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Drug Targets in Neurotrophin Signaling in the Central and Peripheral Nervous System

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Abstract

Neurotrophins are a family of proteins that play an important role in the regulation of the growth, survival, and differentiation of neurons in the central and peripheral nervous system. Neurotrophins were earlier characterized by their role in early development, growth, maintenance, and the plasticity of the nervous system during development, but recent findings also indicate their complex role during normal physiology in both neuronal and non-neuronal tissues. Therefore, it is important to recognize a deficiency in the expression of neurotrophins, a major factor driving the debilitating features of several neurologic and psychiatric diseases/disorders. On the other hand, overexpression of neurotrophins is well known to play a critical role in pathogenesis of chronic pain and afferent sensitization, underlying conditions such as lower urinary tract symptoms (LUTS)/disorders and osteoarthritis. The existence of a redundant receptor system of high-and low-affinity receptors accounts for the diverse, often antagonistic, effects of neurotrophins in neurons and non-neuronal tissues in a spatial and temporal manner. In addition, studies looking at bladder dysfunction because of conditions such as spinal cord injury and diabetes mellitus have found alterations in the levels of these neurotrophins in the bladder, as well as in sensory afferent neurons, which further opens a new avenue for therapeutic targets. In this review, we will discuss the characteristics and roles of key neurotrophins and their involvement in the central and periphery nervous system in both normal and diseased conditions.

Keywords

Neurotrophins; NGF (nerve growth factor); BDNF (brain-derived neurotrophic factor); Bladder and development

Introduction

The physiological role of neurotrophins (NTs) has been an exciting area of study, allowing for a better understanding of the fate of neurons in both the developing and adult nervous system. Of the neurotrophin family, the nerve growth factor (NGF) was the first to be identified and phenotyped by Levi-Montalcini [1]. NGF was then used to derive the

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Compliance with Ethical Standards

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properties of the neurotrophin family. It has been shown that a neurotrophic factors can support the maintenance, survival, differentiation, and growth of neurons and promote nerve regeneration in the setting of spinal cord injury [2]. They arrive in this neuronal environment by secretion from a target tissue, which can be either neuronal or non-neuronal, where they act on the neuronal supply in tissue to support differentiation and survival [3, 4].

Since the discovery of NGF, dozens of other neutrophic factors have also been recognized, each with unique characteristics and roles in biological activity, with distinct expression that confers a functional specificity to target tissue. In addition, factors previously discovered and known for their effects in other systems, including insulin-like growth factors or tumor-derived factors, have also been classified as neurotrophic factors. However, these factors have instead been grouped into different families according to the homology of the nucleotide sequence and, hence, evolutionary relatedness [5].

Indeed, of these related families, the most well-understood and widely expressed factors in the brain seem to be neurotrophins (NTs) [6, 7]. While NGF is the model for the neurotrophin family (NF), it now also includes other factors, namely, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) [4]. As their names suggest, all trophins have demonstrated some level of survival activity on nervous tissue. Interestingly, neurotrophins have also been found to influence growth and development by means other than recovering neurons from cell death. For example, they could alter phenotypes of cholinergic neurons innervating bladder and, therefore, manipulate the function of cholinergic neurons in the bladder [8]. Some neurotrophins support neuron survival up to the point of naturally occurring cell death. After this, they become ineffective as a result of an apparent switch in the neurotrophin receptor expressed by the neuron [9–11]. In discussing their influence on neuronal proliferation, some neurotrophins such as NT-3 have been shown to exert profound survival/neurite outgrowth effects on neural crest (NC) progenitor cells and were also found mitogenic to somite cells in the mixed NC/somite cultures. NT-3 also has potential to increase the survival of the dividing sympathetic neuroblast population; however, it does not directly stimulate mitosis [12–15]. In addition, neurotrophins have been found to influence synaptic activity as increase neurotrophin expression confers a role in the plasticity of the nervous system. Thus, the availability of mice to study with specific neurotrophin disruption is important in deciphering their roles in the central and peripheral nervous system. Studies from these mutant mice reflect that the lacking neurotrophin may not cause cell death, but indeed, it may have compromised their differentiated potential and, hence, altered functional activity [16–19].

The classical “neurotrophin theory” [12] explains the loss of sets of peripheral sympathetic neurons [20], sensory neurons [21], proprioceptive neurons [22], and subsets of sensory neurons in NGF, BDNF, NT-3, and NT-4 knockout mice, respectively [23]. The time course of NT expression is intriguing as it points to the important function played by these NTs in both developing and adult nervous system [7, 24, 25]. Further, the expression of these factors has been shown to be high during early development, a time highlighted by substantial growth, differentiation, and modeling of the nervous system. Expression of NTs subsides in the adult as the number of neurons innervating a target tissue exceeds that usually found in the mature innervated target. The final number of neurons is further reduced

through apoptosis, which also reflects the availability of neurotrophins [26]. Although, some data are available about their role in some diseases (Table 1), but indeed, there is still much to be learned regarding the roles of the neurotrophic factors in the brain and during the earlier development. In this review, we will discuss diverse roles of NTs in the central and peripheral nervous system as well as recent advancement of NT-mediated therapies in different disease conditions (Fig. 1).

Structural Information of Neurotrophins

Neurotrophins are synthesized with ~ 250-amino acid residue precursors and secreted in the form of non-covalently linked dimers, consisting of approximately 120-amino acid residues [27]. Mature forms of specific neurotrophins show extremely high sequence homology and remain conserved during evolution among vertebrates. Even different neurotrophins such as BDNF [28], NT-3, and NT-4 [29] have around 50% sequence homology to NGF. The crystal structure of NGF also exhibits a high similarity to other neurotrophins such as BDNF, NT-3, and NT-4, in which homologous regions in the hydrophobic core lie between three pairs of antiparallel β strands. This hydrophobic core is further stacked by intramolecular cysteine disul-fide bonds between these three strands [30]. This core is further attached with a flat surface, allowing two subunits to give a 2-fold axis symmetry. Further, it is in the regions of the three β hairpin loops (amino acids 29–35, 43–48, and 92–98; numbers refer to NGF), the reverse turns (amino acids 59–66), and the carboxyl and amino terminus that amino acid variations between the neurotrophins can be deciphered. As chimeric molecules contain portions of various neurotrophins, it is the basic residues within the variable regions that are critical for binding the appropriate tyrosine receptor kinase (Trks) [29, 31, 32]. Alternatively, it appears that a different, yet overlapping, set of basic residues is important for binding the P^{75} low-affinity neurotrophin receptor (p75NGFR) [33].

