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Review Article

The involvement of BDNF, NGF and GDNF in aging and Alzheimer's disease

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ABSTRACT: Aging is a normal physiological process accompanied by cognitive decline. This aging process has been the primary risk factor for development of aging-related diseases such as Alzheimer's disease (AD). Cognitive deficit is related to alterations of neurotrophic factors level such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF). These strong relationship between aging and AD is important to investigate the time which they overlap, as well as, the pathophysiological mechanism in each event. Considering that aging and AD are related to cognitive impairment, here we discuss the involving these neurotrophic factors in the aging process and AD.

Key words: BNDF, NGF, GDNF, Aging, Alzheimer's disease

The population is aging, since older individuals (those over 65 years of age) will double between 2000 and 2050 [1]. Aging is a natural physiological process, a progressive deterioration of the overall homeostatic brain mechanisms, accompanied by cognitive decline. A consequence of normal aging is a greater susceptibility to learning and memory impairments generally attributed to a decrease in neuronal plasticity of the cortex and hippocampus. Cognitive processes mediated by hippocampus and prefrontal cortex are most vulnerable to aging process [2]. Both brain regions suffer cellular and synaptic changes during aging that can be directly related to decline of cognitive performance [3].

Considering that the life expectancy of the population has increased, the senescence has been the primary risk factor for development of aging-related diseases such as Alzheimer's disease (AD) [4]. Cognitive deficits are the most common consequences of aging process and AD [4-6]. AD is one of the most common and devastating aging-related neurodegenerative diseases. This illness is characterized by massive neuronal loss, cognitive dysfunction and loss of memory. The incidence and prevalence continuously increases with advancing age. The clinical manifestation of disease occurs usually after the age of 65 [7].

Both aging process and AD are characterized by a progressive deterioration of learning and memory [4-6]. This strong relationship between aging and AD is important to investigate the time which they overlap, as well as, the pathophysiological mechanism in each event such as the involvement of the neurotrophic factors in these processes.

Neurotrophic factors are secreted protein that display important role in the synaptic and neuronal growth,

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pruning, myelination, differentiation, and survival of neuronal [8, 9]. There are three neurotrophic factors that will be addressed in the review: brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF). These neurotrophic factors signaling are also severely affected in aging process and AD which can be correlated with cognitive decline.

Despite the fact that age-related and AD cognitive deficits are well-documented, the underlying BDNF, NGF and GDNF changes in the brain remain largely unclear. Therefore, this review discusses the involving of these neurotrophic factors in the aging process and aging-related diseases such as AD.

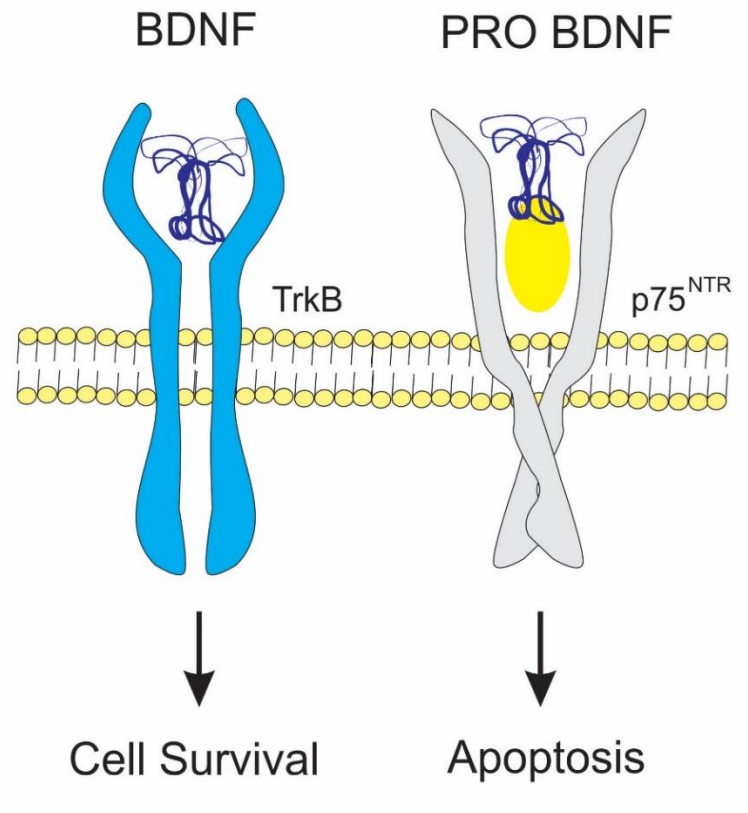

Figure 1. BDNF or pro-BDNF receptor. The BDNF binds to TrkB receptor and this interaction induces the activation of pathway signaling to culminate in cell survival. When the pro-BDNF binds $p75^{NTR}$ can lead to apoptosis. Abbreviations: BDNF, brain-derived neurotrophic factor; $p75^{NTR}$, p75 neurotrophin receptor.

