J Lipid Atheroscler. 2024 May;13(2):122-138
https://doi.org/10.12997/jla.2024.13.2.122
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Review

Check for updates

BDNF Signaling in Vascular Dementia and Its Effects on Cerebrovascular Dysfunction, Synaptic Plasticity, and Cholinergic System Abnormality

Juhyun Song

Department of Anatomy, Chonnam National University Medical School, Hwasun, Korea

OPEN ACCESS

Received: Oct 7, 2023
Revised: Nov 29, 2023
Accepted: Dec 19, 2023
Published online: Feb 22, 2024

Correspondence to
Juhyun Song
Department of Anatomy, Chonnam National University Medical School, 264 Seoyang-ro, Hwasun-eup, Hwasun 58128, Korea.
Email: juhyunsong@chonnam.ac.kr

ORCID iDs
Juhyun Song
https://orcid.org/0000-0002-9165-8507

Funding
This study was supported by the National Research Foundation (NRF) of Korea (grant number: 2022R1A2C1006125).

Conflict of Interest
Juhyun Song is the editor of Journal of Lipid and Atherosclerosis. However, she was not involved in the peer reviewer selection, evaluation or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement
The datasets generated during and/or analyzed during the current study are available

ABSTRACT

Vascular dementia (VaD) is the second most common type of dementia and is characterized by memory impairment, blood–brain barrier disruption, neuronal cell loss, glia activation, impaired synaptic plasticity, and cholinergic system abnormalities. To effectively prevent and treat VaD a good understanding of the mechanisms underlying its neuropathology is needed. Brain-derived neurotrophic factor (BDNF) is an important neurotrophic factor with multiple functions in the systemic circulation and the central nervous system and is known to regulate neuronal cell survival, synaptic formation, glia activation, and cognitive decline. Recent studies indicate that when compared with normal subjects, patients with VaD have low serum BDNF levels and that BDNF deficiency in the serum and cerebrospinal fluid is an important indicator of VaD. Here, we review current knowledge on the role of BDNF signaling in the pathology of VaD, such as cerebrovascular dysfunction, synaptic dysfunction, and cholinergic system impairment.

Keywords: Vascular dementia; Brain-derived neurotrophic factor; Cerebrovascular disorders; Neuronal plasticity; Cholinergic neurons

INTRODUCTION

Dementia prevalence is quickly rising and globally, the number of patients with dementia is projected to reach 100 million by the year 2050.[1,2] The cost of caring for those with dementia is gradually increasing and causing a high economic burden, worldwide.[3] Alzheimer's disease (AD) and vascular dementia (VaD) are the most common types of dementia.[4] Studies indicate that at least 50% of patients with dementia have neurovascular problems accompanied by neurodegenerative pathology.[4] Cerebrovascular dysfunction is an important sign of dementia-associated cognitive decline and neuropsychiatric symptoms.[5] VaD mainly results from hypoperfusion, hypertension, and stroke, and its pathological features include blood–brain barrier (BBB) disruption, cognitive decline, neuroinflammation, and cholinergic system impairment.[6-8] Brain-derived neurotrophic factor (BDNF), a neurotrophic factor, is closely associated with various neuropathological and neuropsychiatric diseases, including VaD, ischemia, depression, anxiety, and AD.[9-11] Several studies indicate that BDNF influences neuronal cell survival, vascular dysfunction, glia activation, neurite outgrowth, synaptic formation, neurotransmitter secretion, and neurogenesis.[12-14] The role of BDNF signaling in

from the corresponding author on reasonable request.

the brain during VaD needs to be re-examined. Here, we review current knowledge about the role of BDNF signaling in VaD, which is characterized by neuropathological features, including cerebrovascular dysfunction, synaptic dysfunction, and cholinergic system abnormalities.

VaD

VaD is the second most common type of dementia[15,16] and accounts for about 20% and 30% of all dementia cases in Western and Asia countries, respectively.[17-19] A recent report estimates that VaD will increase by 40% over the next 30 years.[8] VaD is characterized by a gradual decline in cognitive function because of reduced blood supply to the brain (hypoperfusion),[8] sporadic cerebral small vessel disease, arterial hypertension, atherosclerosis, ischemic stroke, or hemorrhagic brain injury by cerebrovascular diseases.[20-23] Approximately 15% of VaD cases are associated with extracranial artery occlusion [24] and cerebral microinfarction has been reported as an important cause of VaD and AD.[25] The atherosclerotic cerebrovascular mechanisms of primary VaD differ from those of neurodegeneration and age-related loss of neurofibril networks and synaptic dysfunction.[24]

The main pathological features of VaD include BBB disruption, impaired neurovascular coupling, neurodegeneration, cognitive impairment accompanied by language disorder, impaired visuospatial skill, personality disorder, cerebral atrophy, motor dysfunction, inflammation, and cholinergic deficiency.[6,7,26-28] In VaD, BBB disruption is associated with abnormal neurovascular coupling, micro-blood vessel infarction, neural vasculature, glia activation, neuroinflammation, and cerebral hypoperfusion.[29,30] VaD-associated BBB disruption has been associated with chronic cerebral hypoxia, which leads to increased BBB permeability.[31] Moreover, subcortical vascular impairments interfere with the frontostriatal brain circuit, attention ability, and information processing.[15,32] Small vessel diseases, such as micro-infarcts and lacunar infarcts are reported to lead to the development of VaD.[33] In the central nervous system (CNS), the cholinergic system is vulnerable to vascular damage, and cholinergic deficiency is observed in patients with VaD,[34] suggesting that a lack of cholinergic neurotransmitters results in memory loss.[35] VaD has been strongly associated with several genetic polymorphisms, including in the genes, *APOE*, *ACT*, *ACE*, *MTHFR*, *PON1*, *APOE ε4*, and *PSEN-1*.[36-39]

Based on the vascular impairment of cognition classification consensus study (VICCCS) guidelines, VaD can be classified into four subtypes: post-stroke dementia, multi-infarct dementia, subcortical ischemic VaD, and mixed dementia.[40,41] Based on neuroimaging data, the VaD brain exhibits atrophy, abnormal ventricular size, white matter degeneration, small infarction, and hemorrhaging.[40,42] In VaD, white matter degeneration is critical because of its relationship with cognitive decline.[43,44] White matter degeneration includes myelin sheath loss and arteriolosclerosis caused by lacunar infarcts, microinfarcts, and axonal dysfunction.[45] Chronic cerebral hypoxia, which causes oligodendrocyte dysfunction and ultimately, impaired myelin sheath formation has been implicated in VaD-associated cognitive decline.[46-49]

Judging from its pathological features, including cerebrovascular and synaptic dysfunction, abnormal ventricular size, myelin sheath impairment, brain atrophy, memory loss, and cholinergic neuronal loss, VaD is common and complex. Here, we review the features of VaD with a focus on BBB disruption, increased neuroinflammation, poor synaptic plasticity, as well as the impairment of the neurovasculature, the cholinergic system, and neurogenesis.

https://doi.org/10.12997/jla.2024.13.2.122

JLA Journal of Lipid and Atherosclerosis

BDNF IN VaD

1. BDNF signaling

BDNF is a neurotrophic factor that influences various cellular processes in the CNS, such as cell survival, neuronal differentiation, gene expression, neurite outgrowth, and synaptic plasticity.[50,51] In rodents and humans, BDNF is differentially expressed in several brain regions, including the amygdala, cerebellum, hippocampus, dentate gyrus, and cerebral cortex.[52] In the brain, it controls excitatory and inhibitory synaptic transmission and the synaptic plasticity of γ-aminobutyric acid-ergic (GABAergic) and glutamatergic neurons.[53] BDNF can cross the BBB[54] and its serum levels correlate positively with its levels in brain tissues.[55]

During BDNF synthesis, its precursor, proBDNF, is cleaved into mature BDNF (mBDNF) by various proteases, including matrix metalloproteases before being released.[56,57] By binding to the p75 neurotrophin receptor (NTR), ProBDNF can affect cell death and apoptotic response, whereas by binding to the tropomyosin-related kinase B (TrkB) receptor, its mature form can influence neuronal survival.[58]

The levels of BDNF in the CNS are strongly associated with neuropathological and neuropsychiatric symptoms, including seizures, epilepsy, ischemic dementia, depression, anxiety, cognitive impairment, and hypoglycemia.[9,10] When compared with the controls, decreased cerebrospinal fluid BDNF levels have been observed in cases of VaD, mild cognitive impairment, and AD.[11,59-61] Reduced blood BDNF levels have been observed in patients with mild cognitive impairment[62] or impaired episodic memory performance.[63] Several studies indicate that BDNF enhances presynaptic axon terminal activity and influences neurogenesis, dendritic outgrowth, and synaptic plasticity (including the induction of long-term potentiation [LTP] through intercellular signaling pathways like glycogen synthase kinase-3β (GSK3β) signaling), and the maintenance of noradrenergic innervations. ERK1/2 signaling and cAMP-response element-binding protein (CREB) signaling,[64-71] leading to the enhancement of depressive symptoms[72] and cognitive function.[73,74] BDNF has been reported to regulate the control of synaptic strength, including by regulating N-methyl-D-aspartate (NMDA) receptor expression and trafficking[75] and dendritic spine complexity,[71] thereby influencing synaptic consolidation and memory formation.[14] **Fig. 1** shows BDNF/TrkB signaling pathway in vascular system (**Fig. 1**). Below, we summarize the critical roles of BDNF in VaD.

