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Research Paper

Neurotrophin Receptor P75 Modulation Effects on Alzheimer's Disease

Welton Daniel Nogueira Godinho,Luiz Valcyr Diogenes Pereira Neto[1], Gabriel Campelo Ferreira[1],Jonathan Moreira Lopes[1],Mateus dos Santos Feitoza[1],Paula Matias Soares[1].

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Abstract: *The brain of an adult person has approximately 100 billion neurons, each with long and extensive branching. These branches allow individual neurons form connections (synapses) with other neurons. The brain then performs about 100 trillion synapses, which, in turn, enable the message transmission quickly. Alzheimer's disease (D.A) is the most prevalent form of dementia, dementias are mental diseases characterized by progressive changes in the central nervous system, affecting memory, orientation temporo - space, learning, criticism, verbal expression and concentration. In dementia occur personality changes and impaired ability to perform routine tasks with ease before, D.A currently has no cure and is progressive. The neurotrophins promote the survival and differentiation of vertebrate neurons, these growth factors can also induce cell death through p75 neurotrophin (p75NTR), a member of the superfamily of tumor necrosis factor receptor, one of the first signs of disease Alzheimer's is the death of cholinergic neurons in the basal forebrain, which express the highest level of p75 in the adult brain, looking so that the study of this channel and modulation are interesting strategies for increasing the quality of life with thisdisease.*

Keywords:*β-amyloid protein,Alzheimer'sdisease, LM11A-31, Nervous system, Neurotrophin receptor, p75NTR*

I. THE ALZHEIMER'S DISEASE

The Alzheimer's disease (A.D.) is the most prevalent type of dementia, which is a group of diseases that compromises normal performances of the nervous system and is characterized by the progressive brain memory alterations, as well as difficulties in time and space orientation, learning, criticism, verbal expression and concentration. When people suffer from any dementia diseases, they present personality changes and decrease of capability when it comes to performing everyday chores (BARASNEVICIUS, 2002).

A.D. was diagnosed for the first time by the German neurosurgeon Alois Alzheimer, in 1907, when he published a case on which a patient had progressively lost his mental faculties within four years. It was also evidenced by *post mortem* autopsies that dementia-diagnosed patient's brains showed neurofibrillary tangled plaques inside amyloid and neurons. The fact that a single case had not ever been published before 1907 does not mean A.D. did not exist. Instead, people used to associate Alzheimer's disease to any other dementia diseases (CORREA, 1996). After this date, there was a rapid proliferation of deep studies and investigations regarding the Alzheimer's disease (ARAÚJO, 2001).

During the 70's, the first neurochemical indication of what could cause dementia symptoms came up after several observations concerning the variable degeneration of neuronal synthesis and acetylcholine release, usually very severe. This was noticed because there was a reduction on the quantity and on the activity of synthetic enzymes (choline acetyltranferase) and degrading enzymes (acetylcholinesterase), respectively related to neurotransmitter production and to synaptic cleft removal, in the brain cortex and limbic system, as well as cholinergic cellular body losses. However, in the end of 1970 and beginning of 1980, some deficits in other neurotransmitters in the brain tissue were identified, indicating that the A.D. is not limited to the degeneration of only a single group of neurotransmitters. Thus, it is considered multifactorial, which explains the lack on efficiency in most cases with patients who have been receiving cholinergic-based medicine (SELKOE, 2001).

Based on what was said above, the A.D. is a progressive neurodegenerative disorder which is manifested by the deterioration of memories related to a neurofunctional declination, with behavioral disturbs and psychic symptoms. The A.D. presents a heterogeneous etiology with several possible causes, among which: genetic susceptibility, metabolic alterations, protein abnormal processing and neurotransmitter deficits (Fuentes; Slachevenz, 2005).

Age and familiar history are the two well determined risk factors when it comes to A.D. (PAUL *et al.*, 1996). Although its etiology remains indefinite, some significant developments occurred regarding the comprehension of its biochemical and genetic mechanisms. It is known that the fragment of 42 amino-acids responsible for the precursor of the β-amyloid protein is of high relevance concerning the senile plaques' pathogenesis and that most the diseases is associated to this protein overproduction (PJ, 1997; SELKOE, 1997). Some proteins that are part of the neurofibrillary wounds, more specifically, the hyper phosphorylated tau-protein and the ubiquitin, were identified, but their association to the formation of plaques and the neurofibrillary wound and to the cellular injuries remain uncertain (PJ, 1997).