BDNF and aging

BDNF is differentially expressed across several brain tissues. Nutrition, metabolism, behaviour, and stress affected the expression this neurotrophic factor in the central and peripheral nervous systems [10]. BDNF is synthesized from BDNF pro-isoform, which is then cleaved proteolytically (N-terminal domain is removed) inside the neuron or after it is released, creating its final protein form [11]. This mature neurotrophin binds to protein-kinase neurotrophin receptors – tropomyosine-related kinase (Trk) receptors. BDNF is crucial to learning and memory, since it regulates LTD (long-term depression) and LTP (long-term potentiation), synaptic plasticity, axonal sprouting, proliferation of dendritic arbor, and neuronal differentiation [12, 13]. These

mechanisms in the central nervous system are activated through BDNF interaction with Trk B receptors [14]. The pro-BDNF binds to the p75 neurotrophin receptor (p75NTR) [15]. In contrast, when the pro-BDNF binds to p75NTR activates apoptotic pathways in peripheral neurons and glia [16] (Figure 1).

BDNF is capable of modulating diverse biological processes such as aging via interaction with different receptors [17].

In the aging occurs gradual impairment of cognitive abilities which are associated with cortical or hippocampal alterations, two brain regions involved in memory and learning processes [18]. BDNF helps to protect neurons from damage caused by infection or injury. It is a small dimeric protein, structurally related to NGF, which is abundantly and widely expressed in the adult mammalian brain [12, 19] acting also as an important mediator of synaptic plasticity and memory formation [20]. BDNF expression in the central nervous system is modified by many brain insult, such as seizure, stress, ischemia, and hypoglycemia [21, 22]. Alterations in its expression may contribute to some pathologies such as depression, AD, Parkinson's disease and epilepsy [22].

A study involving human adults aged 20–93 years [23], investigated the effects of BDNF polymorphism on multiple indices of memory (prospective, associative, subjective complaints and item). Results suggested that a genetic predisposition to BDNF val66met polymorphism, exerts influence on multiple indices of episodic memory. In some cases, this polymorphism can be alter the subjective memory and perhaps associative memory [24]. Another study performed with men and women of Finnish origin, suggested that BDNF was not associated with cognition in men. However, BDNF level can indicate the impaired memory and general cognitive function in aging women [25].

A preclinical study showed that a chronic BDNF deficiency leads learning deficit dependent on age in animals after seven months. These authors also observed a positive correlation between hippocampus BDNF levels and learning performance during the probe trial involving animals that showed a good learning performance during the long-term memory test [26].

A study in nerve cells from rats reported that γ-secretase inhibitors (GSIs) disrupted the retrograde axonal trafficking of BDNF, suppressed BDNF-induced downstream signalling pathways and induced changes in the distribution of neuronal processes in mitochondria and synaptic vesicles. In contrast, treatment with a novel class of γ-secretase modulators (GSMs) had no significant effect, since knockdown of APP by specific siRNA prevented GSI-induced changes in BDNF axonal trafficking and signalling. It was also reported that GSI effects on APP processing were responsible, at least in part, for BDNF trafficking and signalling deficits [27]. Moreover, a study performed in rats showed that TrkB receptors are markedly decreased in the pituitary during the aging process. It also reported that a possible trophic role of BDNF in the pituitary might be significantly reduced. This can be a result of the decrease in TrkB receptors during aging, since BDNF may be an intercellular messenger to help regulate some pituitary functions. A decrease in BDNF receptors rather than in BDNF itself might contribute to endocrine alterations associated with aging [28].

