

## **Brain-derived neurotrophic factor (BDNF) on cognitive function in the elderly : a literature review**

Brain-derived neurotrophic factor (BDNF) terhadap fungsi kognitif pada lansia : tinjauan Literatur

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### **Abstrak**

Lansia merupakan fase perkembangan manusia, di mana lansia sering dikaitkan dengan ketidakmampuan untuk melakukan aktivitas sehari-hari dan sering mengalami berbagai penyakit degeneratif. Lansia juga mengalami penurunan fungsi organ dan fisiologis, baik dari segi kognitif, fisik, maupun psikologis. Salah satu masalah ini adalah perubahan fungsi kognitif yang berdampak fatal dalam kehidupan sehari-hari lansia. Oleh karena itu, perlu mendalami materi yang lebih kompleks untuk meningkatkan fungsi kognitif. Fungsi kognitif tidak terlepas dari peran Brain-derived neurotrophic factor (BDNF) (BDNF). Tujuan studi ini adalah untuk menggambarkan peran Brain-derived neurotrophic factor (BDNF) pada lansia. Fungsi kognitif memainkan peran penting dalam fungsi mental seseorang dalam proses berpikir dan memberikan stimulasi terhadap lingkungan saat menjalani aktivitas sehari-hari.

Kata kunci : BDNF, Fungsi Kognitif, Lansia

### **Abstract**

Elderly is a phase of human development, the elderly are often associated with the inability to carry out daily activities and often experience various degenerative diseases. The elderly also experience a decrease in organ and physiological functions from cognitive, physical and psychological functions. So one of these problems is the change in cognitive function which is fatal in the daily life of the elderly, it is necessary to deepen more complex material to improve cognitive function, cognitive function is inseparable from the role of Brain-derived neurotrophic factor (BDNF), the purpose of this study is to describe how the role of Brain-derived neurotrophic factor (BDNF) in the elderly. Cognitive function plays an important role in a person's mental function in the process of thinking and providing stimulation to the environment while undergoing daily activities.

Keywords: BDNF, Cognitive Function , Elderly

### **Pendahuluan**

Along with the current developments in the 21st century, there have been many very significant changes, with many of the latest discoveries of artificial intelligence systems and others. This development also affects the world's human population, the increasing number of humans on earth, seen by increasing human life expectancy, currently the productive age group is still the highest and in the future the number of elderly people will increase, so it will be a bad impact if it becomes a global problem, the elderly themselves are less productive and more often experience disorders that can worsen their daily life conditions, one of the changes that occurs in the elderly is a decrease in cognitive, physical and psychological function, this problem will be difficult for the elderly if not given the right intervention(Pranata, 2000). one

of the problems we will discuss is cognitive function in the elderly, cognitive function is inseparable from BDNF, Brain-derived neurotrophic factor (BDNF) is a neurotrophin factor that influences the formation, development of neurons, and maintaining the existence of neurons, Brain-derived neurotrophic factor (BDNF) is a neurotrophin factor that influences the formation, development of neurons, and maintaining the existence of neurons. BDNF can be found and is active in the hippocampus, cortex, and forebrain. Aging is a multifactorial process determined by genetic factors and epigenetic factors. Decreased BDNF levels reduce learning and memory abilities and occur in the elderly or those with neurodegenerative diseases(Noor & Merijanti, 2020).

BDNF plays an important role in the growth, development, and plasticity of proper glutamatergic and GABAergic synapses and through modulation of neuronal differentiation, it affects serotonergic and dopaminergic neurotransmission. BDNF is widely expressed in brain areas with high levels of plasticity, namely the hippocampus, hypothalamus, and cortex. BDNF also plays a role in regulating synaptic transmission and changes in expression regulated by neuronal activity. In developing and mature neurons, the most appropriate electrical stimuli to trigger BDNF release are prolonged depolarization, HFS, or TBS. In cells that cannot be electrically stimulated, the stimuli released by BDNF are different from the primary stimuli on nerve cells(Nikolac Perkovic et al., 2023).

