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Neurotrophic Factors and Neurodegenerative Diseases

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Abstract

Neurotrophic factors (NTFs) are a group of endogenous signaling proteins that promote proliferation, maturation, survival, differentiation and/or regeneration of neural cells. Many researches showed that these proteins support and restore multiple neuronal types such as dopaminergic, sensory, motor, hippocampal, and basal forebrain, enteric, sympathetic and parasympathetic neurons. There are two classic neurotrophic families: neurotrophins (include NGF, BDNF, NT-3, and NT-4/5), and Glial cell line – derived neurotrophic factor (GDNF) family ligands (GFLs) (consist of GDNF, neurturin, artemin, and persephin). On the other hands, NTFs hold great expectations as a potential therapeutic agent for the treatment of neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer Disease (AD), as well as Huntington's disease (HD) and amyotrophic lateral sclerosis and other neurological disorders. In the past few years, a vast number of researchers have investigated different nano and micro formulations loading GFLs as an approach for neurodegenerative treatment.

Introduction

Neurotrophic factors (NTFs) are considered as a group of endogenous signaling proteins that promote wide spectrum of cell events such as proliferation, maturation, survival, differentiation and/or regeneration [1-4]. Neuronal growth and protein synthesis are regulated by NTFs. Moreover, NTFs enhance neurite outgrowth and neurotransmitter synthesis [5,6]. According to previous studies it was assumed that NTFs initially released by glioma cells and were responsible for the development of embryonic midbrain neurons [7,8]. Further research demonstrated that these proteins support and restore multiple neuronal types such as dopaminergic, sensory, motor, hippocampal, basal forebrain, enteric, sympathetic and parasympathetic neurons [9-11]. There are two classic neurotrophic families: neurotrophins, and Glial cell line – derived neurotrophic factor (GDNF) family ligands (GFLs). The first group including Neural Growth factor (NGF), brain-derived neurotrophic factor (BDNF) , NT-3, and NT-4/5, in a way that NGF binds the P75NTR and the P140trk (trkA) receptors [12]; BDNF and NT-4/5 bind the trkB receptor, and NT-3 primarily binds the trkC receptor [5,13,14]. The second consists of GDNF, neurturin, artemin, and persephin [4,15,16] binding to the GFR-alpha1-4 and converge on the transmembrane Ret tyrosine kinase [17-19]. Other classes of trophic factors include: epidermal growth factors, fibroblast growth factors, GP130-binding growth factors (such as CNTF), heparin-binding growth factors, insulin-like growth factors, and transforming growth factors [5,14,20].

Neurotrophic factors are able to activate neuronal repair genes under conditions of neuro degeneration when supra-physiological (i.e., biopharmaceutical) levels are achieved [1]. Therefore, NTFs hold great expectations as a potential therapeutic agent for the treatment of neurodegenerative diseases including Parkinson's disease (PD), Alzheimer Disease (AD), as well as Huntington's Disease (HD), amyotrophic lateral sclerosis (ALS), and other neurological disorders [21,22]. ALS (Lou Gehrig's disease) was the first diseases to be treated by neutrophic factors [23].

GFLs based on hydrophilic nature and high molecular weight (20–35kDa) could not pass through blood-brain barrier [24]. Besides, they fail to cross the layer of ependymal cells, so intracranial administration is required [9]. It is worth noting that GFLs have high affinity to extracellular matrix and cell surface heparin sulphate proteoglycan that can significantly limit their diffusion in neural tissues [25]. Regarding the above-mentioned facts, researchers have worked to develop more complicated delivery system of GFLs [9]. In some areas they could produce encapsulating neurotrophic factors- producing cells in tiny, semi permeable capsule- that can

be implanted anywhere in the body (especially in the brain or in the cerebrospinal fluid) [26]. Having said that in that situation cells would be remained safe from the recipient's immune defense system; in a way that it can be counted as a biological pump [27,28]. In recent decades, a vast number of researchers have found different nano and micro formulations loading GFLs as an approach for neurodegenerative treatment, it is no gain saying that this way has so many benefits [29,30]. For example, they are cheap not only in production but also in storage. Besides they can be easily modified to achieve desirable properties using medicinal chemistry approaches in the pharmaceutical industry [31]. In addition, small molecules can be designed to be able to cross the blood-brain barrier [32]. After reviewing articles, it can be articulated that among all tested growth factors, artemin has a unique property to guide regenerating axons to the topographically correct regions of the spinal cord status-post dorsal root crush [33-35]. Since BDNF has been shown to prevent cell death and stimulates the growth and migration of new neurons in the brain in transgenic mouse models, it can be a suitable candidate for the treatment of Huntington's disease (HD) [36,37]. Regarding the fact that, NTFs levels in the basal forebrain region reduce in AD, administration of NGFs prevent the neural death and stimulates the function of basal forebrain cholinergic neurons that can be a main reason for degeneration in AD [38-40].

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