Receptors Binding Neurotrophins

Tyrosine receptor kinases (Trks), found in multiple forms ranging from a single active protein to large heteromeric complexes, appear to be better conserved than their neurotrophin ligands [34, 35]. Trks have a receptor family of glycosylated proteins of approximately 825-amino acid residues [29, 31, 32]. The name Trk derived from their identification as troponin/receptor kinase gene fusion identified in colon carcinoma; their normal (proto-oncogene) forms have now also been identified. Each Trk receptor consists of an extracellular ligand-binding domain, a single transmembrane domain to transduce signals, and an intracellular tyrosine kinase domain which leads intracellular signaling [34, 35]. These domains may be a part of a single protein or may be distributed among several interacting proteins. Interestingly, it has been shown that each receptor, when transfected into a cell line, can transduce the appropriate NT signal independently of other receptor proteins [36].

Initially, neurotrophins are synthesized in a pro-form, from which they then undergo proteolytic cleavage to become mature neurotrophins. Proteolytic cleavage can occur either inside the cell by plasmin and furin or outside the cell by matrix metalloproteinase. From here, NTs exhibit a strong affinity to bind with Trk receptors and a lesser affinity to the p75

neurotrophin receptor (p75NTR) [37]. Upon binding with neurotrophins, these receptors first dimerize at the cell surface, where the receptor tyrosine residues are next autophosphorylated. While the phosphorylation of tyrosine residues represents a small proportion of proteins phosphorylated in the cell, it is a critical part of neurotrophin-mediated signal transduction and downstream function. The phosphorylated tyrosine residues then recruit intracellular proteins with their ability to transduce signals. At physiologic NT concentrations, a specificity among the Trk receptors exists with binding constants for the high-affinity ligands in the range of 10–11 nM. In this way, neurotrophin receptors can be further classified. NGF binds with TrkA; BDNF and NT-4 bind with TrkB; and NT-3 binds with TrkC. However, there is some overlap due to some redundancy in the structure of these neurotrophin receptors; for example, NT-3 can also bind to TrkA and TrkB, although with lower affinity than to TrkC. In addition, truncated isoforms of TrkB [38] and TrkC [39] also exist. However, because these truncated forms lack cytoplasmic tyrosine kinase catalytic regions, they are unable to elicit the same response to neurotrophin binding. Like the intact receptors, these truncated isoforms are also expressed throughout the developing and adult central and peripheral nervous systems. As the full-length TrkB form is preferentially expressed in neurons, the kinase-deficient TrkB isoform appears to be preferentially expressed in non-neuronal cells [40]. Further, it is still not clear whether the non-catalytic forms of the receptors act as agonists or antagonists, as this may depend on the context in which they are found. They could serve as agonists by concentrating a neurotrophin after neuron injury [41], or, perhaps, an antagonist action also exists, as their presence might decrease the availability of a specific neurotrophin available to competing neurons during innervation. Further, all four neurotrophins can also bind to the low-affinity nerve growth factor receptor, p75NTR. The exact role of the p75NTR receptor has yet to be ascertained. One theory is that it may serve a role in increasing the specificity of the Trk receptor to the neurotrophic ligand. Another idea centers on its potential influences in the retrograde transport of bound neurotrophins [37]. Interestingly, in the study of mutated NT-4, NT binding to p75NTR was hindered, translating to a much less potent TrkB inducer of phosphorylation [32]. These findings then suggest that p75NTR may also a play crucial role in NT-4 signaling.

While Trks are the primary receptors for neurotrophins, the characteristics and various roles of p75NTR are also relevant. This receptor belongs to the tumor necrosis factor receptor superfamily (TNFR), and it contains extracellular cysteine-rich domains (CRDs) and an intracellular death domain. It is the action of intracellular adaptor proteins on the intracellular domain that promotes the enzymatic activity of p75 receptors. p75NTR has a unique ability to interface with both pro- and mature neurotrophin dimers. It is p75NTR signaling with pro-neurotrophins that has been thought to play diverse roles in mediating the fate of a neuron. Interestingly, one structural model was constructed showing an ability of p75NTR to fit into a tertiary complex with TrkA/NGF, although this has yet to be proven [42]. Thus, this receptor has been linked to a wide array of functions in the developing and injured neuron, including apoptosis, remodeling, and synaptic plasticity [43]. On the one hand, p75NTR has been shown to promote Trk-NT neuron survival signaling; however, other studies have found that this receptor has the ability to interact with sortilin (SORCS2) to trigger pro-neurotrophin cell death signals. Further, it has also been reported that this

receptor could also interact with Nogo to promote myelin growth inhibitory effects [42, 43]. While sortilin is unable to contribute to the binding of p75NTR with NTs, it has been shown to regulate the rate of p75NTR cleavage, a critical step in the pathway of pro-neurotrophin cell death [43]. Indeed, the sortilin/p75NTR/ pro-neurotrophin complex has been implicated in the pathway of the pro-neurotrophin induction of cell death [44]. Further study would be valuable to reveal different binding changes induced by pro- and mature neurotrophins, as well as how they are relevant in influencing the fate of the life and death of neurons.

