

## Research Article

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## Evaluation of Brain-Derived Neurotrophic Factor Nano Therapies to Treat Alzheimer's Diseases

Elijah Kurien

Father Michael McGivney Catholic Academy, Ontario, Canada

### ABSTRACT

Alzheimer's disease is a neurodegenerative disorder affecting millions across the world. It is caused by the progressive build-up of Amyloid- $\beta$  plaques and tau tangles resulting in inflammation in neurons, followed by apoptosis. This paper aims to synthesize the findings of various researchers on Alzheimer's Diseases to shed light on a treatment using molecules that promote the survival and proliferation of neurons - neurotrophic factors. Each family of neurotrophic factors has different functions and after evaluating each one, brain-derived neurotrophic factor (BDNF) was shown to have the most potential in treating Alzheimer's disease. Nano therapy was considered as a carrier for BDNF to cross the blood-brain barrier. PolyPGLA was found to be the most effective nanocarrier for BDNF.

### \*Corresponding author

Elijah Kurien, Father Michael McGivney Catholic Academy, Ontario, Canada.

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Examining alternate ways of delivering treatments must be done to develop the most efficacious result.

### Introduction

More than six million Americans are living with Alzheimer's Diseases (AD) today [1]. The neurodegenerative disease, often correlated with aging, develops through gradual neuronal impairment, inflammation and finally apoptosis. While the cause of the disease is still unknown, research has shown the importance of neurotrophic factors in the survival and proliferation of neurons. More recently, it has been discovered that a strong correlation exists between levels of specific neurotrophic factors and the progression of Alzheimer's Diseases [2].

Neurotrophic factors are essential proteins that help aid the central nervous system in developing through promoting neuronal survival, plasticity and differentiation [3]. Their levels are notably high during prenatal and early developmental stages of life; however, over time, their levels significantly decrease [4]. There have been multiple hypotheses posed stating: when administered to mouse models with Alzheimer's Diseases, select few neurotrophic factors have been able to treat the disease; however, many of these treatments have had significant side effects, impractical treatment applications or have shown conflicting results [5]. This paper aims to expel all doubts by examining the progression of the disease and how neurotrophic factors can be effectively used as therapeutics for the disease.

Additionally, current treatments involving neurotrophic administer a specific neurotrophic factor directly into the central nervous system and as a result, can be very expensive and dangerous [6]. While treatments involving neurotrophic factors may ameliorate symptoms, without clinical viability and ease of access to the general these treatments won't be as beneficial as one may hope.

### Methodology

A literature search was conducted through the use of Google Scholar. Information on Alzheimer's Diseases pathology, neurotrophic factors and Nano therapies was filtered for.

### Results

The search yielded a large amount of research that showed promise for the potential applications of nano-therapy. Through the comprehension of the factors causing Alzheimer's Diseases, the significance of neurotrophic factors becomes evident.

### Discussion

#### Alzheimer's Diseases Pathology

The progression of Alzheimer's is slow, gradual and can often be deadly. In a patient with Alzheimer's, neural degeneration and death are present throughout the brain but especially extensive in the entorhinal cortex and the hippocampus, two regions in the brain associated with memory [5]. This leads to patients exhibiting symptoms of memory loss, problem solving and difficulty completing familiar tasks [7]. While the amount of work put into researching Alzheimer's Disease has led to fruitful results when concerning symptoms and adverse effects, scientists are yet to fully uncover the cause of the disease. However, they have managed to determine three hypotheses that have become widely accepted today: the Cholinergic Hypothesis, the Amyloid Beta ( $A\beta$ ) Hypothesis and the Tau Hypothesis [5].

The cholinergic hypothesis postulates that the degeneration of the cholinergic neurons, found in the nucleus basalis of Meynert (known as cholinergic NbM neurons) and send axonal projections to the rest of the brain, leading to the formation of neurofibrillary

tangles (NFT) causing Alzheimer's Disease. Normally, these neurons would release an essential neurotransmitter, acetylcholine (ACh) - a neurotransmitter responsible for memory and learning - however, due to their degeneration they severely decrease the amount of ACh found in the brain [8]. Due to the many projections of cholinergic NbM neurons, it means that the loss of ACh can have far-reaching effects on the rest of the brain. Animal models show that cholinergic neurodegeneration leads to A $\beta$  and Tau tangle formation. A $\beta$  specifically, further decreased the activity of choline acetyltransferase, the enzyme that synthesizes acetylcholine [9]. Both A $\beta$  and tau are known to also increase Acetylcholinesterase levels, a hydrolase that breaks down acetylcholine after an action potential [10]. Drugs such as donepezil, galantamine and rivastigmine are administered to patients with Alzheimer's Diseases because they counteract the increased Acetylcholinesterase through inhibition leaving more acetylcholine in the body [11].