An adult person's brain presents approximately 100 billion neurons, each one with long and extensive ramifications. These ramifications allow individual neurons to connect (synapses) with other neurons. These synapses are responsible for the transmission of information under the form of chemical signals that are released from a neuron to another. Hence, the brain performs about 100 trillion synapses, which permit fast message transmission, creating a cellular base for memories, thoughts, sensations, emotions, movements and abilities (AIRES, 2011). The A.D. damages the proper functioning of neurons and the synaptic transmission, especially due to β-amyloid protein accumulation (Aβ – neuritic plaques) outside of cells and because of the presence of neurofibrillary wounds formed by tau-proteins inside the neurons. This either raises difficulties or completely stop the nutrient and other important molecules transportation to a proper neuron functioning, causing cellular death, which configures cerebral atrophy (FARGO, BLEILER, 2014).

II. THE □-AMYLOID PROTEIN, THE FORMATION OF SENILE PLAQUES AND ITS CONSEQUENCES

The β-amyloid protein consists of a chain of 40-42 aminoacids that accumulate on old people's brain, where the β-amyloid protein precursor is originated, which is a glycoprotein partially located between the interior and exterior of the plasmatic membrane. Therefore, the senile plaques are the result of the abnormal metabolism of the amyloid protein precursor (APP), conducting to the neuronal aggregated formation because of the tau-protein hyper phosphorylation. These are two of the most common injuries related to the Alzheimer's disease. These alterations occur, from the beginning of the disease, on the mesial temporal lobe, including the hippocampus and the parahippocampal gyrus, which are considered essential structures to memory processes. As the disease develops, the degenerative process spreads out to the associative neocortex, culminating in cerebral areas responsible for other cognitive processes (KAWASUMI, 2002). This protein is synthesized by neuronal cells, and its amyloid deposits are in cerebral regions, such as cerebellum, striatum and thalamus, which present core function on the A.D.'s histopathology, because it increases the β-amyloid peptide formation significantly. Hence, the quantity of the β-amyloid peptide deposit advances as the individuals age (NITSCH, 1996).

The β-amyloid peptides facilitate the oxyradical production, which can be directly toxic to neurons and glial cells, because their activity involves the cellular membrane's lipid peroxidation, culminating in a deregulation of calcium homeostasis (MATTSON, 2003), considered an important signaler of synaptic transmissions. The β-amyloid protein is the main element of senile plaques. Senile plaques are produced by the β-amyloid fibrillary peptide deposition on human brains. Analysis were performed and showed that amyloid fibrillary compounds of this protein were present on senile plaques (ARMSTRONG *etal*, 1995). Senile plaques are known for activating the glial cells (responsible for protecting the cerebral parenchyma), as well as the microglia and the astrocytes, which are responsible for the phagocytosis of the degenerating parts of the brain. The senile plaques (neuritic) are distributed throughout the cerebral cortex, thus, years before noticing the dementia symptoms, it is possible to admit that there already is β-amyloid deposition and its respectively deposits on the mesial temporal lobe, compromising the cholinergic neurotransmission. As this process evolves, neurofibrillary glial inflammatory and oxidative reactions are added to it, as well as damages to the cytoskeleton, causing more neurofibrillary tangle formation and senile plaque conversion into neuritic. Therefore, along with the progression of this pathogenic process, former low cognitive symptoms turn into early stages of dementia. On moderate and advanced dementia, neuronal losses are intensified and synaptic and neurochemical dysfunctions appear, affecting the cholinergic, serotonergic and glutamatergic systems, above all. This biological heterogeneity is related to the type and intensity of psychic and cognitive manifestations (SELKOE, 1999).

The histopathological damages on A.D., due to the senile plaques and neurofibrillary wounds accumulation, can cause cerebral disorder and atrophy with progressive memory alteration. Besides β-

amyloid protein, the tau-protein, known as axonal protein, very abundant and soluble in neurons, is also considered part of these neurofibrillary wounds and it can assist it during the vesicular transport as well (Querfurth & Laferla, 2010; Mao & Reddy, 2011). The destabilization of the tau-protein with the microtube cause the neuronal progressive degeneration (CORREA, 1996). The first alteration on an A.D.-affected brain consists of the hyper phosphorylation of the tau-protein by several kinases proteins and phosphatases systems that culminate in protein structural and conformational changes, proved by previous researches that these kinases activations are related to the β-amyloid protein (Maccioni *et al*, 2001).

