreases its motion (47). The importance of tau is connected to its major role in the normal axonal transport mechanism (45). Tau effectuates the outcome of Aβ on axonal transport with an unknown mechanism (45). Aβ-induced malfunction in axonal transport is blocked by dwindling endogenous tau (48). So, it is assumed that δ-secretase might participate in axonal degeneration by interacting with tau (Figure 1).

The activation of TrkB on axon terminals by BDNF gives rise to the stimulation of signal pathways connected to neuronal survival (45). BDNF-TrkB complex emergence is followed by their endocytosis from the plasma membrane, and microtubules in the axons mediate their retrograde transport (49). Impairment of BDNF-mediated TrkB axonal transport occurs in Alzheimer's disease transgenic mouse neurons (50). Although the exact mechanism underlying axonal transport of the BDNF-TrkB still remains mysterious, it is claimed that Aβ oligomers deteriorate retrograde transport of BDNF (45). So, the effect of δ-secretase on the axonal transport of the BDNF-TrkB may be based on its role in Aβ pathology (Figure 2).

CONCLUSION

In this review, we discussed the involvement of δ-secretase in altered BDNF/TrkB signal mechanisms, its role in the pathophysiology of Alzheimer's disease. In addition, we discussed the possible contribution of BDNF downregulation to the deterioration of Alzheimer's disease. As detailed above, in BDNF downregulation, there are many connected processes, including the activity of δ-secretase and the hindering activity of the trophic factor by blockage of the TrkB receptor. Thus, even though the characterization of the relationship between BDNF and disease symptoms is undeniably challenging on account of the multiple processes which regulate the amount of BDNF in tissues, elaborate mechanisms underlying the downregulation and deteriorated axonal transport of BDNF by the activity of δ-secretase should be elucidated to provide more potent therapeutic approaches. In addition, understanding the function of δ-secretase in Alzheimer's disease pathology, the association between the destruction of axonal transport of BDNF and the role of δ-secretase in tau hyperphosphorylation might unravel one part of the molecular mechanism of Alzheimer's disease pathology, in addition to other neurodegenerative and neuropsychiatric disorders. Contributing to axonal degeneration, δ-secretase supports BDNF dislocation, while BDNF has the potential to phosphorylate δ-secretase, which is necessary for its lysosomal translocation. The elusive direct and indirect roles of δ-secretase in the pathological mechanism of neurodegenerative diseases, in particular Alzheimer's disease, may be revealed through further research.

REFERENCES

1. Association As. 2016 Alzheimer's disease facts and figures. Alzheimers Dement 2016; 12(4): 459-509. [CrossRef]
2. Kumar A, Sidhu J, Goyal A, Tsao JW, Doerr C. Alzheimer Disease (Nursing). StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.
3. Ovsepian SV, O'Leary VB, Zaborszky L, Ntziachristos V, Dolly JO. Amyloid plaques of Alzheimer's Disease as hotspots of glutamatergic activity. Neuroscientist 2019; 25(4): 288-97. [CrossRef]
4. Kuznetsov IA, Kuznetsov AV. How the formation of amyloid plaques and neurofibrillary tangles may be related: a mathematical modelling study. Proc Math Phys Eng Sci 2018; 474(2210): 20170777. [CrossRef]
5. Zhang Z, Song M, Liu X, Su Kang S, Duong DM, Seyfried NT, et al. Delta-secretase cleaves amyloid precursor protein and regulates the pathogenesis in Alzheimer's disease. Nat Commun 2015; 6: 8762. [CrossRef]
6. Rodríguez-Martín T, Cuchillo-Ibáñez I, Noble W, Nyenya F, Anderton BH, Hanger DP. Tau phosphorylation affects its axonal transport and degradation. Neurobiol Aging 2013; 34(9): 2146-57. [CrossRef]

Experimed 2023; 13(1): 1-7.

Unlu et al.
Molecular pathogenesis of Alzheimer's Disease

7. Ashrafian H, Zadeh EH, Khan RH. Review on Alzheimer's disease: Inhibition of amyloid beta and tau tangle formation. Int J Biol Macromol 2021; 167: 382-94. [CrossRef]

8. Zhang Z, Song M, Liu X, Kang SS, Kwon IS, Duong DM, et al. Cleavage of tau by asparagine endopeptidase mediates the neurofibrillary pathology in Alzheimer's disease. Nat Med 2014; 20(11): 1254-62. [CrossRef]

9. Xiang J, Wang ZH, Ahn EH, Liu X, Yu SP, Manfredsson FP, et al. Delta-secretase-cleaved Tau antagonizes TrkB neurotrophic signalings, mediating Alzheimer's disease pathologies. Proc Natl Acad Sci U S A 2019; 116(18): 9094-102. [CrossRef]