Neurotrophic Factor-Mediated Intracellular Signaling Pathways

Ras/Erk (Mapk) Cascade

The Ras/ERK pathway is regulated by the activity of proteins, namely, Ras. The small, membrane-associated protein Ras transduces signals from tyrosine kinase to the extracellular signal-regulated kinase (ERK) proteins, among other activities [45]. Ras is a G protein, as its activity depends on the type of guanine nucleotide that is bound to it. However, it is distinct from the heterotrimeric G proteins coupled to several neurotransmitter receptors. Ras becomes active when it binds to guanosine triphosphate (GTP), while the guanosine diphosphate (GDP) binding form remains inactive. Upon the activation of Trks, an adapter protein in the Shc family binds to these receptors. The Shc protein then becomes tyrosine phosphorylated and binds a Grb protein, one example being Grb2. While the Shc protein contains one PTB domain and an SH-2 domain, Grb2 contains two SH-2 domains and one SH-3 domain. Together, these proteins form a complex that activates a GDP–GTP exchange factor, namely, SOS, which subsequently activates Ras through GTP binding. Once activated, Ras recruits a serine kinase (Raf family) to the membrane, where it is then activated. A cascade is then initiated in which Raf activates MEK (from MAPK or ERK kinase). MEK then phosphorylates ERKs [46]. ERKs, also known as mitogen-activated protein kinases (MAPKs), are multifunctional kinases with various activities within the cell. Previously, ERKs have been shown to phosphorylate a diverse array of proteins such as tyrosine hydroxylase (TH), different transcription factors, protein translation regulators, proteins involved in microtubule formation, and many others [16, 17]. ERKs have also been shown to mediate neuron survival, elongation of neuritic processes [18], and levels of specific neuronal enzymes and ion channels [19]. Furthermore, ERKs have been identified as important in the hippocampal long-term potentiation (LTP) in brain slices [47]. While some effects of ERK activation are very rapid because of phosphorylation of membrane receptors, leading to increased activity, others are delayed and persistent because of the genomic changes. The ERK activation is also involved in sensitization of the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor of sensory neurons by NGF in the spinal cord, which underlies chronic pain [48, 49].

Phospholipase C, Gamma 1 (PLC-γ) Cascade

A second NT-signaling pathway involves phospholipase C, gamma 1 (PLC-γ) activation [50, 51]. As seen in the well-understood PLC-β, PLC-γ also cleaves the phospholipid 4, 5-bisphosphatidylinositol phosphates (PIP_2) into diacylglycerol (DAG), and inositol 1,4,5-trisphosphate (IP_3). DAG can then activate protein kinase C (PKC), whereas IP_3 propagates the release of intracellular stores of calcium. Intracellular calcium can influence many

pathways, including the activation of Ca^{2+}/calmodulin-dependent protein kinases or the production of cyclic adenosine monophosphate (cAMP, cyclic AMP, or 3′,5′-cyclic adenosine monophosphate) through some adenylyl cyclases. Consequently, these mechanisms are known to have powerful effects on neurons. Unlike PLC-β, which is under the regulation of heterotrimeric G protein-coupled receptors, PLC-γ is regulated by tyrosine phosphorylation. PLC-γ contains two domains, namely, the SH-2 and SH-3 domains. Once bound to tyrosine phosphorylated receptors, it is recruited to the membrane, where it is phosphorylated, and this phosphorylation then activates PLC activity [52]. However, there is virtually nothing known about the role of PLC-γ in the intact brain; however, it has been proposed to likely exert important effects on neuronal function.

Interaction of Neurotrophin Signaling Cascades

The interactions of downstream signaling pathways of the NT receptors have been found to be somewhat complex. For instance, PI-3-K has been shown to contribute to ERK activation by both Ras-dependent and Ras-independent pathways [53–55]. Further, Ras has been shown to contribute to AKT activation, and both SHC and IRS-1 can bind to the same phosphorylated tyrosine site, but with differing affinities [56]. PLC-γ, however, can activate ERK in neurons and in theory can also terminate PI-3-K signaling by cleaving phosphotidylinositol-3′-phosphate [57]. In addition, many of these proteins exist in multiple different isoforms because of different genes or differential splicing of the same gene. While these isoforms are differentially expressed during development and in different brain regions, still there is a great deal of overlap. Further, the complexity of protein expression and cross talk in these signaling pathways and expression pose a tremendous opportunity for potential sites of drug discovery in brain and the periphery.

Role of Neurotrophins in the Development of Sensory and Motor Neurons in the Periphery

The neurotrophin hypothesis describes the event of neurotrophins located in the target tissue of a neuron binding to the cell membrane, being internalized and traveling in a retrograde fashion to the cell body where they can then affect metabolic function. Developmentally, there is evidence that neurotrophin levels are upregulated as fibers innervate the target peripheral tissue. Later, levels of neurotrophins have been found to decrease in the periphery as a means of controlling neuronal cell number and innervation density [58–60]. Studies on developing sensory ganglion cells have confirmed the influence of neurotrophins on the development of various populations of sensory neurons. Many investigators have found that small, peptide-containing neurons require neurotrophin NGF during development. Furthermore, the exposure of the adult animal or the fetus (via placental circulation) to anti-NGF has been found to prevent the survival of cells expressing TrkA [61]. NGF has been implicated in the growth and differentiation of sympathetic nerve development, and its withdrawal has been linked to pro-apoptotic pathways [62].

NT-3 has been shown to play a pivotal role in the development of excitatory synapses. It is through the binding of TrkC that a TrkC–presynaptic protein tyrosine phosphatase δ (PTPδ) complex can be formed, which in turn promotes synapse activity. Interestingly, NT-3 action

has been found to be independent of receptor concentration when mediating presynaptic differentiation, yet postsynaptic differentiation is mediated by NT-3 in a manner dependent on concentration [63]. This role of NT-3 in enhancing PTPδ–TrkC binding was shown to promote the presynapse-inducing activity of TrkC in rat hippocampal neurons [64]. Further, the significance of this neurotrophin–TrkC interaction has been highlighted by studies involving genetically modified animals demonstrating the relationship between neurotrophins and the sensory fibers' development. Mice lacking TrkC isoforms have been found to die early in postnatal development while expressing a phenotype suggestive of proprioceptive nerve involvement. Moreover, a loss of type Ia sensory fibers and abnormally myelinated axons within sensory tracts of the spinal column have been found in mice with tyrosine kinase lacking TrkC receptors [65]. Interestingly, when transgenic mice were studied with overexpression of the catalytic TrkC isoform in neuronal cells, an anxious behavioral phenotype was noticed, and increased excitatory postsynaptic potentials were recorded in the hippocampal region. The distribution of TrkA and TrkC receptors on sensory neurons supports the neurotrophic action of NGF and NT-3, respectively. Therefore, these findings suggest a fine regulation of the neurotrophin-Trk on neuronal development, with evidence of both low and high activity translating to aberrant neuronal development [65].