BDNF activates tyrosine kinase receptors and subsequently increases neuronal survival, neuroplasticity, and synaptogenesis through various signaling pathways. Activated Trk receptors recruit tyrosine kinase substrates, including PI3K and PLC- $\gamma$ . Neuroplasticity is the brain's ability to change its structure and function in response to experience. This means that our brains are not static; they are constantly changing as we learn new things and encounter new situations. Cognitive function is the mental ability associated with the brain's ability to receive and process information delivered by our sensory systems. In humans, circulating BDNF levels decline with age, and genetic polymorphisms for BDNF have been associated with loss of grey matter volume in old age. When the brain in older adults experiences damage due to aging, cognitive, intellectual, social and occupational function declines. The main types of cognitive impairment that commonly occur in older adults are delirium, dementia and amnesic disorders(Guo et al., 2022).

While it is currently impossible to reverse the aging process, maintaining physical health can help slow it down. A diet rich in fruits and vegetables, and low in red meat and sugar, can help to nourish the brain and improve your prospects for a healthier life. Cognitive function refers to a variety of mental abilities, including learning, thinking, reasoning, remembering, problem solving, decision making, and attention. Cognitive impairment is a condition characterized by limitations in a person's ability to think, remember, and interpret information from the five senses. This condition can be experienced by anyone, including children. Data obtained from the study stated that the cognitive function of the elderly needs a more detailed discussion, so [researchers are interested in conducting research on The role of brain-derived neurotrophic factor (BDNF) on cognitive function in the elderly

### **BDNF synthesis**

Interaction with sortilin is also required for BDNF engagement into the lysosomal pathway. Two mechanistic frameworks explain how proBDNF is sorted into the secretory or degradation pathway. First, targeting of sortilin and its proBDNF cargo to the lysosomal pathway is dependent on sortilin cleavage. Targeting of sortilin and its proBDNF cargo to the secretory pathway requires physical interaction with huntingtin-interacting protein 1

(HAP1)(Chandrasekaran et al., 2021). Neurotrophin scarcity is the result of active processes with temporal and spatial resolution that enable synaptogenesis and competition between different axonal synapses. (Bliss et al., 2021). This is important not only for synaptic scaling of excitatory and inhibitory neurons to maintain homeostasis, but also for synaptic potentiation, including the induction, maintenance, and consolidation phases (Yang et al., 2019). It is interesting that synaptic priming with BDNF can convert weak synaptic activity into strong potentiation via postsynaptic mechanisms(Cortés-Álvarez et al., 2024). Neurotrophin responses depend on a trans-synaptic molecular system consisting of multiple ligands and receptors, whose specificity, sensitivity, and location are important (Kouter et al., 2023).

One way to limit the neurotrophin response to active synapses is to couple the neurotrophin signal to neuronal activity (Adriani et al., 2020). Neuronal activity originating from the pre- and postsynaptic sides can stimulate the secretion of neurotrophins, which can result in the strengthening and maintenance of active synapses (Enette et al., 2020). In contrast, synapses with asynchronous activity between pre- and postsynaptic terminals do not receive neurotrophin support and become weak. domains on the uppermost astrocytes and neurons. However, the synapse is the primary site of its action on neurons BDNF packaged in dense core vesicles of the presynapse ensures anterograde signaling while dendritic BDNF at the postsynapse and in microglia contributes to anterograde signaling A separate mechanism involves common human single nucleotide polymorphisms (SNPs) in the BDNF prodomain (Valkenborghs et al., 2019). The Val66Met polymorphism is the result of a nucleotide change from guanine to adenine at position 196 (G196A) that replaces valine (Val) with methionine (Met) at codon 66. The SNP has been reported to alter the transport of BDNF mRNA transcripts to dendrites for local BDNF synthesis. The Val66Met substitution also disrupts the interaction between proBDNF and sortilin, resulting in a defect. After synthesis in the ER, proBDNF can undergo processing directly in the Golgi apparatus by furin or within secretory vesicles from pathways regulated by other proconvertases. Cleavage of proneurotrophin by furin occurs at the ReXeK/ReR consensus sequence (RVRR in proBDNF) to yield the mature neurotrophin and prodomain. Furin cleaves proBDNF at Arg 128 of the consensus site. Mutation of this consensus site from RVRR to RVAA or MVLR has been shown to play a critical role in generating proBDNF that is cleavage-resistant and insensitive to furin and plasmin and has been exploited to generate recombinant releasable proBDNF to demonstrate its biological activity in vitro and in vivo. Other proconvertases, such as PACE4, PC5, and PC7, have been shown to process proBDNF into mature BDNF and prodomains using the same RVRR site (Jeanneteau et al., 2020).