2. BDNF and cerebrovascular dysfunction VaD

Cerebrovascular dysfunction is a major neuropathology in patients with VaD.[76-78] Because neurons are not in direct contact with blood vessels, they form a unique, stable structural network called the neurovascular unit with glia.[79] The neurovascular unit, which is made up of pericytes, astrocytes, brain endothelial cells, vascular smooth muscle cells, and neurons[79] promotes cerebral blood flow, which relies on a neuronal metabolic interaction called neurovascular coupling.[80] The neurovascular unit influences the homeostasis of the BBB,[81] a physiological barrier composed of pericytes, astrocytes, and brain endothelial cells,[80] which protects the neurovascular system by preventing toxic agents and pathogens in blood circulation from entering the brain parenchyma.[81,82] However, several factors, including hyperglycemia, insulin resistance, small vessel disease, and hypertension can disrupt the BBB.[83] Increased BBB permeability is common in patients with VaD.[84] BBB disruption causes neuroinflammation, glial activation, memory loss, and brain edema.[85,86] Pathological remodeling of the vasculature and microvasculature following atherosclerosis and stroke disrupts blood vessel integrity and results in abnormal and impaired blood supply to the

https://doi.org/10.12997/jla.2024.13.2.122

JLA Journal of Lipid and Atherosclerosis

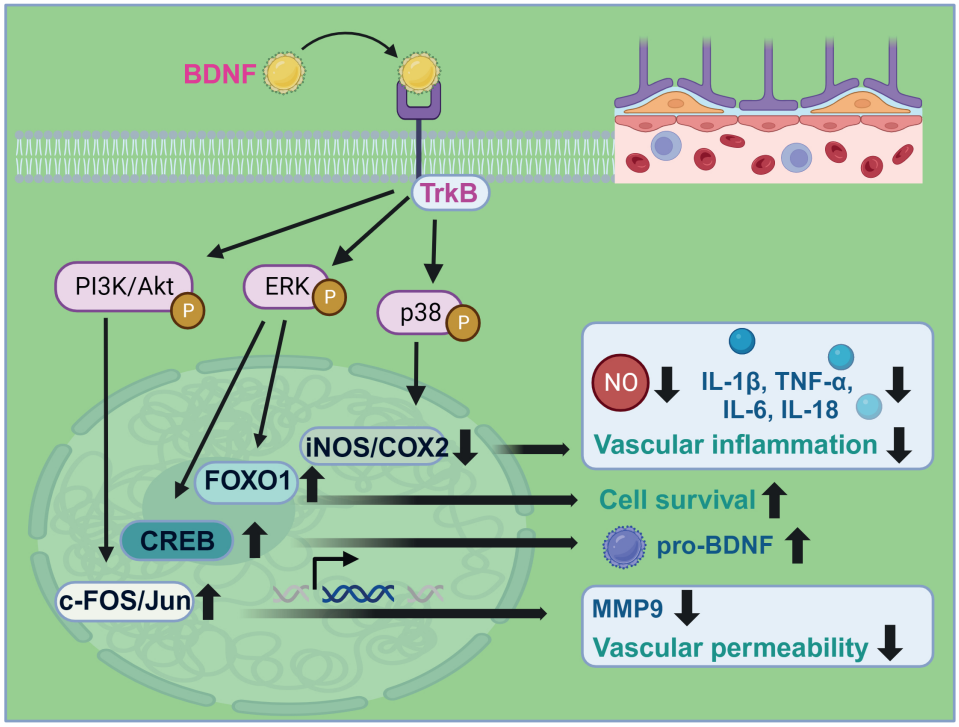

Fig. 1. BDNF/TrkB signaling in vascular system.
BDNF activates PI3K/Akt phosphorylation by binding TrkB receptor, and subsequently reduces MMP9 secretion through the regulation of c-FOS/Jun transcription, and ultimately suppresses vascular permeability. Also, BDNF increases ERK phosphorylation, and subsequently promotes FOXO1 and CREB transcription, and finally boosts cell survival and the production of pro-BDNF by binding TrkB receptor. BDNF/TrkB signaling inhibits p38 phosphorylation, iNOS, and COX2 transcription, finally contributes to the reduction of vascular inflammation by suppressing the secretion of NO, and pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and IL-18.
BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase B; PI3K, phosphoinositide 3-kinases; MMP9, matrix metallopeptidase 9; ERK, extracellular signal-regulated kinase; FOXO1, Forkhead box O1; CREB, cAMP-response element-binding protein; iNOS, inducible nitric oxide synthase; COX2, cyclooxygenase-2; NO, nitric oxide; IL, interleukin; TNF, tumor necrosis factor.

brain, leading to VaD.[87] Several studies have shown that VaD prevalence is significantly associated with cerebrovascular diseases, including stroke and small vessel disease,[23,46,88] which may in turn, cause VaD-associated cognitive impairment.[89]

Among the glial cells, astrocytes, which have terminal processes called astrocyte end-feet, surround blood vessels in the brain, thereby contributing to BBB integrity and promoting neurovascular coupling.[90] Astrocytes are in physical contact with endothelial cells and their end-feet cover the outer surface of the endothelium and surround the cerebrovasculature.[91] The astrocyte end-feet, which cover up to 99% of the cerebrovascular surface, influence angiogenesis and mediate neurovascular coupling.[92] Astrocytes communicate with neurons, oligodendrocytes, microglia, pericyte, and brain endothelial cells and their cellular processes surround synaptic terminals and modulate neuronal activity.[93] Based on their cell function, there are two types of reactive astrocytes, the A1 and A2 astrocytes.[94] Following brain injury, astrocyte activation mediates cerebrovascular recovery.[95] They also defend the brain against oxidative stress[96] and maintain ion homeostasis[97] and neurogenesis by modulating synapse formation.[98] Recent studies show that astrocytes contribute to the maintenance of BBB integrity by interacting with endothelial cells and pericytes[99] and by promoting the expression of tight junction proteins.[100]

https://doi.org/10.12997/jla.2024.13.2.122

Astrocytes may modulate arteriolar tone via a constant low-level efflux of prostaglandin-E2 from astrocyte end-feet.[101] Moreover, interneurons, such as GABAergic interneurons, are crucial for the maintenance of neurovascular coupling homeostasis in the brain cortex via the secretion of several neurotransmitters.[102,103]

Microglia, a type of glial cells that modulate inflammatory cytokine secretion and contribute to neuronal loss, induce oligodendrocytogenesis, white matter integrity, and demyelination, which are involved in memory impairment.[104,105] The loss of white matter integrity and the development of white matter hyperintensities (WMH) are strongly linked to microglia polarization and activity.[106] WMH is a marker of small vessel cerebrovascular disease and is associated with mild cognitive impairment, cognitive decline,[107,108] and dementia development.[109] WMH is associated with demyelination, axonal loss, microglia activation, and cerebral amyloid angiopathy[110] and it contributes to VaD-associated cognitive impairment.[111]

BDNF is known to modulate cerebrovascular dysfunction, such as BBB abnormality, astrocyte reactivation, and microglia activation.[112,113]

Following ischemic brain injury, BDNF promotes vascular remodeling and neovascularization by modulating the migration of neuronal precursors,[114,115] and accelerates revascularization by modulating vascular endothelial growth factor expression.[115] Recent findings indicate that after chronic cerebral hypoperfusion, ERK–CREB–BDNF signaling enhances memory function by improving cerebrovascular function (**Fig. 1**).[116] BDNF release from endothelial cells also promotes neuronal migration via the activation of p75NTR and astrocyte function.[117] It can also improve WMH-associated cognitive impairment by inhibiting hippocampal neuronal loss[118] and preventing BBB permeability and leakage during brain injury.[119]

BDNF and TrkB are expressed in neurons and astrocytes and BDNF–TrkB signaling is a major mediator of astrocyte–neuron communication that influences astrocyte morphogenesis and maturation.[120] Astrocyte-secreted factors include metabolic substrates, neurotransmitters, and their precursors, and trophic factors, such as neurotrophins[121] and BDNF.[122,123]

Microglia are key CNS immune cells that make up 10%–15% of CNS cells.[124] After acute brain injury, reactive microglia modulate sustained inflammation, neuronal cell survival, and BBB disruption.[125] Reactive microglia and astrocytes are thought to release BBB permeability-associated molecules, including MMPs and nitric oxide, thereby inducing BBB leakage.[100,125] BDNF can modulate microglial activation and polarization, which influences the secretion of anti-inflammatory cytokines.[126,127] Collectively, these results indicate that BDNF signaling regulates astrocytes and glial cell function, neuronal function, cell–cell communication, and sustained BBB integrity, thereby improving cerebrovascular dysfunction (**Fig. 2**).