Neutralization of NGF by Antibody and Antisense

Neurotrophins have also been implicated as a potential target of pain therapy, as NTs such as NGF are now recognized as key mediators of pain signaling and tissue injury [66]. In this section, we are discussing multiple studies that have recognized neurotrophin expression and potential treatments applied in the setting of bladder disorders. Therefore, drugs such as tanezumab, a monoclonal antibody to NGF, have been studied and found to confer a reduction in pain in chronic conditions such as osteoarthritis, interstitial cystitis, and chronic lower back pain (CLBP) [67]. In a study by Belanger et al., the effect of tanezumab on the sympathetic nervous system (SNS) of primates given supratherapeutic doses was observed. Of note, they found that administration of this drug for a time period of up to 6 months did not confer any adverse morphologic or functional alteration in the SNS; moreover, they also found that it was not associated with neuronal cell death in adult primates [68].

Successful outcomes in pain reduction of animal models and in patients with chronic pain in osteoarthritis following sequestration of NGF with monoclonal antibody (tanezumab) further support the critical role of NGF in the maintenance of sensory neurons and their sensitization. Autonomic dysreflexia (AD) following spinal cord injury is characterized by NGF overexpression in bladder wall and the activation of C-fiber afferent nerves by bladder distension. NGF overexpression in bladder of patients suffering from AD secondary to spinal cord injury is presumed to sensitize the C-fiber bladder afferent pathways via upregulation of TRPV1 and TRPA1 expression, and sensitized bladder afferents are known to ex-aggerate the arterial blood pressure responses to bladder distention in AD. Yoshizawa et al. reported that NGF overexpression accompanied an increase in TRP channels' (capsaicin receptors, TRPV1 and TRPA1) mRNA levels in the bladder afferent neurons when measured against rats with intact spinal cords. Increased expression of NGF and TRP channel [69] was linked to significantly increased blood pressure in AD via bladder-vascular reflex. Kadewaka et al. found that intravesical application of NGF antisense complexed with

cationic liposomes is a promising treatment for AD [70]. Further, delivery and complexation methods for NGF antisense have been investigated. Kashyap et al. found that NGF antisense oligonucleotides complexed with cationic peptide protamine instead of liposomes reduced the constitutive expression of NGF, as well as its receptor p75 (NTR) in the bladder [71]. It is known that acute exposure of bladder to noxious stimuli induces NGF overexpression, and Majima et al. looked at the effectiveness of liposomal suppression of NGF in the setting of bladder cystitis. They too used an NGF antisense oligonucleotide (OND) complexed to cationic liposomes and evaluated pain behavior in a rat cystitis model. In cystitis rats, intravesical application of liposome-OND improved bladder hypersensitivity [72].

Kashyap et al. also supported these findings by reporting the suppression of NGF overexpression evoked by acute acetic acid exposure. Sequence-specific downregulation of the NGF expression in bladder reduced the inflammation and reduced the frequency of reflex voiding in rodents [66]. Acute exposure to acetic acid is known to cause NGF overexpression, which is linked to overexpression of soluble inter-cellular adhesion molecule-1 (sICAM-1), sE-selectin, chemokine (C–X–C motif) ligand 10 (CXCL-10) and CXCL-1, leptin, monocyte chemoattractant protein-1 (MCP-1), and vascular endothelial growth factor (VEGF) in rat bladder. NGF-antisense treatment downregulated the expression of NGF and other molecules in rat bladder after acute exposure to acetic acid [66]. Furthermore, elevated NGF expression has been associated with differential expression of miRNA, specifically the upregulation of miR-132 and downregulation of miR-221 in the bladder of rats with acetic acid-induced overactivity [73]. MicroRNAs (miRs) represent a new level of epigenetic posttranscriptional control of gene expression and are now considered molecular determinants of clinical outcomes. A clinical study found a differential expression of bladder miR-221 in patients with overactive bladder (OAB) following intradetrusor injection of onabotulinum toxin A [74]. In patients who responded positively to this therapy with low postresidual volumes (PVR), the expression of miR-221 and miR-125b was found to be upregulated by 11- and 2-fold, respectively. Moreover, in patients with high PVR following treatment, a reduced miR-221 expression was implicated in regulating the differentiating action of NGF based on biochemical studies [74].

Urine levels of NGF were found to be elevated in patients with voiding symptoms, implying that elevation in urine is caused by overexpression in the bladder. Analysis of urine specimens of 140 overactive bladder patients (OAB), ranging from 25 to 90 years old, justified the proposed age-related association with a low-grade chronic inflammatory processes in OAB [75]. While urinary NGF is increased in interstitial cystitis, it is also elevated in patients with OAB and detrusor overactivity DO. A recent study proposed use of urinary NGF levels for monitoring the therapeutic response and disease progression [76].

Brain-Derived Neurotrophic Factor

BDNF and its corresponding receptor, TrkB, have been found to be widely expressed in the developing and adult nervous system. Interestingly, BDNF–TrkB signaling has been linked to an increase in BDNF mRNA expression, suggesting the ability of this BDNF to upregulate pro-BDNF release [37]. Mice lacking TrkB receptors [77] have sensory deficits that depict impaired function in large-diameter cutaneous afferents. Mice lacking

neurotrophin BDNF were found to be ataxic, and this reflects a loss of dorsal root ganglions (DRGs), as well as myelinated axons [78]. Although muscle spindles were normal in these knockout animals, the major deficit was in the mechanoreceptors that are in skin of these animals. Furthermore, DRGs show similar losses in cell number in both knockout mice; however, loss in trigeminal ganglia was greater in TrkB knockout than the BDNF one. Therefore, it can be concluded that the TrkB receptor could also bind with ligands other than BDNF, supported by the significant depletion of motorneurons in TrkB knockouts compared to an unchanged number of these motor neurons in BDNF knockouts.