The Amyloid Beta hypothesis suggests that the buildup of A $\beta$  starts the process of degeneration. It starts with the dysregulation of proteolytic processing of the precursor to A $\beta$ , amyloid precursor protein (APP) [5]. APP is a transmembrane glycoprotein that promotes synapse formation and neural plasticity [12]. There are two pathways that the protein can go through, the amyloidogenic and non-amyloidogenic pathways [5]. Current research is unclear as to how these pathways are regulated; however, studies have proposed that APP is self-regulated through its YENPTY domain [13]. The non-amyloidogenic pathway is the normal pathway that causes no harm. The amyloidogenic pathway, on the other hand, cleaves APP in a way that produces A $\beta$ . The enzymes that cleave the protein include  $\alpha$ -secretase,  $\beta$ -secretase and  $\gamma$ -secretase. Gamma secretase generates either A $\beta$  that is 39 residues (A $\beta$ 40) or 43(A $\beta$ 42) residues in length, the hydrophobic nature of A $\beta$ 42 makes it more fibrillogenic and harmful to neurons. Amyloidogenic mouse models have also found that the overproduction of A $\beta$  promotes tau hyperphosphorylation, another key hallmark of AD. This results in significant impairment in axonal transport. While scientists are yet to fully understand why it happens to specific demographics of people compared to others, they have discovered that Apolipoprotein E4 is a major genetic risk factor for Alzheimer's Diseases as it promotes A $\beta$  plaques [5].

The tau hypothesis predicates that tau is the driving force behind the progression of Alzheimer's. The core reasoning for this is due to the fact that hyper phosphorylation of tau is often the first sign of AD before amyloid formation or cholinergic neurodegeneration. However, this does not mean that A $\beta$  plaque formation is dependent on Tau hyper phosphorylation since amyloid plaques without tau tangles have been found in patients that did not have Alzheimer's Diseases [5]. Tau is a microtubule-associated protein and promotes the growth of microtubules that maintain the structure of the neuron. When tau is hyperactive phosphorylated by either cyclin-dependent kinase 5(CDK-5) or glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) the tau forms neurofibrillary tangles, lose their function and result in apoptosis in the neuron [14].

Neurotrophic factors are small molecules found throughout the brain that are essential to the survival and function of neurons. Neurotrophic factors can be classified into 3 main groups: neurotrophins, glial cell line-derived neurotrophic factor family of ligands(GFLs) and neurokines [2].

The neurotrophin family consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3(NT-3) and neurotrophin-4(NT-4). They are first synthesized

as proneurotrophins, packed into vessels and are then cleaved of their N-terminal peptide and C-terminal mature protein(denoted by the prefix "mature-") [2]. These proneurotrophins(denoted by the prefix "pro-") are known to activate pathways associated with the p75 neurotrophin receptor inducing neuronal apoptosis. This is useful during the early stages of life for growth cone retraction [15].

NGF maintains function and promotes the development of neurons in the peripheral nervous system and cholinergic neurons in the central nervous system [16]. BDNF mediates hippocampal plasticity - a hallmark of AD. It was found that in patients with AD, pro-BDNF concentration is increased activating apoptotic pathways while mature-BDNF is decreased. BDNF also decreases Amyloid-beta production through the APP Y687 phosphorylation [17]. There is a slight decrease in NT-3, primarily in the motor cortex; however, the cytokine stays relatively unchanged in AD patients. NT-3 is known to protect against the toxicity of Amyloid-beta. Finally, NT-4/5 is known to induce tau dephosphorylation [5].

Another family of neurotrophic factors is the glial-derived neurotrophic factor family of ligands (GFL). This family is composed of GDNF, artemin, persephin, neurturin. GFLs are fundamental for the survival of neurons specifically in dopaminergic neurons in the midbrain. Most GFLs bind to the GFR $\alpha$ 1 to 4 receptors in the brain [2].