3. BDNF signaling in the cholinergic system and synaptic plasticity during VaD

Cholinergic neurons containing acetylcholine (ACh) are important for cognition because they enhance synapses and the maintenance of novel information.[128] Decreased ACh levels influence cholinergic synaptic clefts and subsequent cognitive decline.[129] Cholinergic innervation from the basal forebrain cholinergic neuron to the cortex and the hippocampus has been recently reported to significantly degenerate in AD-associated dementia.[130] Clinical studies have shown that patients with memory impairments, such as AD, exhibit abnormal acetylcholinesterase activity and reduced ACh levels in the brain.[131-133] The loss of cholinergic neurons and reduced ACh levels have been observed in the hippocampi and cortexes of patients with VaD[134] and

https://doi.org/10.12997/jla.2024.13.2.122

JLA Journal of Lipid and Atherosclerosis

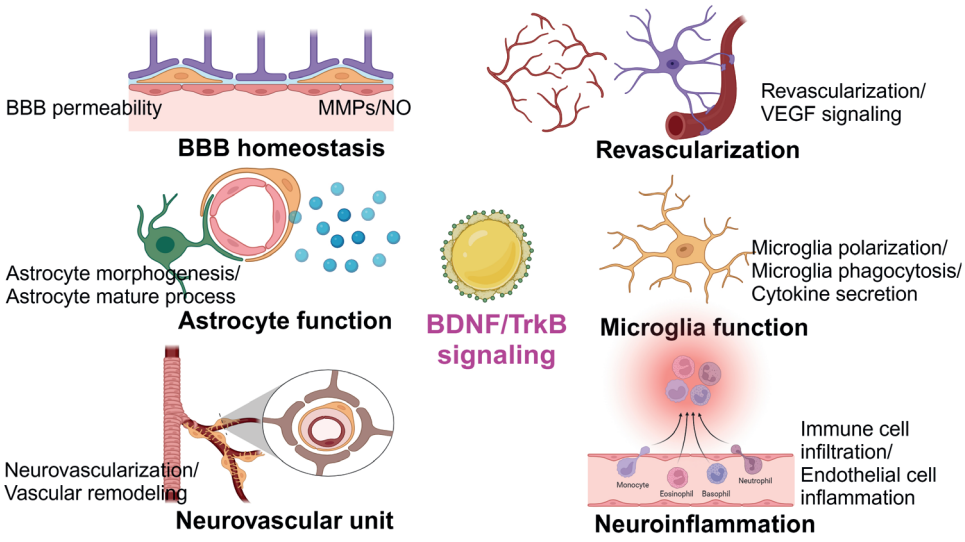

Fig. 2. BDNF/TrkB signaling and cerebrovascular function in vascular dementia.
BDNF/TrkB signaling maintains BBB homeostasis by modulating its permeability through MMPs and NO production, and by regulating revascularization through VEGF signaling. BDNF/TrkB signaling modulates astrocyte morphogenesis and maturation and enhances the neurovascular unit by regulating vascular remodeling. It also controls microglia polarization and function (e.g., phagocytosis and cytokine secretion) and attenuates neuroinflammation.
BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase B; BBB, blood–brain barrier; MMP, matrix metalloproteinase; NO, nitric oxide; VEGF, vascular endothelial growth factor.

about 40% of patients with VaD show abnormal acetylcholinesterase activity and loss of cholinergic neurons in the hippocampus, striatum, and cortex.[135] Cholinergic deficiency is also reported to accelerate inflammation and cognitive decline during ischemic brain injury.[136] Acetylcholinesterase inhibitors can treat neuropathology during VaD by enhancing the cholinergic anti-inflammatory pathway.[137] In VaD, cholinergic system dysfunction aggravates cerebrovascular dysfunction, thereby accelerating memory loss.[138142]

In addition, impaired synaptic plasticity, which causes memory loss, is a key feature of brains affected by VaD.[143,144] Synaptic plasticity is determined by synaptic transmission and synaptic density proteins, such as postsynaptic density protein (PSD)-95.[145] Synaptic plasticity contributes to NMDA receptor signaling and LTP induction, thereby influencing learning and memory function.[145,146] Recent studies have reported deficiencies in PSD-95 and related synaptic proteins in the hippocampi of a VaD model.[147,148]

Some studies have reported that BDNF contributes to the improvement of memory function by activating NMDA receptor signaling[149,150] and that BDNF accelerates synaptogenesis in various subtypes of neurons.[151]

Astrocytes contribute to synaptic plasticity[152,153] by regulating the secretion of neurotransmitters and the extent of synaptic strengthening.[154] The proBDNF that is secreted during neuronal transmission is taken up and recycled, and the regulation of neurotrophin availability and proBDNF–p75NTR signaling influences the removal of some neurotransmitters from the synaptic cleft, which regulates synaptic availability in the brain cortex.[155] Astrocytes are also reported to release proBDNF during necrosis, which induces neuronal apoptosis.[156] BDNF release from astrocytes has been shown to enhance memory function, spine maturation and density, and synaptic plasticity in the 5xFAD mouse model of AD.[157] The recycling of BDNF between glia and neurons is also reported to be essential for LTP stabilization, neurite outgrowth, and memory formation.[158,159] BDNF–TrkB signaling in

https://doi.org/10.12997/jla.2024.13.2.122

astrocytes has been recently found to influence neuronal synaptic activity in the temporal lobe of a mouse model of epilepsy.[160] Serum BDNF levels have been reported to be lower in patients with dementia and cognitive decline.[61] By promoting glutamatergic neurons in the hippocampus and enhancing dendritic spine maturation, BDNF may influence the synaptic plasticity of short- and long-term memory.[161] Numerous studies have strongly associated BDNF with synaptic formation, neuronal proliferation, and neuronal differentiation in the hippocampus, indicating that it is involved in learning and memory.[159,162-164]

Additionally, BDNF activates cognition and neuronal survival-associated intracellular signaling pathways, such as the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK)[165,166] and CREB pathways.[167,168] ERK signaling activation and CREB phosphorylation are essential for LTP induction in the hippocampus.[169] Furthermore, BDNF signaling controls the expression of synaptic density proteins, such as PSD-95 and the synaptic vesicle protein, synaptophysin, which are involved in synapse formation and maturation.[170,171] Using a mouse model of cerebral ischemia, recent studies indicate that BDNF improves memory impairment and hippocampal neuronal synaptic plasticity through BDNF/CREB signaling.[172] It is also reported to boost mitochondrial function in neurons via protein kinase A (PKA) signaling and to protect from neuronal damage [173]. Another recent study found that BDNF contributes to neuronal synaptic plasticity by regulating microglia function.[174] BDNF ameliorates LTP, long-term depression (LTD), axonal sprouting, and dendritic outgrowth proliferation, which are associated with memory function.[175-178] Reduced BDNF levels also influence hippocampal volume,[179] parietal lobe loss,[63] cognitive impairment, AD, and VaD.[11,61-63,180,181] Some studies have found that in the hippocampus, proBDNF reduces synaptic plasticity, LTD impairment, memory dysfunction, and inhibition of dendritic outgrowth.[182-184] BDNF decreases hippocampal neuronal loss in hypoxia-induced vascular cognitive impairment.[185] Microglia have been reported to promote spine formation and maturation in neurons by regulating BDNF secretion.[186] Other studies indicate that through BDNF signaling, microglia might accelerate synapse formation[186] and boost hippocampal neurogenesis via phagocytosis, thereby improving cognitive function.[174,187] Furthermore, BDNF regulates cholinergic neurons and promotes acetylcholine secretion-associated memory processes.[188-190] Alderson et al.[191] suggested that BDNF increases cholinergic neuronal cell survival and differentiation. BDNF is also reported to boost cholinergic neuronal cell survival in the forebrain, which improves memory performance.[192-194] AD is associated with increased acetylcholinesterase activity and decreased ACh expression in the brain cortex and hippocampus and these processes are affected by BDNF signaling.[195-197] Moreover, a significant correlation has been observed between BDNF and cortical AChE levels.[196] Some studies have found that BDNF improves cholinergic neuronal maturation and cholinergic hippocampal innervation[198,199] and that it may promote ACh release, which is associated with memory consolidation.[200,201]

Taken together, available evidence indicates that BDNF signaling may enhance learning and memory function in VaD by improving synaptic plasticity and the cholinergic system (**Fig. 3**).

CONCLUSION

In this review, we have summarized the roles of BDNF signaling in VaD.