In the mice with lost Bdnf gene, 80% have a reduction in vestibular ganglion neurons innervating the inner ear organs and responsible for balance and movement. Furthermore, a 25–44% reduction in neurons of the trigeminal that connects the hindbrain to whisker pads and a 55–65% reduction have been identified in neurons of the nodose and petrosal ganglia (relaying information from the heart, major vessels, lung, and gut to the brain stem). Moreover, a significant reduction in mechanoreceptor neurons of the dorsal root ganglion was also noticed in these mice [78–80]. Mice with disrupted TrkB gene have disruption in sensory neurons [77]. These findings are in accordance with the understanding of BDNF's ability to help cell growth of trigeminal neurons derived from embryos in early stages of innervation [81]. Moreover, BDNF is also important for the differentiation process and supports the differentiation of cortical and hippocampal GABAergic interneurons. Although the number of GABAergic neurons and neural gamma-aminobutyric acid (GABA) was normal in BDNF-lacking mice, the neuronal markers of GABAergic cells, namely, parvalbumin, calbindin, and neuropeptide Y, were decreased. In this way, it is reasonable to consider the compromised synaptic inhibitory activity of these neurons because of downregulated levels of calcium-binding proteins such as parvalbumin and calbindin. Moreover, reduced expression of calbindin was also observed in the medium-sized striatal spiny neurons and the striatal projection to the substantia nigra. Interestingly, reduced expression of neuropeptide Y was noticed only in mutant mice with the specific age of 15–20 days, prompting the question of whether the lack of BDNF prevented altogether, rather than delayed, normal differentiation of a subset of cortical and hippocampal GABAergic neurons. In contrast, BDNF infusion increases the expression of neuropeptide Y and other neuropeptides in hippocampal and cortical neurons. Therefore, reduced neuropeptide Y expression in BDNF knockout mice is corroborated by the increased neuropeptide Yexpression in the setting of BDNF infused into the hippocampus, cortex, and striatum of normal adult rats [82, 83]. Similarly, rats overexpressing BDNF gene in the bladder wall have shown enhanced calcium signaling due to BDNF-mediated enhanced expression and activation of the L-type calcium channel [40].

The role of BDNF in vivo as it influences the development of motor neurons is less clear. BDNF has been shown to support motor neuron survival in lesioned animals [84–86], as well as prevent naturally occurring death and also increase levels of neuronal markers in cultured embryonic motor neurons [87]. In a study of TrkB knockout mice, a role for BDNF in motor neuron development has also been proposed. In the TrkB knockout mice, a reduced number of lumbar spinal and facial nuclear motor neurons has been recorded [77]. Yet, interesting findings were discovered in the motor neurons of BDNF knockout mice as well as mice missing both BDNF and NT-4. Both of which are high-affinity ligands for the TrkB

receptor [78]. Surprisingly, in these mice, motor neuron development was found normal. However, since NT-3 can also activate TrkB, it is possible for some redundancy to exist that allows for sufficient motor neuron development. Thus, while BDNF may participate in motor neuron development, it seems that an absence of this NT can be compensated by other neurotrophins.

Importantly, the differentiation of cholinergic neurons, which are important in cognitive functions and involved in Alzheimer's disease, are influenced by exogenous BDNF. BDNF administration has been shown to protect cholinergic neurons of the basal forebrain against lesion-induced death, influence the neurotransmitter production, and increase the expression of cholinergic markers in vivo and in vitro [87, 88]. It is surprising that deficiencies in cholinergic neurons have yet to be reported for the BDNF knockout, BDNF/NT-4 double knockout, and TrkB knockout mice; however, BDNF overexpression has been shown to induce the expression of choline acetyltransferase at cholinergic nerve terminals innervating the bladder [8, 88]. Furthermore, the enhanced levels of choline acetyltransferase was functionally active as proven by higher contraction amplitude in bladder strips overexpressing BDNF relative to bladder strip overexpression luciferase at a frequency of 8 Hz and above (known to stimulate parasympathetic nerves) in electric field stimulation (EFS) studies using organ bath [88]. BDNF also affects differentiation of dopaminergic neurons. In addition, there have also been no gross deficits in the dopaminergic neurons of the midbrain reported in these mice. For these reasons, a more detailed analysis of these mutant mice is needed to clarify the role of BDNF in the differentiation of these sets of neurons.

BDNF has been associated with the survival of in vitro cultured neuronal cells, namely, rat retinal ganglion cells, cerebellar granule neurons, and neurons of the locus coeruleus when derived from embryonic and adult animals at the appropriate developmental stage. BDNF also interacts with other neurotrophins [89–91], such as trigeminal sensory neurons [92] and cerebellar neurons [91], which appear to switch their dependence from BDNF to NGF and NT-3, respectively. Interestingly, the adult rat hippocampal and cerebral cortical neurons have been shown to express TrkB and TrkC, the receptor for NT-3, indicating that these neurons can respond to both BDNF and NT-3 [94]. BDNF could also act in an autocrine manner. BDNF and TrkB receptors are co-expressed in many hippocampal and cortical neurons [91–94]. Antisense oligonucleotides to BDNF can inhibit survival of cultured neurons from the dorsal root ganglion [95, 96], while overexpression of BDNF in rat bladder was associated with increased retrograde transport of BDNF and NGF in L6 and S1 dorsal root ganglion and hence induced afferent sensitization as shown by increased voiding frequency in rats overexpressing the BDNF gene in their bladder [88]. Further, BDNF expression can be modulated by activity of the GABAergic and cholinergic systems [88, 96, 97], and BDNF in turn can influence neuronal synaptic activity. Thus, the reciprocal influence shared between BDNF and neuronal activity, in addition to the stabilizing effect of BDNF on interneuronal synaptic connections, suggests a complex inter-play that may influence both synaptic plasticity and anatomical reorganization in the mature nervous system [98].