The last family of neurotrophic factors is neurokines. While there is a myriad of identified neurokines, the main ones include ciliary neurotrophic factor (CNTF), cardiotrophin-1(CT-1), leukemia inhibitory factor (LIF), neuropoietin (NPN). CNTF is important in supporting motor, dopaminergic and parasympathetic neurons while LIF supports sensory neurons [2].

This review will be focusing specifically on brain-derived neurotrophic factor, as there is significantly much more research and potential for treatment with these molecules.

### **BDNF Treatments**

Brain-derived neurotrophic factor is an important neurotrophin with the potential to treat AD because it interacts with the TrkB receptor, which is directly correlated to a downregulation in amyloid precursor protein. It also dephosphorylates tau through the same TrkB receptor and PI3K-kinase/AKT-dependent mechanisms. Its regulation can be modulated by the CREB promoter however, in Alzheimer's Diseases, the neurotrophin, along with the TrkB receptor, are found to be downregulated. Other studies have shown that a single nucleotide polymorphism can put individuals at an increased risk of developing AD. If the regulation of BDNF can be controlled in patients with Alzheimer's Diseases, it may prove as an effective treatment [5].

### **Tropomyosin-Related Kinase Receptor B and BDNF**

When BDNF binds to a TrkB receptor, the kinase dimerizes leading to the activation of 3 intracellular pathways.

The first is the PI3K-kinase/AKT-dependent mechanisms, which promote the survival of a neuron. In vivo studies have shown that deficiencies in BDNF have led to an inactivation of this pathway that caused increased apoptosis. It was also found that activation of AKT-dependent mechanisms leads to the inhibition of the p53 tumour suppressor, a gene known to increase the risk of cancer when activated. It must be noted that it is unclear how exactly this activation happens since AKT does not directly phosphorylate p53 [18].

PLC- $\gamma$  receptor activates the inositol triphosphate (IP3) receptor which releases intracellular calcium stores. The calcium then activates CAMK, an enzyme that increases synaptic plasticity. Perfusion of BDNF in rat models has been shown to induce long-term potentiation indicating increased synaptic efficacy [18].

The mitogen-activated protein kinase (MAPK) pathway is activated by Ras small GTP-binding protein, a membrane-bound intracellular molecule. Activation of this pathway is shown to interfere with  $\beta$ -amyloid production in AD. Through this pathway, BDNF promotes long-term potentiation (LTP) and synaptic growth [18].

### Nanotherapy Treatments

To get to the brain, brain-targeted drugs must cross the blood-brain barrier (BBB). Unfortunately, BDNF is a molecule that has been proven to be incapable of crossing the BBB and as a result, alternative methods must be used to deliver the treatment. A commonly used treatment for all drugs that cannot cross the BBB is injecting it directly into the spinal cord, an intrathecal injection [19]. This method is often very expensive, dangerous and invasive so for BDNF to be used as a viable treatment, safer, cheaper methods must be developed. A new treatment being developed is binding BDNF to poly (D, L-lactide-co-glycolide acid) PLGA. PLGA is a nanoparticle approved by the Food and drug administration for drug delivery and is very cheap compared to an intrathecal injection. Research has shown that these injections into the cochlea may be a viable method to treat deafness [20]. It was also found that PEG and anti-A $\beta$  Abs-coated CNPs (A $\beta$ -CNPs-PEG) nanocarriers can prevent oxidative stress caused by the build-up of A $\beta$  and also stimulate neurogenesis [21].

### Conclusion

Though nanoparticle drug-delivery trials are still in their early stages, they show great promise to be able to treat Alzheimer's Diseases. As of today, PEG and PLGA nanocarriers seem to be the most efficient carriers for increasing BDNF levels in the brain. Successful nanotherapy treatments would allow BDNF to be injected as easily as giving blood.