Current evidence suggests that during VaD, BDNF signaling improves cerebrovascular dysfunction by regulating astrocyte and microglial function, BBB permeability,

https://doi.org/10.12997/jla.2024.13.2.122

JLA Journal of Lipid and Atherosclerosis

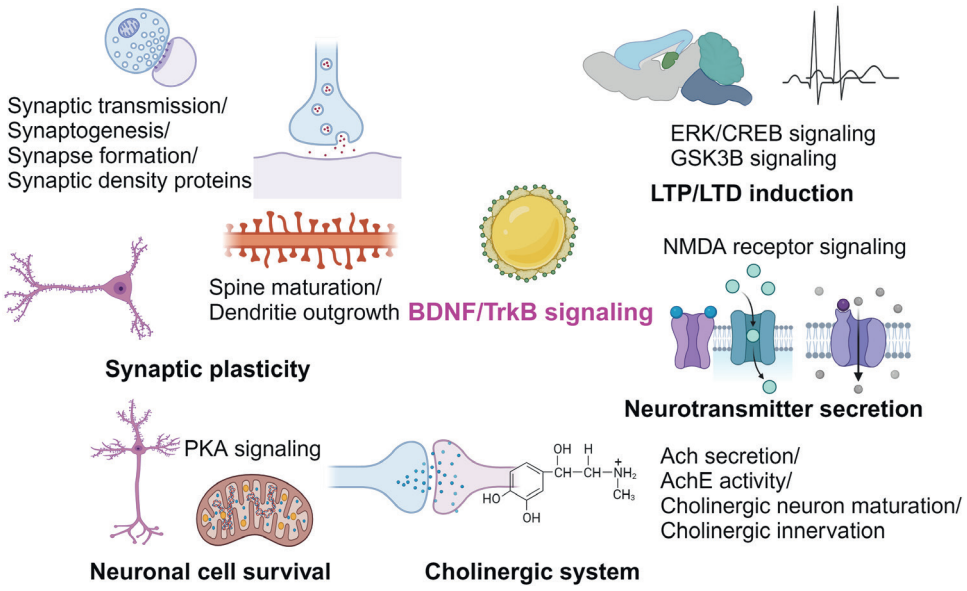

Fig. 3. BDNF/TrkB signaling and memory function in vascular dementia.
During vascular dementia, BDNF/TrkB signaling enhances synaptic plasticity by regulating synaptic transmission, synaptogenesis, synapse formation, synaptic density protein levels, spine maturation, and dendritic outgrowth. It also promotes neuronal cell survival by improving mitochondrial function via protein kinase cAMP-dependent (PKA) signaling and LTP/LTD through the ERK/CREB signaling and GSK3β signaling pathways. Furthermore, BDNF/TrkB signaling regulates neurotransmitter secretion and neuronal cell function through NMDA receptor signaling and controls the cholinergic system via ACh secretion, AChE activity, cholinergic neuron maturation, and cholinergic innervation into the hippocampus.
BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase B; PKA, protein kinase A; LTP, long-term potentiation; LTD, long-term depression; ERK, extracellular signal-regulated kinase; CREB, cAMP-response element-binding protein; GSK3β, glycogen synthase kinase-3β; NMDA, N-methyl-D-aspartate; ACh, acetylcholine; AChE, acetylcholinesterase.

revascularization, and glial–neuron connections (**Fig. 2**). Moreover, studies indicate that during VaD, BDNF signaling enhances memory function by ameliorating synaptic plasticity, synaptogenesis, spine maturation, LTP and LTD induction, and NMDA receptor signaling (**Fig. 3**). Based on current literature, we argue that BDNF signaling improves the cholinergic system by promoting ACh secretion, cholinergic neuronal maturation, and survival, and cholinergic hippocampal innervation, as well as by regulating acetylcholinesterase activity, thereby improving memory consolidation and performance during VaD (**Fig. 3**). Taken together, available evidence emphasizes the importance of BDNF signaling in the treatment of VaD neuropathology.

REFERENCES

1. Wu YT, Beiser AS, Breteler MMB, Fratiglioni L, Helmer C, Hendrie HC, et al. The changing prevalence and incidence of dementia over time - current evidence. Nat Rev Neurol 2017;13:327-339. PUBMED | CROSSREF
2. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013;9:63-75.e2. PUBMED | CROSSREF
3. Velandia PP, Miller-Petrie MK, Chen C, Chakrabarti S, Chapin A, Hay S, et al. Global and regional spending on dementia care from 2000-2019 and expected future health spending scenarios from 2020-2050: an economic modelling exercise. EClinicalMedicine 2022;45:101337. PUBMED | CROSSREF
4. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimers Res Ther 2012;4:40. PUBMED | CROSSREF
5. Grinberg LT, Heinsen H. Toward a pathological definition of vascular dementia. J Neurol Sci 2010;299:136-138. PUBMED | CROSSREF

https://doi.org/10.12997/jla.2024.13.2.122

6. Graff-Radford J. Vascular cognitive impairment. Continuum (Minneap Minn) 2019;25:147-164. PUBMED | CROSSREF
7. Ueno M, Chiba Y, Matsumoto K, Murakami R, Fujihara R, Kawauchi M, et al. Blood-brain barrier damage in vascular dementia. Neuropathology 2016;36:115-124. PUBMED | CROSSREF
8. Li C, Wang Y, Yan XL, Guo ZN, Yang Y. Pathological changes in neurovascular units: lessons from cases of vascular dementia. CNS Neurosci Ther 2021;27:17-25. PUBMED | CROSSREF
9. Tapia-Arancibia L, Rage F, Givalois L, Arancibia S. Physiology of BDNF: focus on hypothalamic function. Front Neuroendocrinol 2004;25:77-107. PUBMED | CROSSREF
10. Buhusi M, Etheredge C, Granholm AC, Buhusi CV. Increased hippocampal proBDNF contributes to memory impairments in aged mice. Front Aging Neurosci 2017;9:284. PUBMED | CROSSREF
11. Ng TK, Ho CS, Tam WW, Kua EH, Ho RC. Decreased serum brain-derived neurotrophic factor (BDNF) levels in patients with Alzheimer's disease (AD): a systematic review and meta-analysis. Int J Mol Sci 2019;20:257. PUBMED | CROSSREF
12. Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. J Neurosci 2001;21:6718-6731. PUBMED | CROSSREF
13. Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors 2004;22:123-131. PUBMED | CROSSREF
14. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol 2005;76:99-125. PUBMED | CROSSREF
15. O'Brien JT, Thomas A. Vascular dementia. Lancet 2015;386:1698-1706. PUBMED | CROSSREF
16. Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology 2018;134:226-239. PUBMED | CROSSREF
17. Battle DE. Diagnostic and Statistical Manual of Mental Disorders (DSM). Codas 2013;25:191-192. PUBMED | CROSSREF
18. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. BioMed Res Int 2014;2014:908915. PUBMED | CROSSREF
19. Rosa G, Giannotti C, Martella L, Massa F, Serafini G, Pardini M, et al. Brain aging, cardiovascular diseases, mixed dementia, and frailty in the oldest old: from brain phenotype to clinical expression. J Alzheimers Dis 2020;75:1083-1103. PUBMED | CROSSREF
20. Gorelick PB, Counts SE, Nyenhuis D. Vascular cognitive impairment and dementia. Biochim Biophys Acta 2016;1862:860-868. PUBMED | CROSSREF
21. Faraco G, Iadecola C. Hypertension: a harbinger of stroke and dementia. Hypertension 2013;62:810-817. PUBMED | CROSSREF
22. Pendlebury ST, Rothwell PM; Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. Lancet Neurol 2019;18:248-258. PUBMED | CROSSREF
23. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, et al. Vascular cognitive impairment and dementia: JACC Scientific Expert Panel. J Am Coll Cardiol 2019;73:3326-3344. PUBMED | CROSSREF
24. Kalaria RN. Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. Acta Neuropathol 2016;131:659-685. PUBMED | CROSSREF
25. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol 2007;62:406-413. PUBMED | CROSSREF
26. van de Pol L, Gertz HJ, Scheltens P, Wolf H. Hippocampal atrophy in subcortical vascular dementia. Neurodegener Dis 2011;8:465-469. PUBMED | CROSSREF
27. Wang J, Zhang HY, Tang XC. Cholinergic deficiency involved in vascular dementia: possible mechanism and strategy of treatment. Acta Pharmacol Sin 2009;30:879-888. PUBMED | CROSSREF
28. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 2010;375:773-775. PUBMED | CROSSREF
29. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease--systematic review and meta-analysis. Neurobiol Aging 2009;30:337-352. PUBMED | CROSSREF
30. Wong SM, Jansen JF, Zhang CE, Hoff EI, Staals J, van Oostenbrugge RJ, et al. Blood-brain barrier impairment and hypoperfusion are linked in cerebral small vessel disease. Neurology 2019;92:e1669-e1677. PUBMED | CROSSREF

