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Review

Nanoparticle-mediated growth factor delivery systems: A new way to treat Alzheimer's disease

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ABSTRACT

The number of people diagnosed with Alzheimer's disease (AD) is increasing steadily as the world population ages, thus creating a huge socio-economic burden. Current treatments have only transient effects and concentrate on a single aspect of AD. There is much evidence suggesting that growth factors (GFs) have a great therapeutic potential and can play on all AD hallmarks. Because GFs are prone to denaturation and clearance, a delivery system is required to ensure protection and a sustainable delivery. This review provides information about the latest advances in the development of GF delivery systems (GFDS) targeting the brain in terms of *in vitro* and *in vivo* effects in the context of AD and discusses new strategies designed to increase the availability and the specificity of GFs to the brain. This paper also discusses, on a mechanistic level, the different delivery hurdles encountered by the carrier or the GF itself from its injection site up to the brain tissue. The major mass transport phenomena influencing the delivery systems targeting the brain are addressed and insights are given about how mechanistic mathematical frameworks can be developed to use and optimize them.

Contents

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia (over 60–80%), targeting mostly the elderly with a prevalence of 2–10% of people aged 65 years [1]. With the aging of the world population, more and more people will be diagnosed with AD, thus creating a huge socio-economic burden [1,2].

AD is characterized by three major pathophysiological hallmarks. The first one is the dysregulation of the cholinergic systems, which has been shown to be correlated with the cognitive impairments of patients developing AD [3,4]. The second hallmark is the senile plaque accumulation made of β-amyloid peptide aggregates. β-Amyloid peptides are derived from amyloid precursors that can undergo several cleavages by β-, γ- and α-secretase. In AD, β-amyloid peptides accumulate and lead to toxic fibrillary aggregation also known as senile plaques [5]. Those aggregates severely impair the viability of neurons by disrupting brain parts composed of unmyelinated neurons, dendrites and glial cells also known as neuropil [6]. Finally, the third hallmark of AD is the apparition of neurofibrillary tangles resulting from the hyperphosphorylation of Tau protein [7,8]. Tau is a microtubule-associated protein found mostly in the axons [9]. Internal cell dysregulations observed in AD patients cause a hyperphosphorylation of Tau, which severely impairs the axon integrity and the neurotransmitter transport [7,10]. Moreover, there is increasing evidence showing that those three hallmarks are closely interconnected, which tend to indicate that future therapeutic approaches should act simultaneously on all of them [11–15].

The current treatments for AD are mostly acetylcholinesterase inhibitors (Rivastigmine, Dopenezil, Galantamine) or NMDAR inhibitor (Memantine). Those inhibitors show only transient effects without stopping the progression of the disease and are principally administered orally or transdermally [16–18]. Other treatments focus on senile plaques or the hyperphosphorylation state of Tau proteins [19–21]. Treatments that focus on β-amyloid peptides have mostly failed in clinical studies due to a lack of effectiveness or the presence of severe side effects such as liver toxicity, immunogenicity and low specificity for the brain [20]. Meanwhile, treatments focusing on the hyperphosphorylation of Tau, which target glycogen synthase kinase 3 beta (GSK3β) known as one of the most important Tau kinases, are currently under clinical studies [20].

Growth factors (GFs) such as bone morphogenetic proteins (BMPs) [22–25], insulin-like growth factor (IGF-1/IGF-2) [26,27], basic fibroblast growth factor (bFGF) [28–30] and neurotrophins (nerve growth factors, NGF [31–33]; glial-derived neurotrophic factor, GDNF [34] and brain-derived neurotrophic factor, BDNF [35,36]) are very promising therapeutic molecules. Those GFs can normally be found in the brain and play a crucial role during the developmental stages of the central nervous system (CNS) [37–43]. There is also much evidence showing that those GFs can act simultaneously on several AD hallmarks. For example, it has been shown that BMP-9 could successfully reduce senile plaque in rodents and promote the cholinergic differentiation and maintenance [22,23,25]. Other studies have also shown that IGF-2 and NGF can significantly reduce the senile plaques and the level of Tau hyperphosphorylation [27,32,33,44,45].