Neurotrophin-3

NT-3 and its receptor, TrkC [99], are also widely present in the developing and adult nervous system [21]. Mice with NT-3 disruption [21, 100, 101] have severe loss of proprioceptive neurons, which is an important finding, as these nerves are responsible for relaying information regarding limb position. Proprioceptive 1a afferents are an integral part of the muscle-motor neuron circuit that mediates the stretch reflex, also known as the muscle spindle. They are key in relaying information from the peripheral muscle spindles to motor neurons in the spinal cord and ascending projections of spinocerebellar neurons. Therefore, the greatly decreased or missing population of 1a afferents and muscle spindles is observed in mice lacking NT-3 and in the NT-3 receptor (TrkC) [99]. Of the mice that were heterozygous for disrupted NT-3, muscle spindles were present at 50% the normal number, which is indicative of a direct relationship between NT-3 availability with 1a afferents' survival. The observed loss of proprioceptive neurons in the NT-3-disrupted mice occurs in parallel with the previous findings that NT-3 is expressed in the target tissues, muscles, and motor neurons. Further, it has been found that proprioceptive neurons expressing TrkC and NT-3 support the viability of in vitro cultured proprioceptive neurons derived from the trigeminal mesencephalic nucleus [102]. In addition, proprioceptive Golgi tendon organs were also found to be missing, suggesting that 1b afferents synapsing with these structures would also be absent. Furthermore, the motor neurons of the ventral roots were reduced by approximately 30%, in contrast with motor neurons of the spinal cord, which were normal.

NT-3-lacking mice have a decreased population of sympathetic neurons present in the superior cervical ganglion [21] without any change in peripheral sympathetic sensory innervation, which was observed in the NGF and TrkA knockout mice [103, 104]. Sympathetic neurons depend on NGF for survival during the innervation of targets, so mice lacking NT-3 could reflect all of the NT-3-dependent events that occur prior to target innervation. Furthermore, NT-3 also promotes in vitro survival of sympathetic neuroblasts, which later become sympathetic precursors [13]. Thus, a reduced population of sympathetic neurons in mice lacking the NT-3 gene reflects that NT-3 has earlier effects on sympathetic phenotype. The effect of NT-3 on the neuronal population of the nodose ganglia is much more clear as the reduction of neurons was partial (47%) in the NT-3-lacking mice, and the NT-3 antibody also reduced neurons' population in the nodose ganglion in the developing quail embryo [21]. This decrease in nodose neuronal population indicates decreased neuronal interconnection to the nodose ganglion rather than protection against naturally occurring death. This was theorized as the timing of NT-3 neutralization is very important and preceded the stage of neuronal death [105]. An involvement of NT-3 in early development is also suggested as it was highly expressed in other areas of the developing embryo before natural cell death. NT-3 can induce the differentiation of cultured enteric multipotent neural crest cells into neurons or glia [14], and work as a mitogen for neural crest cells cultured in the presence of somites and also those cultured with oligodendrocyte precursor cells [106]. Further, NT-3 could help in the differentiation of neural tube progenitors to motor neurons expressing the BEN/SC1 epitope [15] and could carry signals from the neural tube for conversion of the epithelial dermatome progenitors to mesenchyme

cells of the dermis [107]. In-depth studies of the NT-3 knockout mice could clear its role in early embryogenesis.

NT-3 enhances the survival of in vitro cultured embryonic noradrenergic neurons of the locus coeruleus, as well as in vivo survival of noradrenergic neurons of the locus coeruleus after the exposure of 6-hydroxydopamine. Reports are also there showing that NT-3 mediates survival and differentiation of cultured dopaminergic and cholinergic neurons derived from the developing substantia nigra [108], induces the cholinergic phenotype in cultured rat motor neurons and protection of Purkinje cells [109], and stimulates neurite outgrowth in cultured hippocampal pyramidal neurons [110]. NT-3 enhances GABA release in cultured developing hypothalamic neurons of rat during the developmental period when GABA is depolarizing and calcium elevating, but not later when GABA is inhibitory, suggesting that one mechanism through which NT-3 may influence neuronal development is via presynaptic potentiation of GABA excitation [111].

Neurotrophin-4

NT-4 (also called NT-4/5 or NT-5) mRNA is present in major regions of the brain, as well as several other tissues. Unlike all other neurotrophins or their receptor knockout mice, the mice lacking NT-4 are found to thrive and exhibit no overt phenotypic abnormalities, and they are able to reproduce [22]. However, mice lacking NT-4 have around 57% loss in the sensory population of nodose–petrosal and a 50% loss in the geniculate ganglion's population. As mentioned previously, BDNF and NT-4 share the same TrkB receptor. Therefore, mice lacking BDNF have around 61% reduction of nodose- petrosal neurons and a 48% reduction in geniculate population [22, 23]. However, double-knockout mice lacking BDNF and NT-4 genes reflect that this reduction of nodose–petrosal neurons was in different subsets of the neuronal population, as double knockout mice have around 94% reduction in number of neurons of nodose–petrosal ganglion [112]. On the other hand, trigeminal sensory ganglia, which showed neuronal loss in the BDNF knockout mouse, remained unaffected in the mouse lacking NT-4. The difference in the lost population in the NT-4/BDNF double knockout (79–94%) to the 47% loss of nodose neurons in the single NT-3 or BDNF knockout mouse [21] showed that some populations of nodose neurons have a dichotomous nature, which is affected by NT-3 and either NTF-4 or BDNF. It was previously discussed in the BDNF section that disruption of NT-4 alone or NT-4 and BDNF together did not affect the same number of motor neurons, the absence of this phenomenon was surprising, as the survival and differentiation promoting the activity of NT-4 on cultured motor neurons and axotomized motor neurons was predicted to be a result of decreased motor neuron population [59, 86].