It was also reported that the administration of exogenous BDNF produced a marked increase in the multi-threshold locus coeruleus (LC), accompanied with a decrease in threshold current. Besides, no morphological changes to the noradrenergic axons were observed in the BDNF-infused cortex [29]. The infusion of anti-BDNF led to a dose-dependent reduction of the multi-threshold LC neurons, accompanied with an increase in threshold current. The results of this study also suggest that BDNF may contribute to functional changes in the pre-synaptic axon terminals of LC neurons in the aging brain [29]. Furthermore, BDNF is necessary for the maintenance of noradrenergic innervations in the aged brain [30]. Therefore, BDNF display an important role in aging process.

BDNF and Alzheimer's disease

Studies have demonstrated the role of BDNF in both animal models, and patients with AD. BDNF is important in neuronal growth and neuronal survival, participating in the synaptic processes of memory. Evidence has suggested the involvement of BDNF with AD pathology. Studies have shown alterations in the levels of this neurotrophin in AD patients. Results show reduction (21-30%) in pro-BDNF in patients with MCI (mild cognitive impairment) and major reduction (40%) in terminal patients. These results suggest the involvement of BDNF with cognitive dysfunction in AD patients [31]. Another studies have shown BDNF levels diminished in AD patients as compared to controls [32-37]. Lee (2009) also observed a BDNF levels decrease in both AD and MCI patients [38]. Other results showed increase in the BDNF levels in these patients. Authors suggest that this increase may be an upregulation of BDNF [39, 40]. Reductions in the levels of BDNF, NGF and GDNF were observed in 26 patients with moderate AD and 62 with MCI [41]. Changes in BDNF levels are well related to cognitive impairment. Studies analyzing frontotemporal dementia (FTD), Lewy body dementia (LBD), vascular dementia (VAD) and AD found a decrease in BDNF levels, when compared to controls [42].

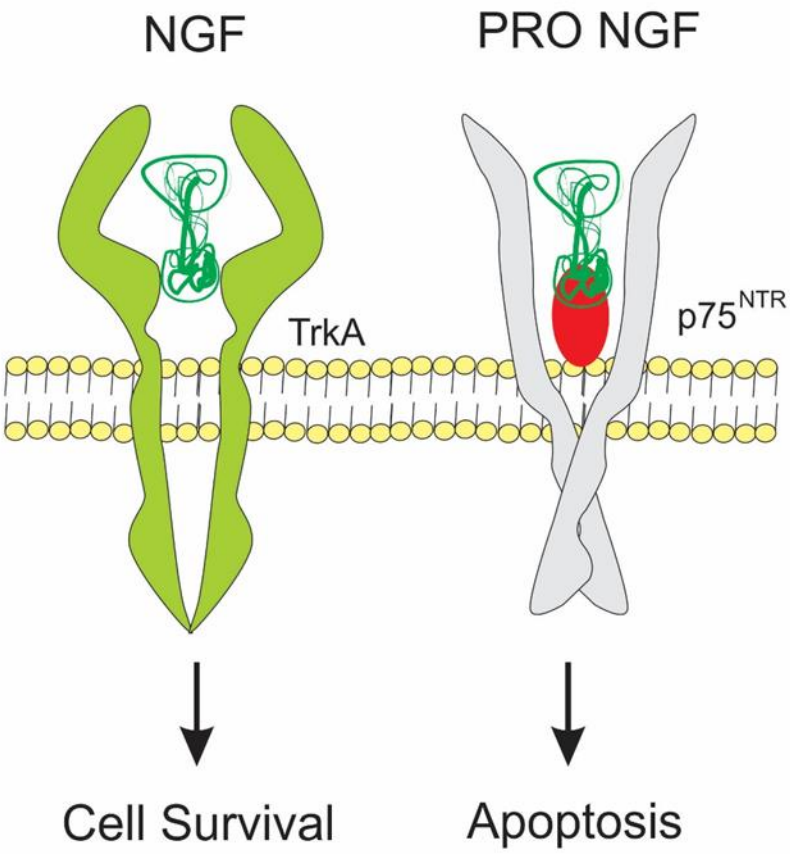

Figure 2. NGF or pro-NGF receptor. The NGF binds to TrkA receptor and this interaction induces the activation of pathway signaling to culminate in cell survival. When the pro-NGF binds $p75^{NTR}$ can lead to apoptosis. Abbreviations: NGF, nerve growth factor; $p75^{NTR}$, p75 neurotrophin receptor.