31. Ueno M, Tomimoto H, Akiguchi I, Wakita H, Sakamoto H. Blood-brain barrier disruption in white matter lesions in a rat model of chronic cerebral hypoperfusion. J Cereb Blood Flow Metab 2002;22:97-104. PUBMED | CROSSREF
32. Stebbins GT, Nyenhuis DL, Wang C, Cox JL, Freels S, Bangen K, et al. Gray matter atrophy in patients with ischemic stroke with cognitive impairment. Stroke 2008;39:785-793. PUBMED | CROSSREF
33. Strozyk D, Dickson DW, Lipton RB, Katz M, Derby CA, Lee S, et al. Contribution of vascular pathology to the clinical expression of dementia. Neurobiol Aging 2010;31:1710-1720. PUBMED | CROSSREF
34. Marshall GA, Shchelchkov E, Kaufer DI, Ivanco LS, Bohnen NI. White matter hyperintensities and cortical acetylcholinesterase activity in parkinsonian dementia. Acta Neurol Scand 2006;113:87-91. PUBMED | CROSSREF
35. Kim JO, Lee SJ, Pyo JS. Effect of acetylcholinesterase inhibitors on post-stroke cognitive impairment and vascular dementia: a meta-analysis. PLoS One 2020;15:e0227820. PUBMED | CROSSREF
36. Dwyer R, Skrobot OA, Dwyer J, Munafo M, Kehoe PG. Using Alzgene-like approaches to investigate susceptibility genes for vascular cognitive impairment. J Alzheimers Dis 2013;34:145-154. PUBMED | CROSSREF
37. Yin YW, Li JC, Wang JZ, Li BH, Pi Y, Yang QW, et al. Association between apolipoprotein E gene polymorphism and the risk of vascular dementia: a meta-analysis. Neurosci Lett 2012;514:6-11. PUBMED | CROSSREF
38. Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80:844-866. PUBMED | CROSSREF
39. Markus HS, Schmidt R. Genetics of vascular cognitive impairment. Stroke 2019;50:765-772. PUBMED | CROSSREF
40. Skrobot OA, Black SE, Chen C, DeCarli C, Erkinjuntti T, Ford GA, et al. Progress toward standardized diagnosis of vascular cognitive impairment: guidelines from the Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement 2018;14:280-292. PUBMED | CROSSREF
41. Skrobot OA, O'Brien J, Black S, Chen C, DeCarli C, Erkinjuntti T, et al. The Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement 2017;13:624-633. PUBMED | CROSSREF
42. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37:2220-2241. PUBMED | CROSSREF
43. Roseborough A, Hachinski V, Whitehead S. White matter degeneration-a treatable target? JAMA Neurol 2020;77:793-794. PUBMED | CROSSREF
44. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666. PUBMED | CROSSREF
45. Hase Y, Horsburgh K, Ihara M, Kalaria RN. White matter degeneration in vascular and other ageing-related dementias. J Neurochem 2018;144:617-633. PUBMED | CROSSREF
46. Grinberg LT, Thal DR. Vascular pathology in the aged human brain. Acta Neuropathol 2010;119:277-290. PUBMED | CROSSREF
47. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Jolles J, Koudstaal PJ, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. Brain 2005;128:2034-2041. PUBMED | CROSSREF
48. Uiterwijk R, Staals J, Huijts M, de Leeuw PW, Kroon AA, van Oostenbrugge RJ. MRI progression of cerebral small vessel disease and cognitive decline in patients with hypertension. J Hypertens 2017;35:1263-1270. PUBMED | CROSSREF
49. van den Berg E, Geerlings MI, Biessels GJ, Nederkoorn PJ, Kloppenborg RP. White matter hyperintensities and cognition in mild cognitive impairment and Alzheimer's disease: a domain-specific meta-analysis. J Alzheimers Dis 2018;63:515-527. PUBMED | CROSSREF
50. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 2001;24:677-736. PUBMED | CROSSREF
51. Bekinschtein P, Cammarota M, Medina JH. BDNF and memory processing. Neuropharmacology 2014;76:677-683. PUBMED | CROSSREF
52. Timmusk T, Palm K, Metsis M, Reintam T, Paalme V, Saarma M, et al. Multiple promoters direct tissue-specific expression of the rat BDNF gene. Neuron 1993;10:475-489. PUBMED | CROSSREF
53. Wardle RA, Poo MM. Brain-derived neurotrophic factor modulation of GABAergic synapses by postsynaptic regulation of chloride transport. J Neurosci 2003;23:8722-8732. PUBMED | CROSSREF
54. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 1998;37:1553-1561. PUBMED | CROSSREF
55. Klein AB, Williamson R, Santini MA, Clemmensen C, Ettrup A, Rios M, et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int J Neuropsychopharmacol 2011;14:347-353. PUBMED | CROSSREF

56. 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;306:487-491. PUBMED | CROSSREF
57. Ahmed AO, Mantini AM, Fridberg DJ, Buckley PF. Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. Psychiatry Res 2015;226:1-13. PUBMED | CROSSREF
58. Greenberg ME, Xu B, Lu B, Hempstead BL. New insights in the biology of BDNF synthesis and release: implications in CNS function. J Neurosci 2009;29:12764-12767. PUBMED | CROSSREF
59. Forlenza OV, Miranda AS, Guimar I, Talib LL, Diniz BS, Gattaz WF, et al. Decreased neurotrophic support is associated with cognitive decline in non-demented subjects. J Alzheimers Dis 2015;46:423-429. PUBMED | CROSSREF
60. Ventriglia M, Zanardini R, Bonomini C, Zanetti O, Volpe D, Pasqualetti P, et al. Serum brain-derived neurotrophic factor levels in different neurological diseases. BioMed Res Int 2013;2013:901082. PUBMED | CROSSREF
61. Weinstein G, Beiser AS, Choi SH, Preis SR, Chen TC, Vorgas D, et al. Serum brain-derived neurotrophic factor and the risk for dementia: the Framingham Heart Study. JAMA Neurol 2014;71:55-61. PUBMED | CROSSREF
62. Forlenza OV, Diniz BS, Teixeira AL, Ojopi EB, Talib LL, Mendonça VA, et al. Effect of brain-derived neurotrophic factor Val66Met polymorphism and serum levels on the progression of mild cognitive impairment. World J Biol Psychiatry 2010;11:774-780. PUBMED | CROSSREF
63. Peng S, Wuu J, Mufson EJ, Fahnestock M. Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. J Neurochem 2005;93:1412-1421. PUBMED | CROSSREF
64. Nakai S, Matsunaga W, Ishida Y, Isobe K, Shirokawa T. Effects of BDNF infusion on the axon terminals of locus coeruleus neurons of aging rats. Neurosci Res 2006;54:213-219. PUBMED | CROSSREF
65. Matsunaga W, Shirokawa T, Isobe K. BDNF is necessary for maintenance of noradrenergic innervations in the aged rat brain. Neurobiol Aging 2004;25:341-348. PUBMED | CROSSREF
66. Scott Bitner R. Cyclic AMP response element-binding protein (CREB) phosphorylation: a mechanistic marker in the development of memory enhancing Alzheimer's disease therapeutics. Biochem Pharmacol 2012;83:705-714. PUBMED | CROSSREF
67. Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. Science 2018;361:eaan8821. PUBMED | CROSSREF
68. Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 1996;381:706-709. PUBMED | CROSSREF
69. Hu YS, Long N, Pigino G, Brady ST, Lazarov O. Molecular mechanisms of environmental enrichment: impairments in Akt/GSK3β, neurotrophin-3 and CREB signaling. PLoS One 2013;8:e64460. PUBMED | CROSSREF
70. Lu Y, Christian K, Lu B. BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? Neurobiol Learn Mem 2008;89:312-323. PUBMED | CROSSREF
71. Alonso M, Medina JH, Pozzo-Miller L. ERK1/2 activation is necessary for BDNF to increase dendritic spine density in hippocampal CA1 pyramidal neurons. Learn Mem 2004;11:172-178. PUBMED | CROSSREF
72. Pláteník J, Fišar Z, Buchal R, Jirák R, Kitzlerová E, Zvěřová M, et al. GSK3β, CREB, and BDNF in peripheral blood of patients with Alzheimer's disease and depression. Prog Neuropsychopharmacol Biol Psychiatry 2014;50:83-93. PUBMED | CROSSREF
73. Di Loreto S, Falone S, D'Alessandro A, Santini S Jr, Sebastiani P, Cacchio M, et al. Regular and moderate exercise initiated in middle age prevents age-related amyloidogenesis and preserves synaptic and neuroprotective signaling in mouse brain cortex. Exp Gerontol 2014;57:57-65. PUBMED | CROSSREF
74. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 2011;108:3017-3022. PUBMED | CROSSREF
75. Caldeira MV, Melo CV, Pereira DB, Carvalho RF, Carvalho AL, Duarte CB. BDNF regulates the expression and traffic of NMDA receptors in cultured hippocampal neurons. Mol Cell Neurosci 2007;35:208-219. PUBMED | CROSSREF
76. Villeneuve S, Reed BR, Madison CM, Wirth M, Marchant NL, Kriger S, et al. Vascular risk and Aβ interact to reduce cortical thickness in AD vulnerable brain regions. Neurology 2014;83:40-47. PUBMED | CROSSREF
77. Shih AY, Hyacinth HI, Hartmann DA, van Veluw SJ. Rodent models of cerebral microinfarct and microhemorrhage. Stroke 2018;49:803-810. PUBMED | CROSSREF

78. Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. Exp Neurol 2015;272:97-108. PUBMED | CROSSREF
79. Maki T, Hayakawa K, Pham LD, Xing C, Lo EH, Arai K. Biphasic mechanisms of neurovascular unit injury and protection in CNS diseases. CNS Neurol Disord Drug Targets 2013;12:302-315. PUBMED | CROSSREF
80. Armulik A, Genové G, Mäe M, Nisancioglu MH, Wallgard E, Niaudet C, et al. Pericytes regulate the blood-brain barrier. Nature 2010;468:557-561. PUBMED | CROSSREF
81. Winkler EA, Bell RD, Zlokovic BV. Central nervous system pericytes in health and disease. Nat Neurosci 2011;14:1398-1405. PUBMED | CROSSREF
82. Muoio V, Persson PB, Sendeski MM. The neurovascular unit - concept review. Acta Physiol (Oxf) 2014;210:790-798. PUBMED | CROSSREF
83. Rosenberg GA. Neurological diseases in relation to the blood-brain barrier. J Cereb Blood Flow Metab 2012;32:1139-1151. PUBMED | CROSSREF
84. Wallin A, Blennow K, Fredman P, Gottfries CG, Karlsson I, Svennerholm L. Blood brain barrier function in vascular dementia. Acta Neurol Scand 1990;81:318-322. PUBMED | CROSSREF
85. Koizumi T, Taguchi K, Mizuta I, Toba H, Ohigashi M, Onishi O, et al. Transiently proliferating perivascular microglia harbor M1 type and precede cerebrovascular changes in a chronic hypertension model. J Neuroinflammation 2019;16:79. PUBMED | CROSSREF
86. Jiang X, Andjelkovic AV, Zhu L, Yang T, Bennett MV, Chen J, et al. Blood-brain barrier dysfunction and recovery after ischemic stroke. Prog Neurobiol 2018;163-164:144-171. PUBMED | CROSSREF
87. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet 2008;371:1612-1623. PUBMED | CROSSREF
88. Jellinger KA. Pathology and pathogenesis of vascular cognitive impairment-a critical update. Front Aging Neurosci 2013;5:17. PUBMED | CROSSREF
89. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:2672-2713. PUBMED | CROSSREF
90. Lind BL, Brazhe AR, Jessen SB, Tan FC, Lauritzen MJ. Rapid stimulus-evoked astrocyte Ca^{2+} elevations and hemodynamic responses in mouse somatosensory cortex *in vivo*. Proc Natl Acad Sci U S A 2013;110:E4678-E4687. PUBMED | CROSSREF
91. Abbott NJ. Astrocyte-endothelial interactions and blood-brain barrier permeability. J Anat 2002;200:629-638. PUBMED | CROSSREF
92. Mathiisen TM, Lehre KP, Danbolt NC, Ottersen OP. The perivascular astroglial sheath provides a complete covering of the brain microvessels: an electron microscopic 3D reconstruction. Glia 2010;58:1094-1103. PUBMED | CROSSREF
93. Allen NJ, Eroglu C. Cell biology of astrocyte-synapse interactions. Neuron 2017;96:697-708. PUBMED | CROSSREF
94. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 2017;541:481-487. PUBMED | CROSSREF
95. Patabendige A, Singh A, Jenkins S, Sen J, Chen R. Astrocyte activation in neurovascular damage and repair following ischaemic stroke. Int J Mol Sci 2021;22:4280. PUBMED | CROSSREF
96. Skowrońska M, Albrecht J. Oxidative and nitrosative stress in ammonia neurotoxicity. Neurochem Int 2013;62:731-737. PUBMED | CROSSREF
97. Semyanov A, Verkhratsky A. Astrocytic processes: from tripartite synapses to the active milieu. Trends Neurosci 2021;44:781-792. PUBMED | CROSSREF
98. Eroglu C, Barres BA. Regulation of synaptic connectivity by glia. Nature 2010;468:223-231. PUBMED | CROSSREF
99. Spampinato SF, Bortolotto V, Canonico PL, Sortino MA, Grilli M. Astrocyte-derived paracrine signals: relevance for neurogenic niche regulation and blood-brain barrier integrity. Front Pharmacol 2019;10:1346. PUBMED | CROSSREF
100. Lécuyer MA, Kebir H, Prat A. Glial influences on BBB functions and molecular players in immune cell trafficking. Biochim Biophys Acta 2016;1862:472-482. PUBMED | CROSSREF
101. Rosenegger DG, Tran CH, Wamsteeker Cusulin JI, Gordon GR. Tonic local brain blood flow control by astrocytes independent of phasic neurovascular coupling. J Neurosci 2015;35:13463-13474. PUBMED | CROSSREF
102. Cauli B, Tong XK, Rancillac A, Serluca N, Lambolez B, Rossier J, et al. Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. J Neurosci 2004;24:8940-8949. PUBMED | CROSSREF

103. Hu H, Gan J, Jonas P. Interneurons. Fast-spiking, parvalbumin+ GABAergic interneurons: from cellular design to microcircuit function. Science 2014;345:1255263. PUBMED | CROSSREF

104. Zhang LY, Pan J, Mamtilahun M, Zhu Y, Wang L, Venkatesh A, et al. Microglia exacerbate white matter injury via complement C3/C3aR pathway after hypoperfusion. Theranostics 2020;10:74-90. PUBMED | CROSSREF

105. Qin C, Fan WH, Liu Q, Shang K, Murugan M, Wu LJ, et al. Fingolimod protects against ischemic white matter damage by modulating microglia toward M2 polarization via STAT3 pathway. Stroke 2017;48:3336-3346. PUBMED | CROSSREF

106. Lee J, Hamanaka G, Lo EH, Arai K. Heterogeneity of microglia and their differential roles in white matter pathology. CNS Neurosci Ther 2019;25:1290-1298. PUBMED | CROSSREF

107. Bangen KJ, Preis SR, Delano-Wood L, Wolf PA, Libon DJ, Bondi MW, et al. Baseline white matter hyperintensities and hippocampal volume are associated with conversion from normal cognition to mild cognitive impairment in the Framingham Offspring Study. Alzheimer Dis Assoc Disord 2018;32:50-56. PUBMED | CROSSREF

108. Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TL, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network. Ann Neurol 2016;79:929-939. PUBMED | CROSSREF

109. Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. Neurobiol Aging 2015;36:27-32. PUBMED | CROSSREF

110. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Assoc 2015;4:001140. PUBMED | CROSSREF

111. Alber J, Alladi S, Bae HJ, Barton DA, Beckett LA, Bell JM, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): knowledge gaps and opportunities. Alzheimers Dement (N Y) 2019;5:107-117. PUBMED | CROSSREF

112. Ding H, Chen J, Su M, Lin Z, Zhan H, Yang F, et al. BDNF promotes activation of astrocytes and microglia contributing to neuroinflammation and mechanical allodynia in cyclophosphamide-induced cystitis. J Neuroinflammation 2020;17:19. PUBMED | CROSSREF

113. Zhang Y, Pardridge WM. Blood-brain barrier targeting of BDNF improves motor function in rats with middle cerebral artery occlusion. Brain Res 2006;1111:227-229. PUBMED | CROSSREF

114. Grade S, Weng YC, Snapyan M, Kriz J, Malva JO, Saghatelyan A. Brain-derived neurotrophic factor promotes vasculature-associated migration of neuronal precursors toward the ischemic striatum. PLoS One 2013;8:e55039. PUBMED | CROSSREF

115. Kermani P, Rafii D, Jin DK, Whitlock P, Schaffer W, Chiang A, et al. Neurotrophins promote revascularization by local recruitment of TrkB+ endothelial cells and systemic mobilization of hematopoietic progenitors. J Clin Invest 2005;115:653-663. PUBMED | CROSSREF

116. Kim MS, Kim BY, Kim JI, Lee J, Jeon WK. Mumefural improves recognition memory and alters ERK-CREB-BDNF signaling in a mouse model of chronic cerebral hypoperfusion. Nutrients 2023;15:3271. PUBMED | CROSSREF

117. Snapyan M, Lemasson M, Brill MS, Blais M, Massouh M, Ninkovic J, et al. Vasculature guides migrating neuronal precursors in the adult mammalian forebrain via brain-derived neurotrophic factor signaling. J Neurosci 2009;29:4172-4188. PUBMED | CROSSREF

118. Brenner EK, Weigand AJ, Edwards L, Thomas KR, Edmonds EC, Bondi MW, et al. Brain derived neurotrophic factor interacts with white matter hyperintensities to influence processing speed and hippocampal volume in older adults. J Alzheimers Dis 2023;93:141-149. PUBMED | CROSSREF

119. Géral C, Angelova A, Lesieur S. From molecular to nanotechnology strategies for delivery of neurotrophins: emphasis on brain-derived neurotrophic factor (BDNF). Pharmaceutics 2013;5:127-167. PUBMED | CROSSREF

120. Holt LM, Hernandez RD, Pacheco NL, Torres Ceja B, Hossain M, Olsen ML. Astrocyte morphogenesis is dependent on BDNF signaling via astrocytic TrkB.T1. eLife 2019;8:e44667. PUBMED | CROSSREF

121. Bonvento G, Bolaños JP. Astrocyte-neuron metabolic cooperation shapes brain activity. Cell Metab 2021;33:1546-1564. PUBMED | CROSSREF

122. Kinboshi M, Mukai T, Nagao Y, Matsuba Y, Tsuji Y, Tanaka S, et al. Inhibition of inwardly rectifying potassium (Kir) 4.1 channels facilitates brain-derived neurotrophic factor (BDNF) expression in astrocytes. Front Mol Neurosci 2017;10:408. PUBMED | CROSSREF

123. Alderson RF, Curtis R, Alterman AL, Lindsay RM, DiStefano PS. Truncated TrkB mediates the endocytosis and release of BDNF and neurotrophin-4/5 by rat astrocytes and Schwann cells *in vitro*. Brain Res 2000;871:210-222. PUBMED | CROSSREF

124. Kabba JA, Xu Y, Christian H, Ruan W, Chenai K, Xiang Y, et al. Microglia: housekeeper of the central nervous system. Cell Mol Neurobiol 2018;38:53-71. PUBMED | CROSSREF