### **Role of BDNF**

Indeed, synaptic plasticity refers to the underlying mechanisms for encoding and storing memories in the brain. BDNF has been shown to be important for the formation and consolidation of long-term memories because its release in response to neural activity and because its binding to receptors on the membrane of nerve cells induces changes in the strength of neural connections. In addition, we know that changes in synaptic connections(Gutierrez et al., 2020), together with increased number, size, and complexity of dendritic spines, is the morphological basis of LTP and memory storage. That is, BDNF-TrkB signaling may play an effective role in enhancing memory function by supporting the expression of proteins that regulate the plastic changes underlying spatial memory processes. (Stringham et al., 2019). BDNF has also been shown to be involved in the formation of recognition memory by promoting the growth and survival of neurons in the perirhinal cortex, a brain region important for object recognition memory.(Notaras & van den Buuse, 2019).

Overall, for these reasons, a detailed understanding of the role of BDNF in the brain may play an important role in developing new therapeutic strategies to address memory impairment in neurodegenerative diseases.(Nikolac Perkovic et al., 2023). BDNF downregulation as an early molecular biomarker may be effective in disease prevention (Yang et al., 2019). Role of BDNF as an Early Biomarker Due to the important role of BDNF in learning and memory processes. That dysfunction or downregulation of the BDNF pathway is involved in the pathogenesis of neurodegenerative disorders including dementia, which are mainly characterized by neuronal damage, synaptic dysfunction, and cognitive decline. Post-mortem brain tissue evaluation from patients with neurodegenerative diseases revealed that neuronal degeneration was strictly associated with decreased serum BDNF levels. Thus, experimental evidence confirms the relationship between BDNF downregulation and neuronal damage, indicating recovery of the neurodegenerative phenotype after BDNF administration and/or upregulation. (Pisani et al., 2023).

### **BDNF's mechanism of action**

Brain-derived neurotrophic factor (BDNF) is known to bind to two different types of receptors on the cell surface, namely TrkB (tropomyosin receptor kinase B) and p75NTR (p75 neurotrophin receptor).(Kang et al., 2020). TrkB is a tyrosine kinase receptor that plays a critical role in neuronal survival, growth, and differentiation. BDNF binding to TrkB will trigger the activation of various intracellular signaling pathways, such as the MAPK/ERK and PI3K/Akt pathways. Activation of these pathways plays a role in regulating gene expression, protein synthesis, and synaptic function, which are important for memory and learning.(Notaras & van den Buuse, 2019).

p75NTR is a low-affinity nerve growth factor receptor that has multiple roles in influencing cells. BDNF binding to p75NTR can trigger a variety of cellular responses, including apoptosis (programmed cell death) or cell survival, depending on the context and cell type.(Kim et al., 2024). p75NTR is also involved in inflammatory processes and immune responses in the nervous system. The interaction of BDNF with these two receptors allows this growth factor to exert diverse effects on nerve cells. The balance between TrkB and p75NTR activation will determine the fate and function of nerve cells. Understanding the interaction of BDNF with its receptors has important implications for the development of therapies for various neurodegenerative and psychiatric diseases. For example, increasing TrkB activity and decreasing p75NTR activity could potentially protect neurons from damage and improve cognitive function. BDNF is a neurotrophin protein that plays a critical role in the growth, development, and survival of neurons(Duarte & Walz, 2019).

BDNF has significant effects on synaptic plasticity, which is the brain's ability to adapt and form new connections between neurons. Receptor Binding: BDNF works by binding to its receptors on the surface of neuronal cells. The primary receptor for BDNF is TrkB (Tropomyosin receptor kinase B). In addition, BDNF can also bind to the p75NTR receptor, although the role of p75NTR in BDNF's mechanism of action is still not fully understood. Signaling Pathway Activation BDNF binding to TrkB triggers the activation of various intracellular signaling pathways, including the MAPK/ERK and PI3K/Akt pathways. These pathways play a role in regulating gene expression, protein synthesis, and synaptic function. Effects on Synaptic Plasticity: BDNF facilitates various processes associated with synaptic plasticity, such as: Neuronal growth and differentiation: BDNF promotes the growth of dendrites and axons, and increases the complexity of neuronal structures(Ng et al., 2021). Increased neurotransmitter release: BDNF increases the release of neurotransmitters from presynaptic neurons, strengthening signals between neurons. Modulation of receptor sensitivity: BDNF modulates the sensitivity of neurotransmitter receptors on postsynaptic

neurons, influencing the neuron's response to signals. Formation of new synapses: BDNF plays a role in the formation of new synapses (synaptogenesis) and the strengthening of existing synapses. Neuronal protection: BDNF also has neuroprotective effects, protecting neurons from damage caused by oxidative stress, inflammation, or other toxic factors. (Duarte & Walz, 2019).