10. Chen SD, Wu CL, Hwang WC, Yang DI. More Insight into BDNF against neurodegeneration: Anti-apoptosis, anti-Oxidation, and suppression of autophagy. Int J Mol Sci 2017; 18(3): 545 [CrossRef]

11. Miranda-Lourenço C, Ribeiro-Rodrigues L, Fonseca-Gomes J, Tanqueiro SR, Belo RF, Ferreira CB, et al. Challenges of BDNF-based therapies: From common to rare diseases. Pharmacol Res 2020; 162: 105281. [CrossRef]

12. Boyd JG, Gordon T. Neurotrophic factors and their receptors in axonal regeneration and functional recovery after peripheral nerve injury. Mol Neurobiol 2003; 27(3): 277-324. [CrossRef]

13. Huang EJ, Reichardt LF. Trk receptors: Roles in neuronal signal transduction. Annu Rev Biochem 2003; 72: 609-42. [CrossRef]

14. Teng KK, Felice S, Kim T, Hempstead BL. Understanding proneurotrophin actions: Recent advances and challenges. Dev Neurobiol 2010; 70(5): 350-9. [CrossRef]

15. Yamada K, Nabeshima T. Brain-derived neurotrophic factor/TrkB signaling in memory processes. J Pharmacol Sci 2003; 91(4): 267-70. [CrossRef]

16. Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol 2009; 5(6): 311-22. [CrossRef]

17. Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T. Mouse and rat BDNF gene structure and expression revisited. J Neurosci Res 2007; 85(3): 525-35. [CrossRef]

18. Lessmann V, Brigadski T. Mechanisms, locations, and kinetics of synaptic BDNF secretion: An update. Neurosci Res 2009; 65(1): 11-22. [CrossRef]

19. Kowiański P, Lietzau G, Czuba E, Waśkow M, Steliga A, Moryś J. BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. Cell Mol Neurobiol 2018; 38(3): 579-93. [CrossRef]

20. Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S, et al. Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 2004; 306(5695): 487-91. [CrossRef]

21. Ghosh A, Carnahan J, Greenberg ME. Requirement for BDNF in activity-dependent survival of cortical neurons. Science 1994; 263(5153): 1618-23. [CrossRef]

22. Malik SC, Sozmen EG, Baeza-Raja B, Le Moan N, Akassoglou K, Schachtrup C. In vivo functions of p75(NTR): challenges and opportunities for an emerging therapeutic target. Trends Pharmacol Sci 2021; 42(9): 772-88. [CrossRef]

23. Roux PP, Barker PA. Neurotrophin signaling through the p75 neurotrophin receptor. Prog Neurobiol 2002; 67(3): 203-33. [CrossRef]

24. Lee-Hotta S, Uchiyama Y, Kametaka S. Role of the BDNF-TrkB pathway in KCC2 regulation and rehabilitation following neuronal injury: A mini review. Neurochem Int 2019; 128: 32-8. [CrossRef]

25. Yoshii A, Constantine-Paton M. Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. Dev Neurobiol 2010; 70(5): 304-22. [CrossRef]

26. Guo W, Nagappan G, Lu B. Differential effects of transient and sustained activation of BDNF-TrkB signaling. Dev Neurobiol 2018; 78(7): 647-59. [CrossRef]

27. Zhang Z, Tian Y, Ye K. δ-secretase in neurodegenerative diseases: Mechanisms, regulators and therapeutic opportunities. Transl Neurodegener 2020; 9: 1. [CrossRef]

28. Dall E, Brandstetter H. Structure and function of legumain in health and disease. Biochimie 2016; 122: 126-50. [CrossRef]

29. Liu C, Sun C, Huang H, Janda K, Edgington T. Overexpression of legumain in tumors is significant for invasion/metastasis and a candidate enzymatic target for prodrug therapy. Cancer Res 2003; 63(11): 2957-64.

30. Wang ZH, Liu P, Liu X, Manfredsson FP, Sandoval IM, Yu SP, et al. Delta-secretase phosphorylation by srpk2 enhances its enzymatic activity, provoking pathogenesis in Alzheimer's Disease. Mol Cell 2017; 67(5): 812-25.e5. [CrossRef]

31. Xia Y, Wang ZH, Zhang Z, Liu X, Yu SP, Wang JZ, et al. Delta- and beta- secretases crosstalk amplifies the amyloidogenic pathway in Alzheimer's disease. Prog Neurobiol 2021; 204: 102113. [CrossRef]

32. Hanger DP, Anderton BH, Noble W. Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. Trends Mol Med 2009; 15(3): 112-9. [CrossRef]