As both NT-4 and BDNF share a similar TrkB receptor, it is not surprising that, in most cases, the addition of exogenous NT-4 to culture neurons or in vivo administration of NT-4 has similar effects as administration of BDNF. NT-4 induces differentiation of cultured spinal [113] and basal forebrain cholinergic neurons, hippocampal neurons, and cerebellar granule cells [114, 115], in addition to survival of in vitro embryonic culture of dopaminergic neurons from mesencephalon and noradrenergic neurons from the locus coeruleus [116]. Further, the differentiation of dopaminergic, GABAergic, and serotonergic

neurons in and near the substantia nigra can also be activated by administration of NT-4 in vivo [117]. NT-4 also appears to transiently support the survival of trigeminal and jugular neurons during embryonic development by exerting these effects in a parallel manner as seen in BDNF.

Neurotrophins in the CNS

Of the neurotrophin family members, NGF has the most restricted specificity in CNS and targets specifically cholinergic neurons in the brain region. However, in periphery and other regions of the nervous system, it acts on sympathetic and sensory nerves. Both BDNF and NT-3 are expressed in cortical and neocortical structures, while NT-4 is widely expressed in adult mammals compared to other NTs [118, 119], but its levels remain low compared to other NTs. Interestingly, and perhaps not surprisingly, studies have clearly depicted that after development, these factors are involved in the ongoing remodeling of neuronal functionality underlying the plasticity of neurons [2, 33]. These findings lead to the discussion of a major limitation in the treatment of CNS diseases, which is the loss of regenerative capacity of the brain at an early age. Improper development of nerve circuits is devastating in adults, which makes restorative therapy more difficult. This was previously seen in a broad range of neurologic disorders, such as Parkinson’s or Alzheimer’s disease, stroke, and other inflammatory diseases, including multiple sclerosis [120]. In addition, disorders such as myoclonus or epilepsy reflect in-appropriate neural connections or the lack of the proper feed-back loop of neuronal functionality. Moreover, in some psychiatric diseases, similar deficits or the lack of proper functionality is seen. Chemical and anatomic abnormalities in the nervous system have been documented in affective diseases, such as anxiety disorders and schizophrenia [121]. Therefore, methods that stimulate the regeneration potential of the brain, as in during development, are likely to show great potential in reversing the anomalous functions to normal functions in these neurologic disorders or psychiatric diseases [122].

In some cases, specific neurotrophins and other factors have shown their role in these anomalous changes, including that of hippocampal plasticity and long-term potentiation [123–125] to the acquisition of new songs by songbirds [126–128]. Nowadays, neuronal models are explained by the alteration of neurotrophic factor signaling to prove synaptic alterations or strengthening. In contrast to the original models, which describe retrograde neurotrophin signaling from a target organ, these signaling events also work in an anterograde or autocrine manner. Moreover, studies have shown a change in the rapid expression of these neurotrophic factors in adults, which proves their active involvement with other environment factors [129, 130].

A new finding regards the ability of DRG neurons to express mRNA for neurotrophins and corresponding Trk receptors [131]. Therefore, there is potential for an autocrine or paracrine mechanism. In this way, the release of a neurotrophin from the soma or dendrites is then able to activate receptors in the same or nearby cells. This idea significantly differs from the neurotrophic hypothesis, which is discussed above. Furthermore, the idea of axonal release also suggests other targets for neurotrophins, such as Schwann cells, other spinal cord neurons (with the ability to propagate axo–axonal synapses on sensory terminals), and

peripheral tissues innervated by peripheral axons [132, 133]. Thus, it is reasonable to indicate the roles of neurotrophins to extend well beyond the mechanism implied by the neurotrophic hypothesis. As noted previously, motor neurons are also highly selective in their expression of neurotrophins and their corresponding receptors. It has been found that, in the developmental period of the nerve, BDNF is transported to a much greater extent than NT-3 or NGF in both neonates and in adults [77, 82]. However, there has been the observation of some NT-3 found in the ventral horn after muscle injection, although this was not in association with large motor neurons. One possibility is for NT-3 to be transported by spindle afferents, which have TrkC receptors, to their terminals in the ventral horn. As presumed from the transport result, motor neurons express the receptor for BDNF (TrkB) [29]. Motor neurons also express the mRNA for NT-3 [134], and it is not unreasonable to suggest a paracrine action of NT-3 on spindle afferents, as they project monosynaptically to motor neurons and are known to express Trk C receptors. The functional importance of BDNF to motor neurons during development has been demonstrated by its ability to protect axotomized motor neurons from cell death when applied to these specific axons in neonates [135]. This result may parallel the observed effects of NGF in rescuing sympathetic neurons from the effects of axotomy [136]. Still, it is not known whether this protection of axotomized motor neurons further extends to reversing desynapsis [137], as was found in the case of NGF and axotomized sympathetic neurons. However, the role of BDNF in motor development is not an exclusive one as it has already been shown in BDNF-deficient mice [138]. This suggests the possibility of TrkB receptors' interaction and activation on motor neurons by a different neurotrophin [139], and in fact, it was proven recently that NT-4/5 could also interact with TrkB receptors [139, 140]. In accordance with the presumed role of TrkB in motor neuron development, mice lacking the TrkB gene suffer from significant loss of motor neurons. Therefore, a continued area of study could further characterize the role of an activated TrkB receptor in modulating motor neuron survival into adulthood.