On the other hand, some results have shown increases in the levels of BDNF in AD patients when compared to controls and MCI [40]. Increased expression of TrκB was found in CA1 region of the hippocampus of patients in early stages of AD [43]. Other results also demonstrated an increase in the levels of BDNF in both AD and MCI patients, not disease severity or acetylcholinesterase administration dependent [39]. Beyond BDNF, Glycogen synthase kinase-3β (GSK3β) and cAMP-response element-binding protein (CREB) are signaling molecules that can be involved in the neurodegenerative progression [44, 45]. A study showed that platelet GSK3β activity, lymphocyte CREB activity and plasma BDNF have been related to AD. Increased GSK3B and CREB activity was found in AD patients with depressive symptoms. This increase in CREB can be explained by the presence of depressive symptoms in these patients or because of low BDNF levels in patients suffering with depression [33]. These changes in the levels of BDNF may be well related to the several stages of AD pathology. Decreased levels have been observed in later stages and an increase in the initial stages, which may be a regulatory organism of memory loss. Another remarkable characteristic is the BDNF val66met polymorphism. However, some results shows that it is not associated with development of AD. In a sample of 149 patients, no relationship was found with genotype vall66met [46]. According another studies, there is no association between vall66met and BDNF changes in AD [47-50]. Further studies are required to understand the exact relationship between polymorphism

and dysfunction to BDNF levels in AD. Population studies have shown to date, a small sample size and this may be a weakness for these studies.

Preclinical reports have investigated possible pharmacological treatments to increase BDNF levels in transgenic mice [51-53] or in animals subjected to administration of amyloid β peptide. Treatments with caffeine in AD transgenic animals shows increased levels of BDNF, and chronic treatments with caffeine improved both BDNF levels and cognitive impairment. Pioglitazone, a hypoglycemiant drug, restores BDNF levels and attenuates the inflammatory markers in an animal model of AD induced by amyloid β peptide administration. The oral administration of fingolimod improved both BDNF levels and cognitive impairment observed in animals [54, 55].

It is observed that additional research is needed to understand the relationship between BDNF and AD. A potential treatment with BDNF seems to be a possible therapeutic target for patients, perhaps improving cognitive dysfunction.

NGF and aging

NGF is a glycoprotein that consists of three sub-units: α-NGF that is inactive; β-NGF that is biologically active and γ-NGF that processes the NGF precursor into its mature form. NGF is synthesized as a precursor from pro-NGF and is either secreted outside the cells or cleaved intracellularly into mature NGF. The secretion of NGF can be a mixture of pro-NGF and mature NGF. There are three types of NGF receptors, these being; TrkA, p75 and sortilin. The trophic effect of NGF is mediated through of TrkA and p75 receptors [56, 57], while the neurotoxic effect of pro-NGF is mediated through p75 in conjunction with sortilin [58] (Figure 2). Pro-NGF is the predominant form of NGF in central nervous system [59].

It has been related that increase proNGF levels induce apoptosis in various types of cells under seizures and spinal cord injury [60, 61]. Moreover, evidence indicate that pro-NGF inhibit the proliferation and differentiation of hippocampal neural stem or progenitor cells from postnatal mice [62]. These effects of pro-NGF might be mediated through p75NTR [63] (Figure 2). In this context, a study performed by Al-Shawi et al (2008) indicated that proNGF leads cell death in basal forebrain and peripheral sympathetic neurons of old rat. This effect not found in young animals. Moreover, pro-NGF was elevated during aging in the projection areas of some populations of vulnerable central and peripheral neurons [64]. Terry et al., (2011) showed age-related impairments in spatial learning and deficits in recognition memory. These effects were accompanied by elevated levels of the pro-NGF, p75NTR and sortilin in the prefrontal cortex and hippocampus of aged rats [65].

Growth factors like NGF are important in the neuronal plasticity and survival of forebrain cholinergic neurons (cerebral cortex, hippocampus, basal forebrain and hypothalamus), which are memory-related [66]. [67] found decreased levels of NGF in the hippocampus of 28-month-old Fischer rats, while [68] showed that NGF levels were decreased in the cortex of 24-month-old wistar rats. Considering that NGF is important for cognitive functions, and it was found to have decreased with aging, this neurotrophic factor might contribute to an age-dependent decline in cognitive function [67-69]. Therefore, it plays a significant role in memory and cognition, and the development, survival and maintenance of cholinergic neurons [70], usually in the aging brain.