33. Kang SS, Ahn EH, Ye K. Delta-secretase cleavage of Tau mediates its pathology and propagation in Alzheimer's disease. Exp Mol Med 2020; 52(8): 1275-87. [CrossRef]

34. Liao J, Chen C, Ahn EH, Liu X, Li H, Edgington-Mitchell LE, et al. Targeting both BDNF/TrkB pathway and delta-secretase for treating Alzheimer's disease. Neuropharmacology 2021; 197: 108737. [CrossRef]

35. Wang ZH, Wu W, Kang SS, Liu X, Wu Z, Peng J, et al. BDNF inhibits neurodegenerative disease-associated asparaginyl endopeptidase activity via phosphorylation by AKT. JCI Insight 2018; 3(16): e99007 [CrossRef]

36. Huuha AM, Norevik CS, Moreira JBN, Kobro-Flatmoen A, Scrimgeour N, Kivipelto M, et al. Can exercise training teach us how to treat Alzheimer's disease? Ageing Res Rev 2022; 75: 101559. [CrossRef]

37. Wang ZH, Gong K, Liu X, Zhang Z, Sun X, Wei ZZ, et al. C/EBPβ regulates delta-secretase expression and mediates pathogenesis in mouse models of Alzheimer's disease. Nat Commun 2018; 9(1): 1784. [CrossRef]

38. Xia Y, Wang ZH, Liu P, Edgington-Mitchell L, Liu X, Wang XC, et al. TrkB receptor cleavage by delta-secretase abolishes its phosphorylation of APP, aggravating Alzheimer's disease pathologies. Mol Psychiatry 2021; 26(7): 2943-63. [CrossRef]

39. Basurto-Islas G, Grundke-Iqbal I, Tung YC, Liu F, Iqbal K. Activation of asparaginyl endopeptidase leads to Tau hyperphosphorylation in Alzheimer disease. J Biol Chem 2013; 288(24): 17495-507. [CrossRef]

40. Basurto-Islas G, Gu JH, Tung YC, Liu F, Iqbal K. Mechanism of tau hyperphosphorylation involving lysosomal enzyme asparagine endopeptidase in a mouse model of brain ischemia. J Alzheimers Dis 2018; 63(2): 821-33. [CrossRef]

41. Madeira A, Pommet JM, Prochiantz A, Allinquant B. SET protein (TAF1beta, I2PP2A) is involved in neuronal apoptosis induced by an amyloid precursor protein cytoplasmic subdomain. Faseb J 2005; 19(13): 1905-7. [CrossRef]

42. Liu GP, Wei W, Zhou X, Zhang Y, Shi HH, Yin J, et al. I(2)(PP2A) regulates p53 and Akt correlatively and leads the neurons to abort apoptosis. Neurobiol Aging 2012; 33(2): 254-64. [CrossRef]

43. Sleigh JN, Rossor AM, Fellows AD, Tosolini AP, Schiavo G. Axonal transport and neurological disease. Nat Rev Neurol 2019; 15(12): 691-703. [CrossRef]

Unlu et al.
Molecular pathogenesis of Alzheimer's Disease

Experimed 2023; 13(1): 1-7.

44. Terenzio M, Schiavo G, Fainzilber M. Compartmentalized signaling in neurons: from cell biology to neuroscience. Neuron 2017; 96(3): 667-79. [CrossRef]

45. Ye X, Tai W, Zhang D. The early events of Alzheimer's disease pathology: From mitochondrial dysfunction to BDNF axonal transport deficits. Neurobiol Aging 2012; 33(6): 1122.e1-10. [CrossRef]

46. Brandt R, Léger J, Lee G. Interaction of tau with the neural plasma membrane mediated by tau's amino-terminal projection domain. J Cell Biol 1995; 131(5): 1327-40. [CrossRef]

47. Cuchillo-Ibanez I, Seereeram A, Byers HL, Leung KY, Ward MA, Anderton BH, et al. Phosphorylation of tau regulates its axonal transport by controlling its binding to kinesin. Faseb J 2008; 22(9): 3186-95. [CrossRef]

48. Vossel KA, Zhang K, Brodbeck J, Daub AC, Sharma P, Finkbeiner S, et al. Tau reduction prevents Aβ-induced defects in axonal transport. Science 2010; 330(6001): 198. [CrossRef]

49. Segal RA. Selectivity in neurotrophin signaling: Theme and variations. Annu Rev Neurosci 2003; 26: 299-330. [CrossRef]

50. Poon WW, Blurton-Jones M, Tu CH, Feinberg LM, Chabrier MA, Harris JW, et al. β-Amyloid impairs axonal BDNF retrograde trafficking. Neurobiol Aging 2011; 32(5): 821-33. [CrossRef]