125. Haruwaka K, Ikegami A, Tachibana Y, Ohno N, Konishi H, Hashimoto A, et al. Dual microglia effects on blood brain barrier permeability induced by systemic inflammation. Nat Commun 2019;10:5816. PUBMED | CROSSREF

126. Long T, He W, Pan Q, Zhang S, Zhang D, Qin G, et al. Microglia P2X4R-BDNF signalling contributes to central sensitization in a recurrent nitroglycerin-induced chronic migraine model. J Headache Pain 2020;21:4. PUBMED | CROSSREF

127. Charlton T, Prowse N, McFee A, Heiratifar N, Fortin T, Paquette C, et al. Brain-derived neurotrophic factor (BDNF) has direct anti-inflammatory effects on microglia. Front Cell Neurosci 2023;17:1188672. PUBMED | CROSSREF

128. Weon JB, Jung YS, Ma CJ. Cognitive-enhancing effect of *Dianthus superbus* var. *Longicalycinus* on scopolamine-induced memory impairment in mice. Biomol Ther (Seoul) 2016;24:298-304. PUBMED | CROSSREF

129. Farlow MR, Cummings J. A modern hypothesis: the distinct pathologies of dementia associated with Parkinson's disease versus Alzheimer's disease. Dement Geriatr Cogn Disord 2008;25:301-308. PUBMED | CROSSREF

130. Orciani C, Hall H, Pentz R, Foret MK, Do Carmo S, Cuello AC. Long-term nucleus basalis cholinergic depletion induces attentional deficits and impacts cortical neurons and BDNF levels without affecting the NGF synthesis. J Neurochem 2022;163:149-167. PUBMED | CROSSREF

131. Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM. Alzheimer's disease: targeting the cholinergic system. Curr Neuropharmacol 2016;14:101-115. PUBMED | CROSSREF

132. Maurer SV, Williams CL. The cholinergic system modulates memory and hippocampal plasticity via its interactions with non-neuronal cells. Front Immunol 2017;8:1489. PUBMED | CROSSREF

133. Han Y, Yang H, Li L, Du X, Sun C. Schisanhenol improves learning and memory in scopolamine-treated mice by reducing acetylcholinesterase activity and attenuating oxidative damage through SIRT1-PGC-1α-Tau signaling pathway. Int J Neurosci 2019;129:110-118. PUBMED | CROSSREF

134. Gottfries CG, Blennow K, Karlsson I, Wallin A. The neurochemistry of vascular dementia. Dementia 1994;5:163-167. PUBMED | CROSSREF

135. Court JA, Perry EK. Neurotransmitter abnormalities in vascular dementia. Int Psychogeriatr 2003;15 Suppl 1:81-87. PUBMED | CROSSREF

136. Kumaran D, Udayabanu M, Kumar M, Aneja R, Katyal A. Involvement of angiotensin converting enzyme in cerebral hypoperfusion induced anterograde memory impairment and cholinergic dysfunction in rats. Neuroscience 2008;155:626-639. PUBMED | CROSSREF

137. Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. Brain Behav Immun 2005;19:493-499. PUBMED | CROSSREF

138. Román GC. Cholinergic dysfunction in vascular dementia. Curr Psychiatry Rep 2005;7:18-26. PUBMED | CROSSREF

139. Román GC, Kalaria RN. Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. Neurobiol Aging 2006;27:1769-1785. PUBMED | CROSSREF

140. Borlongan CV, Sumaya IC, Moss DE. Methanesulfonyl fluoride, an acetylcholinesterase inhibitor, attenuates simple learning and memory deficits in ischemic rats. Brain Res 2005;1038:50-58. PUBMED | CROSSREF

141. Naritomi H. Experimental basis of multi-infarct dementia: memory impairments in rodent models of ischemia. Alzheimer Dis Assoc Disord 1991;5:103-111. PUBMED | CROSSREF

142. Kalaria R. Similarities between Alzheimer's disease and vascular dementia. J Neurol Sci 2002;203-204:29-34. PUBMED | CROSSREF

143. Liu B, Tang J, Zhang J, Li S, Yuan M, Wang R. Autophagy activation aggravates neuronal injury in the hippocampus of vascular dementia rats. Neural Regen Res 2014;9:1288-1296. PUBMED | CROSSREF

144. Dong J, Zhao J, Lin Y, Liang H, He X, Zheng X, et al. Exercise improves recognition memory and synaptic plasticity in the prefrontal cortex for rats modelling vascular dementia. Neurol Res 2018;40:68-77. PUBMED | CROSSREF

145. Grossberg S. From brain synapses to systems for learning and memory: object recognition, spatial navigation, timed conditioning, and movement control. Brain Res 2015;1621:270-293. PUBMED | CROSSREF

146. Yuen EY, Ren Y, Yan Z. Postsynaptic density-95 (PSD-95) and calcineurin control the sensitivity of N-methyl-D-aspartate receptors to calpain cleavage in cortical neurons. Mol Pharmacol 2008;74:360-370. PUBMED | CROSSREF

147. Sinclair LI, Tayler HM, Love S. Synaptic protein levels altered in vascular dementia. Neuropathol Appl Neurobiol 2015;41:533-543. PUBMED | CROSSREF

148. Liu B, Liu J, Zhang J, Mao W, Li S. Effects of autophagy on synaptic-plasticity-related protein expression in the hippocampus CA1 of a rat model of vascular dementia. Neurosci Lett 2019;707:134312. PUBMED | CROSSREF

149. Lee SH, Ko IG, Kim SE, Hwang L, Jin JJ, Choi HH, et al. Aqueous extract of Cordyceps alleviates cerebral ischemia-induced short-term memory impairment in gerbils. J Exerc Rehabil 2016;12:69-78. PUBMED | CROSSREF

150. Sawamoto A, Okuyama S, Yamamoto K, Amakura Y, Yoshimura M, Nakajima M, et al. 3,5,6,7,8,3′,4′-Heptamethoxyflavone, a citrus flavonoid, ameliorates corticosterone-induced depression-like behavior and restores brain-derived neurotrophic factor expression, neurogenesis, and neuroplasticity in the hippocampus. Molecules 2016;21:541. PUBMED | CROSSREF

151. Koshimizu H, Matsuoka H, Nakajima Y, Kawai A, Ono J, Ohta KI, et al. Brain-derived neurotrophic factor predominantly regulates the expression of synapse-related genes in the striatum: insights from *in vitro* transcriptomics. Neuropsychopharmacol Rep 2021;41:485-495. PUBMED | CROSSREF

152. Khakh BS, Sofroniew MV. Diversity of astrocyte functions and phenotypes in neural circuits. Nat Neurosci 2015;18:942-952. PUBMED | CROSSREF

153. Allen NJ, Lyons DA. Glia as architects of central nervous system formation and function. Science 2018;362:181-185. PUBMED | CROSSREF

154. Durkee CA, Araque A. Diversity and specificity of astrocyte-neuron communication. Neuroscience 2019;396:73-78. PUBMED | CROSSREF

155. Bergami M, Santi S, Formaggio E, Cagnoli C, Verderio C, Blum R, et al. Uptake and recycling of pro-BDNF for transmitter-induced secretion by cortical astrocytes. J Cell Biol 2008;183:213-221. PUBMED | CROSSREF

156. Chen Z, Tang HB, Kang JJ, Chen ZY, Li YL, Fan QY, et al. Necroptotic astrocytes induced neuronal apoptosis partially through EVs-derived pro-BDNF. Brain Res Bull 2021;177:73-80. PUBMED | CROSSREF

157. de Pins B, Cifuentes-Díaz C, Thamila Farah A, López-Molina L, Montalban E, Sancho-Balsells A, et al. Conditional BDNF delivery from astrocytes rescues memory deficits, spine density, and synaptic properties in the 5xFAD mouse model of Alzheimer disease. J Neurosci 2019;39:2441-2458. PUBMED | CROSSREF

158. Vignoli B, Battistini G, Melani R, Blum R, Santi S, Berardi N, et al. Peri-synaptic glia recycles brain-derived neurotrophic factor for LTP stabilization and memory retention. Neuron 2016;92:873-887. PUBMED | CROSSREF

159. Lu B, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat Rev Neurosci 2013;14:401-416. PUBMED | CROSSREF

160. Fernández-García S, Sancho-Balsells A, Longueville S, Hervé D, Gruart A, Delgado-García JM, et al. Astrocytic BDNF and TrkB regulate severity and neuronal activity in mouse models of temporal lobe epilepsy. Cell Death Dis 2020;11:411. PUBMED | CROSSREF

161. Alonso M, Vianna MR, Depino AM, Mello e Souza T, Pereira P, Szapiro G, et al. BDNF-triggered events in the rat hippocampus are required for both short- and long-term memory formation. Hippocampus 2002;12:551-560. PUBMED | CROSSREF

162. Choudhary AK, Lee YY. Neurophysiological symptoms and aspartame: what is the connection? Nutr Neurosci 2018;21:306-316. PUBMED | CROSSREF

163. Kutlu MG, Gould TJ. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. Learn Mem 2016;23:515-533. PUBMED | CROSSREF