### References

1. Alzheimer's Diseases and Dementia (2022) Alzheimer's Disease Facts and Figures. Alzheimer's Association. <https://www.alz.org/alzheimers-dementia/facts-figures>
2. Tuane Bazanella Sampaio, Anne Suely Savall, Maria Eduarda Ziani Gutierrez, Simone Pinton (2017) Neurotrophic factors in Alzheimer's and Parkinson's diseases: Implications for pathogenesis and therapy. *Neural Regeneration Research* 12: 549-557.
3. Linker R, Gold R, Luhder F (2009) Function of neurotrophic factors beyond the nervous system: Inflammation and autoimmune demyelination. *Critical Reviews™ in Immunology* 29: 43-68.
4. Platholi J, Lee FS (2018) Neurotrophic factors. *Handbook of Developmental Neurotoxicology* 55-64.
5. Schindowski K, Belarbi K, Buée L (2008) Neurotrophic factors in Alzheimer's disease: Role of Axonal Transport. *Genes, Brain and Behavior* 7: 43-56.
6. Deng P, Anderson JD, Yu AS, Annett G, Fink KD, et al. (2016) Engineered BDNF producing cells as a potential treatment for neurologic disease. *Expert Opinion on Biological Therapy* 16: 1025-1033.
7. Alzheimer's Diseases and Dementia (2022) Alzheimer's Association. [https://www.alz.org/alzheimers-dementia/10\\_signs](https://www.alz.org/alzheimers-dementia/10_signs)
8. Colovic MB, Krstic DZ, Lazarevic Pasti TD, Bondzic AM, Vasic VM (2013) Acetylcholinesterase inhibitors: Pharmacology and toxicology. *Current Neuropharmacology* 11: 315-335.
9. Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, et al. (2018) The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain* 141: 1917-1933.
10. Majdi A, Sadigh Eteghad S, Rahigh Aghsan S, Farajdokht F, Vatandoust SM, et al. (2020) Amyloid- $\beta$ , TAU, and the cholinergic system in Alzheimer's disease: Seeking direction in a tangle of clues. *Reviews in the Neurosciences* 31: 391-413.
11. Patel B, Holland NW (2011) Adverse effects of acetylcholinesterase inhibitors. *Adverse Effects of Acetylcholinesterase Inhibitors*. Consultant 360. <https://www.consultant360.com/articles/adverse-effects-acetylcholinesterase-inhibitors>
12. Priller C, Bauer T, Mitteregger G, Krebs B, Kretzschmar HA, et al. (2006) Synapse formation and function is modulated by the amyloid precursor protein. *Journal of Neuroscience* 26: 7212-7221.
13. O'Brien RJ, Wong PC (2011) Amyloid precursor protein processing and alzheimer's disease. *Annual Review of Neuroscience* 34: 185-204.
14. Thomson P (2020) Amyloid hypothesis vs TAU Hypothesis: Stressmarq <https://www.stressmarq.com/amyloid-hypothesis-vs-tau-hypothesis/?v=3e8d115eb4b3>
15. Fahnestock M, Shekari A (2019) PRONGF and neurodegeneration in alzheimer's disease. *Frontiers in Neuroscience* 13: 129.
16. Aloe L, Rocco ML, Bianchi P, Manni L (2012) Nerve growth factor: From the early discoveries to the potential clinical use. *Journal of Translational Medicine* 10: 239.
17. Xia Y, Wang ZH, Liu P, Edgington Mitchell L, Liu X, et al. (2020) TrkB receptor cleavage by Delta-secretase abolishes its phosphorylation of app, aggravating Alzheimer's disease pathologies. *Molecular Psychiatry* 26: 2943-2963.
18. Mohammadi A, Amooeian VG, Rashidi E (2018) Dysfunction in brain-derived neurotrophic factor signaling pathway and susceptibility to schizophrenia, parkinson's and alzheimer's diseases. *Current Gene Therapy* 18: 45-63.
19. What are intrathecal injections? (2020) SCA source. <https://scasource.net/2020/08/14/snapshot-intrathecal-injections/>
20. Khalin I, Kocherga G, Abu Bakar M, Alyautdin R (2015) Targeted delivery of brain-derived neurotrophic factor for the treatment of blindness and deafness. *International Journal of Nanomedicine* 10: 3245-3267.
21. Weiyan Zhang, Wenyue Wang, David X Yu, Zhicheng Xiao, Zhiyong He (2018) Application of nanodiagnostics and nanotherapy to CNS diseases. *Future Medicine* 13: 2341-2361.

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