β-amyloid oligomers also directly interact with glutamatergic receptors (NMDA), (ALBERDI *et al.*, 2010). The stimulation of these receptors cause strong and continuous increase on the incomes of Ca^{2+}, inducing neuronal death because of the inflow of this ion. The neuronal death is directly proportional to the quantity of β-amyloid oligomers present in the system, thus the higher the quantity of this protein the stronger stimulation of the NMDA receptors, culminating in an also more intense inflow of Ca^{2+}. The posterior effect is the endocytosis of AMPA and NDMA receptors (SATTLER & TYMIANSKI, 2001). The glutamate is one of the main and most abundant central nervous system excitatory neurotransmitters, which role is related to mechanisms of neural plasticity. These physiological mechanisms are responsible for behavioral processes, such as cognition and memory (BERNE & LEVY, 2009).

Besides the above mentioned deleterious alterations, β-amyloid plaques and neurofibrillary wounds have been registered during immune cells deposition and infiltration in A.D.-diagnosed people's brains (LETIEMBRE *et al.*, 2009). High levels of these kind of cells unleash inflammatory processes through astrocytic and microglial activation, mobilizing macrophages and lymphocytes through the hematoencephalic barrier, releasing pro-inflammatory cytokines and other inflammatory factors, contributing to the progressive compromising of the cerebral tissue, accelerating the development of the A.D. (DAS & BASU, 2008). All the consequences mentioned above are related to the synaptic signaling alterations, discussed on the last topic.

III. THE P75NTR RECEPTOR

Levi-Montalcini's studies (1968) provided proof that the nerve growing factor (NGF) protein acts on the trophic modulation and on the development of the peripheral nervous system sensory neurons. The NGF was also found within the central nervous system (Cns) (Whittemore & Seiger, 1987), in which it presents a trophic function towards cholinergic cerebral neurons. Although the exact NGF mechanism requires a further investigation, an important function is the capability of binding to a receptor at the surface of a cell located above other cells which respond to the NGF. This receptor can be found in monkey, primate and human brains (Woolf, Gould & Butcher, 1989).

Several evidences suggest that one of these targets is the neurotrophin receptor p75NTR. This receptor bonds to the nerve growing factor (NGF) along with other co-receptors, such as the Trk and the sortilne (LEE *et al.*, 2001; TENG *et al.*, 2010). This receptor has a peculiar characteristic of promoting degeneration of or signaling survival, related to the type and level of its ligand, to the presence or absence of these co-receptors and to other factors (IBANEZ & SIMI, 2012). Researches in cell cultures suggest that the β-amyloid could be one of the ligands that would signalize the degeneration without activating the other path (PERINI *et al.*, 2002). The P75NTR expressiveness is enhanced on A.D.-diagnosed patients' brains (Chakravarthy *et al.*, 2010; Chakravarthy *et al.*, 2012). The NGF role on signalizing through p75NTR and TrkA, regulating the trophic state of the basal forebrain cholinergic neurons (BFCNs), has been particularly well evidenced on the development (Greferath *et al.*, 2000).

Therefore, cellular apoptosis, differentiation and survival are apparently controlled by two transmembrane glycoproteins: the p75-kinase neurotrophin receptor and the tropomyosin receptor (Trk) (Yoon, Casaccia-Bonnefil & Chao, 1998). The former is an element of the tumor necrosis factor (TNF) from the receptors' super-family (Geetha, Kenchappa, Wooten & Carter, 2005) with multiple functions. P75 is also related to cellular apoptosis, survival and differentiation, neurite growth (CHEN *et al.*, 2009), Schwann's cell myelination (POWELL, TWOMEY, JAIN & MCCARTHY, 2009), and Schwann's cell development (Khursigara *et al.*, 2001).On the other hand, Trk is a tyrosine-kinase selective ligand receptor, which interacts with p75 to signalize the neuronal cell survival or apoptosis. However, TrkA, a Trk subtype, is considered a neuroprotective agent in several cell lines (FRIEDMAN, 2000).