The best administration route for GFs seems to be the intranasal injection due to a high capillary density, a large surface area, the proximity to the brain and also because of the high endocytosis activity of nasal endothelial cells [46–52]. However, several biological barriers can severely impair the transportation of GFs across the brain such as the blood–brain barrier (BBB), which regulates the passage of molecules from the blood to the brain through active transport and specific cell receptors [53–55]. The GFs are also sensitive to enzymatic degradation, clearance and denaturation in the blood or in the brain [51]. For instance, BMPs show a very small half-life of about 6–7 min in non-primate mammals [56]. Delivery systems that can extend the life-span of GFs and provide for their controlled, sustained and local release could overcome all these problems. However, the physical–chemical properties of the delivery carriers, such as their size, overall surface charge and chemical composition will greatly influence their capacity to specifically target brain tissue and they will need to be carefully analyzed to determine their cytotoxicity, biocompatibility and biodegradability [57–59].

There is also a need to understand the delivery mechanisms involved from the injection site to the brain. This knowledge can then further help to build explanatory and predictive models that enable realistic simulations. A number of mass transport phenomena govern the release of the GFs from their delivery systems; the main ones are diffusion, swelling, erosion, convection and interactions [60]. These mass transport phenomena have a massive influence on the rate at which GFs are released and must be taken into account when targeting the brain, as they are involved from the site of injection to the delivery within the brain itself [61–63]. Research is uncovering more knowledge about the diffusion of molecules in the brain [47,64–66], but only a few mathematical frameworks have been proposed that model the mass transport of drugs in the brain [61]. Hence, our understanding of the phenomena underlying this transport is far from adequate. We need to develop and adapt mathematical models to describe these transport phenomena as they concern the delivery of GFs to the brain.

This paper first describes the particularity of the BBB affecting significantly the brain uptake of therapeutics and presents the different administration routes proposed to overcome those hurdles. Secondly, the latest advances in the development of brain-targeted GF delivery systems (GFDS) are reviewed and some of the new strategies used to address specific molecules across biological barriers into the brain are discussed. The different materials, their advantages and limitations in the context of GF delivery as well as their *in vitro* or in vivo effects on GF liberation are also addressed. This paper then focuses on the mass transport phenomena that can be encountered by GFDS dealing with the release mechanisms that should be considered and the mass transport of the carrier itself across the BBB up to the brain tissue. This chapter examines how they can be modeled by adapting existing mechanistic frameworks to GFs.

2. Growth factor to treat Alzheimer's disease and their CNS delivery

2.1. Overview of growth factors as therapeutic molecules

There is increasing evidence from the literature showing the promising therapeutic effects of several GFs on different AD hallmarks [25,45,67,68]. GFs act as first messengers by interacting with their receptors, localized at the cell surface. This interaction can then trigger the activation of signaling pathways which in turn, modulate several cell behaviors such as survival, proliferation and differentiation [69–71]. It has been reported that signaling pathways such as phosphoinositide 3 kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) composed by extracellular signal-regulated kinase ERK were dysfunctional in AD and the use of GFs could restore them [31,72,73]. Fig. 1 and Table 1 summarize the major GFs that have shown a therapeutic potential as well as their mode of action and *in vitro* and *in vivo* effects. Those can be naturally found in the CNS and are involved both in the development of the embryonic brain and the homeostasis of the adult CNS [31,38,74–76]. GFs also have the ability to play simultaneously on several pathophysiological symptoms of AD, which render them very attractive as an alternative therapeutic avenue. For instance, BMP-9 has been shown to decrease beta amyloid peptide deposits (senile plaque), protect cholinergic neurons of the basal forebrain and upregulate the cholinergic system by increasing the synthesis of vesicular transporter protein and acetylcholine transferase (AchT) and cholinergic fiber volume [22,23,25]. Other GFs such as IGF-1 and IGF-2 can regulate the hyperphosphorylation state of Tau protein by activating the PI3K/AKT pathway and by decreasing the deposits of β-amyloid peptides [27,44,68]. Moreover, other GFs such as bFGF can increase neurogenesis