### **BDNF on cognitive function**

BDNF (Brain-Derived Neurotrophic Factor) is a protein that plays an important role in synaptic plasticity, which is the brain's ability to change and adapt connections between neurons. (Tomás et al., 2023). Synaptic plasticity is the basis of learning and memory. BDNF affects cognitive function by promoting neuron growth and survival. (Kang et al., 2020). BDNF promotes the growth of new neurons (neurogenesis) in the hippocampus, an area of the brain important for learning and memory. BDNF also increases the survival of existing neurons, protecting them from damage. Enhances Synaptic Transmission (Bélanger et al., 2021). BDNF increases the release of neurotransmitters, such as glutamate, which is important for communication between neurons. BDNF also facilitates long-term potentiation (LTP), a synaptic strengthening process believed to be the basis of learning and memory. Modulating Synaptic Plasticity BDNF regulates the formation and pruning of synapses, allowing the brain to adapt to new experiences. (Montejo Carrasco et al., 2022).

BDNF also modulates dendritic spine density, which is the site of synaptic contact. Protects against Neuronal Damage. BDNF protects neurons from damage caused by stress, injury, and neurodegenerative diseases. BDNF also reduces inflammation in the brain, which can impair cognitive function. (Arrieta et al., 2020). BDNF Effects on Specific Cognitive Functions: Learning and Memory: BDNF improves learning and memory, both short-term and long-term memory. Attention and Executive Function: BDNF improves the ability to focus, control impulses, and plan (Duarte & Walz, 2019). Language and Communication BDNF plays a role in language and communication development. Decision Making and Problem Solving BDNF facilitates effective decision making and problem solving. Low levels of BDNF have been linked to a variety of cognitive disorders, such as Alzheimer's disease, depression, and schizophrenia. (Mudjihartini, 2021). Increasing BDNF levels through interventions such as exercise, cognitive behavioral therapy (CBT), and medication may help improve cognitive function. BDNF is a key factor in synaptic plasticity and cognitive function. Understanding the mechanisms of action of BDNF may help develop strategies to improve brain health and prevent cognitive decline. (Duarte & Walz, 2019).

### **BDNF in elderly**

As we age, there is a natural decline in BDNF levels in various regions of the brain, especially in the hippocampus and prefrontal cortex. (Yap et al., 2021). The hippocampus plays an important role in the formation of new memories, while the prefrontal cortex plays a role in executive functions such as decision making and planning. (Ng et al., 2021). Decreased BDNF in this area contributes to age-related cognitive decline. physical activity, the brain will be stimulated so that it can increase a protein in the brain called Brain Derived Neurotrophic Factor (BDNF) (Ng et al., 2019). This BDNF protein plays an important role in keeping nerve cells fit and healthy. However, if BDNF levels are low, it will cause dementia. (Sauliyusta & Rekawati, 2016). (pro)BDNF density was relatively high and p75 density was relatively low. In the GCL and PL, (pro)BDNF density was relatively low and p75 density was relatively high. (pro)BDNF and p75 densities were similar in the hilus and ML. TrkB(T1) density was generally lower than both (pro)BDNF and p75, consistent with previous reports of low levels in the adult human hippocampus. (Dunham et al., 2009).

## Kesimpulan dan Saran

Brain derived neurotrophic factor has several functions, including axonal regulation, dendritic growth, role in neurotransmitter release, and long term potentiation (LTP). In accordance with these functions, BDNF has a role as a major regulator of synaptic plasticity. BDNF plays an important role in maintaining brain health and cognitive function in the elderly. Understanding the mechanisms and impacts of BDNF decline in aging can help in developing prevention and intervention strategies to improve the quality of life of the elderly and reduce the risk of neurodegenerative diseases.

An elderly person is someone who is over 60 years old. Elderly or elderly is defined as a condition of decline, weakness, increased susceptibility to various diseases and environmental changes, loss of mobility and physiological changes associated with age. Cognitive decline in the elderly is the biggest cause of dependence on others to care for themselves (Meryska et al., 2024).

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