NGF and Alzheimer's disease

Recent studies have shown that NGF plays a role in aging as well as in age-related diseases such as AD, since aging can interact with preexisting abnormalities in trophic signaling to trigger cholinergic and cognitive decline as observed in AD [71].

There are different evidences about NGF level in clinical and preclinical studies. For instant, [72] observed no differences of NGF levels in the in serum, brain-spinal fluid, and brain (hippocampus and parietal cortex) in AD patients. NGF levels in the dentate gyrus of AD patients were higher [40]. Also reported no significant differences in the plasma NGF levels of AD patients as compared to control group. In contrast, [73] found increase of NGF levels in cerebrospinal fluid of AD patients. [74] showed that the amyloid β (25-35) administration intrececebroventricular for 14 days, in mouse, induced reduction of NGF protein expression, which might contribute to the cognitive impairments found in this animal model of AD.

An interesting study has shown the effects of NGF treatment on patients with AD. Results showed that after treatment lasting for 12 months, patients had improvements in cognitive function, and lower levels of amyloid β in their cerebrospinal fluid [75]. Increased pro-NGF was observed in *post-mortem* studies of patients with AD [76]. In another study, six AD patients were treated with NGF for 12 months. Results were positive, showing lower levels of amyloid β in their cerebrospinal fluid. However, most patients showed signs of brain atrophy, as evidenced by increases in phosphorylated tau [77]. Reductions in NGF levels can be caused by decreased cholinergic activity, and the death of parts of the post frontal and temporal cortex, as seen in AD patients [78]. Side effects were also noted with NGF

treatments. After three months of treatment, it was found that patients had back pain, which brought an interruption in the treatment. Despite the small sample numbers used in the study, the authors suggest that other alternative routes of administration or lower doses may minimize side effects [79].

Pre-clinical research has focused on NGF, seeking cognitive improvements and increased levels of neurotrophins. transgenic animals observed increases in the levels of NGF, BDNF, and NT3, and reductions in the number of hippocampal amyloid β (1-40)- and amyloid β (1-42) -positive amyloid plaques after the treatment with insulin-like growth factor 2 (IGF2) [80]. Already it has been found that treatment with valproate (VPA) in animals with AD decreased the nuclear factor kappa B (NFκB) of IL-1β mRNA. VPA has also increased NGF levels in the hippocampus of animals that were 5 and 10 months of age [81]. Moreover, it is important emphasize that amyloid β blocks neuronal function via the inhibition of kinesin 5, consequently reducing the transport of cell-surface NGF/NTR(p75) in PC 12 cells [82].

In contrast to NGF, increases in pro-NGF have been related to AD patients [83-85] and patients affected by MCI [83]. These studies indicated that NGF and pro-NGF might be an important target in AD.

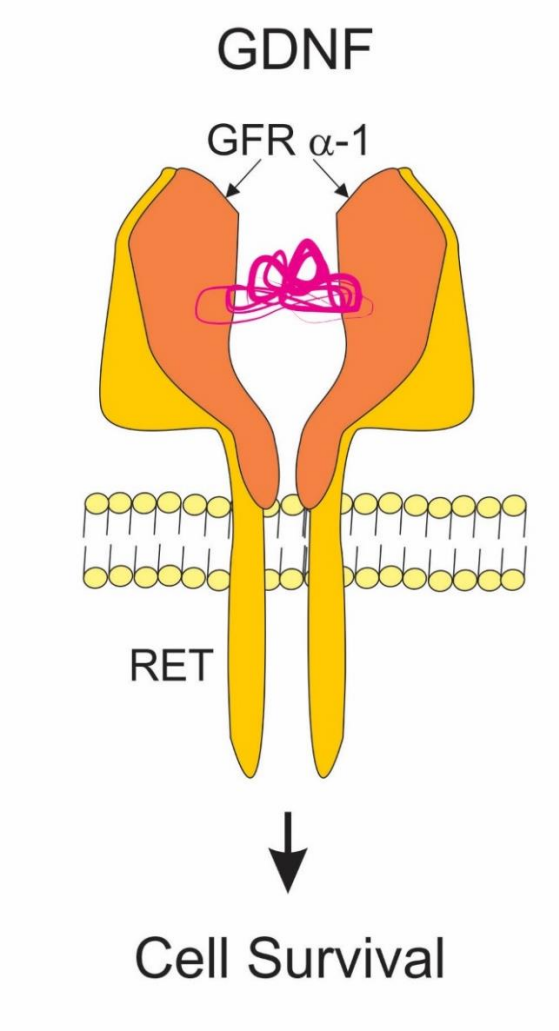

Figure 3. GDNF receptor. The GDNF binds to a multi-component receptor complex compound by GFR α1 and RET inducing cell survival. Abbreviations: GDNF, glial cell-derived neurotrophic factor; GFRα1, GDNF receptor alpha1; RET, signaling component rearranged during transfection.

