Neurobiology of Disease 97 (2017) 139–155

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Neurotrophin receptor agonists and antagonists as therapeutic agents: An evolving paradigm

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ARTICLE INFO

Article history:
Received 23 December 2015
Revised 10 August 2016
Accepted 16 August 2016
Available online 18 August 2016

Keywords:
Small molecule
Mimetic
Neurotrophin
Receptor
Neurodegeneration
Therapy

ABSTRACT

Neurodegenerative disorders are prevalent, complex and devastating conditions, with very limited treatment options currently available. While they manifest in many forms, there are commonalities that link them together. In this review, we will focus on neurotrophins – a family of related factors involved in neuronal development and maintenance. Neurodegenerative diseases often present with a neurotrophin imbalance, in which there may be decreases in trophic signaling through Trk receptors for example, and/or increases in pro-apoptotic activity through p75. Clinical trials with neurotrophins have continuously failed due to their poor pharmacological properties as well as the unavoidable activation of p75. Thus, there is a need for drugs without such setbacks. Small molecule neurotrophin mimetics are favorable options since they can selectively activate Trks or inactivate p75. In this review, we will initially present a brief outline of how these molecules are synthesized and their mechanisms of action; followed by an update in the current state of neurotrophins and small molecules in major neurodegenerative diseases. Although there has been significant progress in the development of potential therapeutics, more studies are needed to establish clear mechanisms of action and target specificity in order to transition from animal models to the assessment of safety and use in humans.

Contents

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Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2016.08.004
0969-9961/

1. Introduction

No neurodegenerative disease has an effective treatment or cure. These diseases manifest as a variety of phenotypes, but they all share at least the common feature of dysregulation of neurotrophins and their receptors Trk and p75 (Appel, 1981, Kruttgen et al., 2003). This commonality has been documented in animal models and in humans for neurological diseases including Alzheimer's disease (AD) (Schindowski et al., 2008, Cuello et al., 2010), age-associated cognitive impairment (Mufson et al., 2000, Saragovi, 2005), Down's syndrome (Sendera et al., 2000, Dorsey et al., 2006), Parkinson's disease (PD) (Rangasamy et al., 2010), Huntington's disease (HD) (Alberch et al., 2004), amyotrophic lateral sclerosis (ALS) (Ekestern, 2004); for retinopathies like retinitis pigmentosa (RP) (Thanos and Emerich, 2005), glaucoma (Rudzinski et al., 2004, Nafissi and Foldvari, 2016), diabetic retinopathy (DR) (Bikbova et al., 2014), and for a corneal disease named dry eye (Rolando and Zierhut, 2001).

Trk-signals are normally required for neuronal maintenance and function, and defects in Trk-receptor tyrosine kinase activation (*e.g.* reduced receptor expression, impaired cellular transport, agonist deficiency) are associated with early stages of neurodegeneration. This supports the view that Trk-agonism may be therapeutic. This notion is however complicated by the fact that in some neurodegenerative pathologies (*e.g.* glaucoma, Down's syndrome, ALS) the Trk-receptor mRNA can be processed to a truncated isoform lacking the kinase domain (Dorsey et al., 2006, Bai et al., 2010b, Yanpallewar et al., 2012).

The p75 receptors are implicated in normal developmental pruning and neuronal death. When upregulated and activated in certain tissues, they can cause neurotoxicity associated with neurodegenerative diseases. This supports the view that p75-antagonism may be therapeutic (Saragovi and Gehring, 2000, Saragovi et al., 2009).

While the rationale for targeting Trk and p75 is robust, clinical validation is mostly absent because it requires the use of disease-modifying drugs acting through these receptors. Regrettably, the use of the neurotrophins themselves as drugs has mostly failed in spite of significant efforts and growingly sophisticated –yet risky– delivery methods (Weissmiller and Wu, 2012). The poor pharmacological profile of these large proteins, short half-lives, inability to penetrate tissue barriers, undesirable high potency and pleiotropic effects, and the activation of multiple receptors (where p75 activity can negate the benefit of Trk activity) can reduce a therapeutic benefit (Peleshok and Saragovi, 2006).

These difficulties and failures led to the general view that targeting neurotrophin receptors may be generally ineffective or unsafe, with a bad risk/benefit ratio. As an alternative, the therapeutic use of small molecules and of (ant)agonistic anti-receptor antibodies has been proposed and was expected to be devoid of the aforementioned drawbacks (Peleshok and Saragovi, 2006). Here, we will discuss the development of agents that can modulate partial or biased signals, selectively through either Trk or p75 receptors, and that have desirable pharmacokinetics and pharmacodynamic properties. Clinical evaluation of these agents has just begun, and appears promising.

2. The neurotrophin family

The neurotrophin (NTF) family of proteins forms a class of functionally and structurally related proteins that regulate growth, differentiation and survival of central and peripheral neurons (Reichardt, 2006, Skaper, 2008). NTFs include Nerve Growth Factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 4/5 (NT-4/5) and neurotrophin-3 (NT-3). All of these proteins are initially produced as a precursor pro-NTF, and are thereafter processed into the mature NTF.

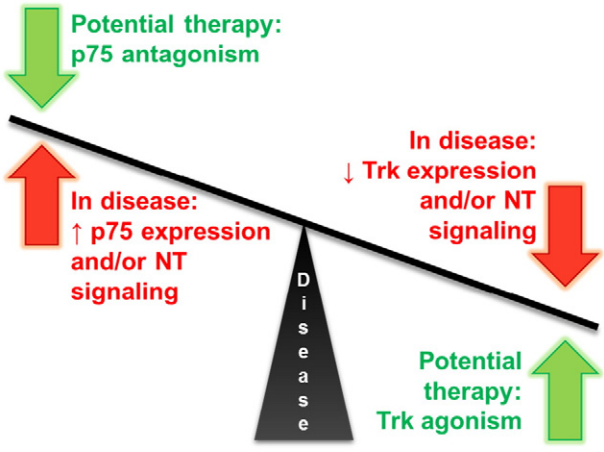

Fig. 1. Disease mechanisms and potential therapeutics. The neurotrophin imbalance underlying neurodegenerative diseases can be a disease-modifying therapeutic target. The pathogenic mechanisms of increased p75 expression and/or signaling can be counteracted by p75 antagonism. A decrease in Trk expression and/or signaling can be therapeutically corrected by Trk agonism. Trk agonism may also counteract the action of p75.