The various functions of p75 depend on the type of ligand, on the type of cell in which it is expressed and on the presence or absence of the Trk receptor. P75NTR induces growth through a nerve growth factor (NGF) and survival mediated by neuronal cells which express TrkA (DAVIES, 2003). However, p75 expressing neurons without Trk co-expression suffer apoptosis after being treated with NGF (FRIEDMAN, 1999). In other words, when there is a reduction or absence of Trk activation, the apoptosis occurs after the NGF and p75NTR binding (FRIEDMAN, 2000). Although, the p75 expressiveness without Trk is not enough to induce astrocytes and oligodendrocytes apoptosis; this suggests that the cells' destination depends not only on Trk expression, but possibly also on other factors (FRIEDMAN, 2000).

One of the first Alzheimer's disease signs is the death of basal forebrain cholinergic neurons, which expresses the highest level of p75NTR in adults' brains (COULSON & DOES, 2006). The disease also conducts to the loss of hippocampus and cerebral cortex cholinergic neurons, which is very critic to memory (HAINES, 2006). Former studies show that neuronal loss is observed on Alzheimer-diagnosed patients' basal forebrain who are dependent on p75NTR (Defreitas, Mcquillen & Shatz, 2001).

Similarly to neurotrophins, the β-amyloid (Ab) also works as a p75NTR ligand (HAINES, 2006). The Ab (1-42) pathological accumulation is an Alzheimer's disease characteristic (DEFREITAS, Mcquillen & Shatz, 2001). TrkA reduces cleavage through the amyloidogenic precursor protein (APP) path to form β-amyloid peptides while p75 increases cleavage, proving neurotoxicity mediated by p75NTR (SOTTHIBUNFHU *et al.*, 2008). Reduction on TrkA levels can be observed on Alzheimer-diagnosed patients' basal forebrain cholinergic neurons, along with higher levels of pro-neurotrophins in their parietal cortex. This suggests that neuronal death on Alzheimer's disease can also be attributed to the apoptosis mediated by p75NTR signaling (VOLOSIN *et al.*, 2006).

IV. THE LM11A-31 AS A □-AMYLOID COMPETITOR

The LM11A-31 is an amino acid spinoff which is soluble in water and thus get to the central nervous system (KNOWLES *et al.*, 2013; TEP *et al.*, 2013). It presents structural and chemical characteristics that are similar to the NGF domain, which interacts with the p75NTR (MASSA *et al.*, 2006). The LM11A-31 stops the atrophy of cholinergic neurons and cognitive deficits in a A.D.-diagnosed rat model when it starts receiving doses of this amino acid spinoff in early pathological stages, right after Ab plaques appear (NGUYEN *et al.*, 2014). These studies suggest that ligands of p75 might avoid LM11A-31 binding to the β-amyloid protein, which consists important possibilities for future researches.

Simmons' 2014 study reproduced the experiment in older animals in which the disease dissemination was higher. However, all his experiments utilized genetically modified animals. He also used LM11A-31 and its respective p75NTR blocker in an induced model through β-amyloid 41, in which one could clearly notice this peptide presence and its respective degeneration. Hence, interesting perspectives are open to new researches, *i.e.*, p75NTR modulation is considered a promising therapeutic strategy to A.D.

The reduction of β-amyloid (Ab) levels during initial phases of this disease still is a very important goal during the treatment of this pathology. Although, efficient therapies will probably require neurodegeneration decreases (LONGO & MASSA, 2004).

V. CONCLUSION

The nervous system is complex: its functional cell – the neurons – present several integrations which mediate and modify its integrations. Its responses, also complex and not always predictable, are changed in pathological stages like in the Alzheimer's disease. This brief review explained that the A.D. symptoms, as consequences of its two main damages (the senile plaques and the neurofibrillary wounds), are oxidative and inflammatory process alterations, exaggerated inflow of calcium (causing apoptosis), synaptic dysfunction implicating in long term potentiation and neurotrophic signaling.

Understanding how neurotrophins and their receptors work provides perspectives of ways of fighting this pathology, an irreversible and progressive disease, which currently cannot be cured. Nowadays, researches are focused on avoiding the before mentioned consequences of this disease to become even more harmful. Former researches showed that modeling the neurotrophin receptor p75NTR is a valid strategy to maintain neuron survival, differentiation and growth, avoiding encephalic atrophy and degeneration, which characterizes this pathology.

Positive results could be achieved with the LM11A-31 in researches using transgenic cell cultures and transgenic animals, indicating that the p75NTR should be considered a therapeutic target to the Alzheimer's disease (A.D.). P75NTR and TrkA signaling by NGF is essential when it comes to maintaining the nervous system alive and properly functioning, and this signaling is interrupted on A.D.-diagnosed patients' brains.

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