GDNF and aging

GDNF (originally isolated from the supernatant of a rat glioma cell-line) is an important growth factor for the development, survival, and maintenance of midbrain dopaminergic neurons [86, 87]. GDNF interacts to a multi-component receptor complex compound by ligand binding cell surface component GDNF receptor alpha1 (GFRα1) and signaling component rearranged during transfection (RET) receptor tyrosine kinase [88, 89] (Figure 3).

It's known that motor function and all dopaminergic system have a decline with normal age and Parkinson's disease patients have an intense decline in this system [90]. The potential of GDNF against age-related cognitive deterioration has not been fully explored. [91], had assayed GDNF for its neurotrophic effects against the neuronal atrophy that causes cognitive deficits in old age, and they found that spatial learning and memory testing showed a significant gain in cognitive abilities due to GDNF exposure. However, the specificity of GDNF to dopaminergic area is the reason that it has been studied for potential use for the treatment of Pankinson's Disease, with clinical trials currently in progress. In this context, [92] has been studying GDNF administration as therapeutic option for neurodegeneration. It has been described that GDNF could exert neuroprotective and neurorestorative effects on substantia nigra neurons in animal models of Parkinson's Disease, as well as in patients [93, 94].

Other systems also seem to be related to GDNF. [95] suggest that reduced levels of GDNF induce excess glutamate release and deregulation of glutamate transporter-1, causing excitotoxicity in the nervous system that precedes dopaminergic degeneration. In this sense, a study performed by [96], showed GDNF expression level was increased with age in the frontal cortex, but was not in the hippocampus, in the age-dependent changes in LC noradrenergic innervations suggesting that these innervations may be locally regulated by different neurotrophic factors that exert their trophic actions at different target sites.

It has also been found to have trophic and protective effects on noradrenergic neurons in the LC, as well as peripheral motor neurons [97-99]. It has already been shown to prevent both neurons and glial cells from oxidative stress [100, 101]. [102] indicate that GDNF can protect nigrostriatal dopamine neurons against the effects of 6-hydroxydopamine in aged as well as young adult rats. Moreover, an additional study showed a significant increase of GDNF protein content in the spinal cord of old (24-month-old) rats subjected to 2 weeks of exercise [103].

GDNF and Alzheimer's disease

GDNF has been hardly studied and depletion of this neurotrophic factor seems to be linked with disease, pathology and symptoms such as AD [92]. A study performed by [104] showed that the GDNF administration can protect against AD-like chances induced by injection of aluminum complexes in rabbit.

Disturbances in cholinergic neurons may occur as a consequence of effects concerning catecholaminergic neurons and it can be related with AD. [105] found increased GDNF in cerebrospinal fluid and decreased serum concentration of GDNF in patients with AD in early stages suggesting an adaptive process of the impaired brain. [106] showed increased GDNF levels in plasma of AD patients. Moreover, in *postmortem* middle temporal gyrus of AD patients, [107] observed that mature GDNF peptide was down-regulated. In the same line, a study found the serum GDNF levels significantly reduced in MCI and AD patients [108]. In contrast, [40] observed no significant differences in the GDNF levels of plasma of AD patients and control group showed.

Recently, [109], have reported that GDNF was down regulated in 3xTgAD mice (a transgenic strain of mice) and 6 months of voluntary exercise was capable of reverse this effect. Furthermore, it has reported that 10-month-old 3xTg-AD mice subjected to 6 months of overexpressing GDNF (recombinant lentiviral vectors), showed improvement in the learning and memory. This GDNF neuroprotective effect induced a potent upregulation of BDNF, indicating that together may important against neurons atrophy and degeneration [110].

Conclusion

The major risk factor for neurodegeneration and cognitive decline is the aging of the brain. The changes in neurotrophic factors expression are not well characterized during human brain development and aging. Knowing these changes may elucidate structural, metabolic, and functional brain processes over the lifespan, as well vulnerability to neurodevelopmental or neurodegenerative diseases.

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