164. Babu H, Ramirez-Rodriguez G, Fabel K, Bischofberger J, Kempermann G. Synaptic network activity induces neuronal differentiation of adult hippocampal precursor cells through BDNF signaling. Front Neurosci 2009;3:49. PUBMED | CROSSREF

165. Gutiérrez-Vargas JA, Múnera A, Cardona-Gómez GP. CDK5 knockdown prevents hippocampal degeneration and cognitive dysfunction produced by cerebral ischemia. J Cereb Blood Flow Metab 2015;35:1937-1949. PUBMED | CROSSREF

166. Sweatt JD. The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memory. J Neurochem 2001;76:1-10. PUBMED | CROSSREF

167. Cunha C, Brambilla R, Thomas KL. A simple role for BDNF in learning and memory? Front Mol Neurosci 2010;3:1. PUBMED | CROSSREF

168. Jiang T, Wang XQ, Ding C, Du XL. Genistein attenuates isoflurane-induced neurotoxicity and improves impaired spatial learning and memory by regulating cAMP/CREB and BDNF-TrkB-PI3K/Akt signaling. Korean J Physiol Pharmacol 2017;21:579-589. PUBMED | CROSSREF

169. Lu B. BDNF and activity-dependent synaptic modulation. Learn Mem 2003;10:86-98. PUBMED | CROSSREF

170. Tartaglia N, Du J, Tyler WJ, Neale E, Pozzo-Miller L, Lu B. Protein synthesis-dependent and -independent regulation of hippocampal synapses by brain-derived neurotrophic factor. J Biol Chem 2001;276:37585-37593. PUBMED | CROSSREF

171. Yoshii A, Constantine-Paton M. Postsynaptic localization of PSD-95 is regulated by all three pathways downstream of TrkB signaling. Front Synaptic Neurosci 2014;6:6. PUBMED | CROSSREF

172. Yuan J, Gao J, Su KQ, Feng XD. Electroacupuncture improves learning and memory impairment and enhances hippocampal synaptic plasticity through BDNF/TRKB/CREB signaling pathway in cerebral ischemia-reperfusion injury rats. Zhen Ci Yan Jiu 2023;48:843-851. PUBMED | CROSSREF

173. Swain M, K Soman S, Tapia K, Dagda RY, Dagda RK. Brain-derived neurotrophic factor protects neurons by stimulating mitochondrial function through protein kinase A. J Neurochem 2023;167:104-125. PUBMED | CROSSREF

174. Wang W, Li Y, Ma F, Sheng X, Chen K, Zhuo R, et al. Microglial repopulation reverses cognitive and synaptic deficits in an Alzheimer's disease model by restoring BDNF signaling. Brain Behav Immun 2023;113:275-288. PUBMED | CROSSREF

175. Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem 2002;9:224-237. PUBMED | CROSSREF

176. Murer MG, Yan Q, Raisman-Vozari R. Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. Prog Neurobiol 2001;63:71-124. PUBMED | CROSSREF

177. Sartori CR, Vieira AS, Ferrari EM, Langone F, Tongiorgi E, Parada CA. The antidepressive effect of the physical exercise correlates with increased levels of mature BDNF, and proBDNF proteolytic cleavage-related genes, p11 and tPA. Neuroscience 2011;180:9-18. PUBMED | CROSSREF

178. Leckie RL, Oberlin LE, Voss MW, Prakash RS, Szabo-Reed A, Chaddock-Heyman L, et al. BDNF mediates improvements in executive function following a 1-year exercise intervention. Front Hum Neurosci 2014;8:985. PUBMED | CROSSREF

179. Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, et al. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci 2010;30:5368-5375. PUBMED | CROSSREF

180. Lee JG, Shin BS, You YS, Kim JE, Yoon SW, Jeon DW, et al. Decreased serum brain-derived neurotrophic factor levels in elderly Korean with dementia. Psychiatry Investig 2009;6:299-305. PUBMED | CROSSREF

181. Yasutake C, Kuroda K, Yanagawa T, Okamura T, Yoneda H. Serum BDNF, TNF-alpha and IL-1beta levels in dementia patients: comparison between Alzheimer's disease and vascular dementia. Eur Arch Psychiatry Clin Neurosci 2006;256:402-406. PUBMED | CROSSREF

182. Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA, et al. Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat Neurosci 2005;8:1069-1077. PUBMED | CROSSREF

183. Yang J, Harte-Hargrove LC, Siao CJ, Marinic T, Clarke R, Ma Q, et al. proBDNF negatively regulates neuronal remodeling, synaptic transmission, and synaptic plasticity in hippocampus. Cell Reports 2014;7:796-806. PUBMED | CROSSREF

184. Chen J, Zhang T, Jiao S, Zhou X, Zhong J, Wang Y, et al. proBDNF accelerates brain amyloid-β deposition and learning and memory impairment in APPswePS1dE9 transgenic mice. J Alzheimers Dis 2017;59:941-949. PUBMED | CROSSREF

185. Vetrovoĭ OV, Rybnikova TS, Samoĭlov MO. Effect of hypoxic postconditioning on the expression of antiapoptotic protein Bcl-2 and neurotrophin BDNF in CA1 hippocampal field of rats surviving severe hypoxia. Morfologiia 2014;145:16-20. PUBMED

186. Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR 3rd, Lafaille JJ, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 2013;155:1596-1609. PUBMED | CROSSREF

187. Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, et al. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 2010;7:483-495. PUBMED | CROSSREF

188. Blokland A. Acetylcholine: a neurotransmitter for learning and memory? Brain Res Brain Res Rev 1995;21:285-300. PUBMED | CROSSREF

189. da Penha Berzaghi M, Cooper J, Castrén E, Zafra F, Sofroniew M, Thoenen H, et al. Cholinergic regulation of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) but not neurotrophin-3 (NT-3) mRNA levels in the developing rat hippocampus. J Neurosci 1993;13:3818-3826. PUBMED | CROSSREF

190. Tyler WJ, Pozzo-Miller LD. BDNF enhances quantal neurotransmitter release and increases the number of docked vesicles at the active zones of hippocampal excitatory synapses. J Neurosci 2001;21:4249-4258. PUBMED | CROSSREF

191. Alderson RF, Alterman AL, Barde YA, Lindsay RM. Brain-derived neurotrophic factor increases survival and differentiated functions of rat septal cholinergic neurons in culture. Neuron 1990;5:297-306. PUBMED | CROSSREF

192. Iulita MF, Bistué Millón MB, Pentz R, Aguilar LF, Do Carmo S, Allard S, et al. Differential deregulation of NGF and BDNF neurotrophins in a transgenic rat model of Alzheimer's disease. Neurobiol Dis 2017;108:307-323. PUBMED | CROSSREF

193. Fahnestock M, Garzon D, Holsinger RM, Michalski B. Neurotrophic factors and Alzheimer's disease: are we focusing on the wrong molecule? J Neural Transm Suppl 2002;62:241-252. PUBMED | CROSSREF

194. Hachisu M, Konishi K, Hosoi M, Tani M, Tomioka H, Inamoto A, et al. Beyond the hypothesis of serum anticholinergic activity in Alzheimer's disease: acetylcholine neuronal activity modulates brain-derived neurotrophic factor production and inflammation in the brain. Neurodegener Dis 2015;15:182-187. PUBMED | CROSSREF

195. McNerney MW, Heath A, Narayanan SK, Yesavage J. Repetitive transcranial magnetic stimulation improves brain-derived neurotrophic factor and cholinergic signaling in the 3xTgAD mouse model of Alzheimer's disease. J Alzheimers Dis 2022;86:499-507. PUBMED | CROSSREF

196. Khairy EY, Attia MM. Protective effects of vitamin D on neurophysiologic alterations in brain aging: role of brain-derived neurotrophic factor (BDNF). Nutr Neurosci 2021;24:650-659. PUBMED | CROSSREF

197. Luo H, Xiang Y, Qu X, Liu H, Liu C, Li G, et al. Apelin-13 suppresses neuroinflammation against cognitive deficit in a streptozotocin-induced rat model of Alzheimer's disease through activation of BDNF-TrkB signaling pathway. Front Pharmacol 2019;10:395. PUBMED | CROSSREF

198. Sakata K, Overacre AE. Promoter IV-BDNF deficiency disturbs cholinergic gene expression of CHRNA5, CHRM2, and CHRM5: effects of drug and environmental treatments. J Neurochem 2017;143:49-64. PUBMED | CROSSREF

199. Ward NL, Hagg T. BDNF is needed for postnatal maturation of basal forebrain and neostriatum cholinergic neurons *in vivo*. Exp Neurol 2000;162:297-310. PUBMED | CROSSREF

200. Slonimsky JD, Yang B, Hinterneder JM, Nokes EB, Birren SJ. BDNF and CNTF regulate cholinergic properties of sympathetic neurons through independent mechanisms. Mol Cell Neurosci 2003;23:648-660. PUBMED | CROSSREF

201. Gil-Bea FJ, Solas M, Mateos L, Winblad B, Ramírez MJ, Cedazo-Mínguez A. Cholinergic hypofunction impairs memory acquisition possibly through hippocampal Arc and BDNF downregulation. Hippocampus 2011;21:999-1009. PUBMED | CROSSREF