Multiple Roles of Neurotrophins

Studies involving NGF indicate a much clearer role of this NT and its ability to persist after the early developmental processes, as well as to alter the nociceptive properties of nerves. BDNF overexpression in rat bladder by transfection of the BDNF transgene enhanced the micturition frequency in bladder and enhanced the retrograde transport of BDNF to DRG. These and other studies indicate that BDNF also has effects on sensory afferents to implicate BDNF's role in afferent sensitization [141–144]. NGF is well known to affect afferent sensitization [145, 146]. It is also important to understand that nociceptive afferents have completely different physiological and pharmacological properties, both peripherally and centrally (i.e., sensitization), than low-threshold afferents used as targets of the other neurotrophins. Another function that has been demonstrated by neurotrophins in adults is the ability to restore function to damage neurons [31, 89] and also increase the function of neighboring normal neurons [147]. In support of these ideas, it is reported that peripheral nerve damage leads to a rapid increase in the expression of NGF mRNA Schwann cells, as well as in damaged tissue followed by inflammatory cell invasion [66, 140, 148]. In another study, a larger, yet slower, increase in BDNF mRNA limited to Schwann cells of the distal stump has also been reported [149, 150]. Because of what we know thus far, maximum

efforts have been made to investigate whether neurotrophins can stimulate the growth or prevent the degeneration at CNS those that are damaged in neurodegenerative disorders such as Alzheimer's and Parkinson's [151]. Now, people are looking at other roles of neurotrophins, at peripheral and other tissue systems. The NGF's role gives a new idea of relevance to NT molecules originally viewed as factors, as important in development. These molecules show potential use as agents to reverse neurodegenerative processes, as well as broader influences on neural function. Thus, the neurotrophins occupy a wide influence over both the central and peripheral nervous system, with activity throughout the span of a life cycle.

On the other hand, with neurotrophins such as NGF showing high expression relating to pain in inflammatory conditions, drugs that can block these NTs are currently a focus in studies today. Alternatively, the regenerative and antiapoptotic roles of NTs and neuronal dysfunction in the bladder have been studied in the setting of other chronic diseases, such as diabetes mellitus. In one study looking at streptozotocin (STZ)-induced diabetic rats, a progressive increase in the bladder weight, urine volume produced, residual urine, and intercontraction intervals was found [152]. Consequently, a hyposensitive, underactive bladder was induced by DM in these rats, which further resulted in signs of inflammation with increased urine NGF levels, prostaglandin receptor EP1 and EP3, yet a decreased bladder urothelial NGF and prostaglandin E2 (PGE2) expression. Therefore, with this inverse relationship between NGF in the urine and the bladder, it has been proposed that there might be some destruction of NGF receptors, resulting in increased NGF loss in the urine [152]. Therefore, in this situation, a possible blunting of the regenerative and antiapoptotic characteristics of this NT by loss in the urine could be one promising area of study in diabetes. Perhaps, because low levels have been recorded in diabetes, there is some role for gene therapy to restore NGF levels in these patients suffering from diminished bladder function [152]. There is much evidence to date indicating the powerful biological effects of NGF in the setting of neuronal disease, and so, there is a strong incentive to analyze further their functional actions and to develop techniques with localized delivery to modulate their action.

Other Classes of Neurotrophic Factors and Their Signaling Systems

Neurotrophic factors form other families of protein such as the glial cell line-derived neurotrophic factor (GDNF), which have been found to have profound effects on both dopaminergic and motor neurons, as well as enteric neurons [153–155]. For example, in the setting of disc degeneration, NGF and GDNF have been shown to instigate symptoms such as pain, bowel urgency, and paraesthesia. However, artemin, a member of the GDNF family, has been shown to transduce signals through the GFR-α receptor in sensory afferent nerves, proposing a potential use for it in the repair of sensory afferent nerves. In a recent study, artemin injection was linked to the re-establishment of spinal connections and nerve regeneration. However, although proof of pain reduction in humans who received artemin in phase II trials is still to be established, its safe and tolerable nature further promotes it as a potential analgesic therapy [67, 156]. In addition to artemin, the GDNF family also includes persephin and neurturin. This family is closer to the transforming growth factor-β (TGF-β) family, and it signals through a heteromeric signaling complex [157]. Further, a common

component of GDNF receptor complexes is the Ret protein. This protein spans the membrane and expresses an intracellular tyrosine kinase (TK) domain. While this domain is less understood compared to the Trk receptor, it has been shown to activate some of the same intracellular signaling pathways as Trk receptors, including the Ras/ERK pathway and PI-3-K [158]. Ret interacts with several receptor-binding proteins, GFR-α subunits 1–4, which do not span the membrane, but have interactions with the extracellular surface through a glycosylphosphatidylinositol moiety. The α subunit of GFR is responsible for ligand specificity and participates in the activation of the Ret. Furthermore, these subunits can also prompt the activation of src-like tyrosine kinases, which is independent of Ret. Because of the known neuroprotective activities of the GDNF family of proteins, an interest has developed in understanding their role in the pathogenesis and potential mechanisms of treatment in diseases such as addiction, Parkinson's disease, and amyotrophic lateral sclerosis [154, 155]. Another large class of receptors that couple to intracellular tyrosine kinases comprises the Janus kinases (JAKs) [159, 160]. The JAKs consist of extracellular binding components, one of which can span the membrane, yet is unable to exert intrinsic activity. Instead, these components employ an effect by activating other specific JAK family members. The JAKs could then activate several other intracellular effector molecules such as IRS proteins, SHC, and others. Moreover, they are well known to interact with another group of proteins called STATs, which work as signal transducers and activators of transcription proteins. STAT proteins bind to JAK, and upon phosphorylation of tyrosine residues, they are then released and translocate to the nucleus. Here, they exert a direct effect as DNA-binding transcriptional activators. Importantly, many other neurotrophic factors could also activate the JAK/STAT pathway, including ciliary neurotrophic factor (CNTF), growth hormone, leptin, and many cytokines [161]. Still, while it is currently an area of intense study, there is much to be learned regarding the role of STAT-mediated transcription, especially in the brain.

Conclusion

The action of neurotrophins on the Trk family of receptors plays an important role in regulating the survival and growth of neurons in both the central and peripheral nervous system (Fig. 2). Drugs acting on these receptors are currently being tested in the clinic to halt neurodegenerative diseases. Overexpression of NGF in peripheral organs is being targeted by monoclonal antibodies to reduce pain and afferent sensitization. Future research is warranted to advance the understanding of neurotrophins in physiology and pharmacology.

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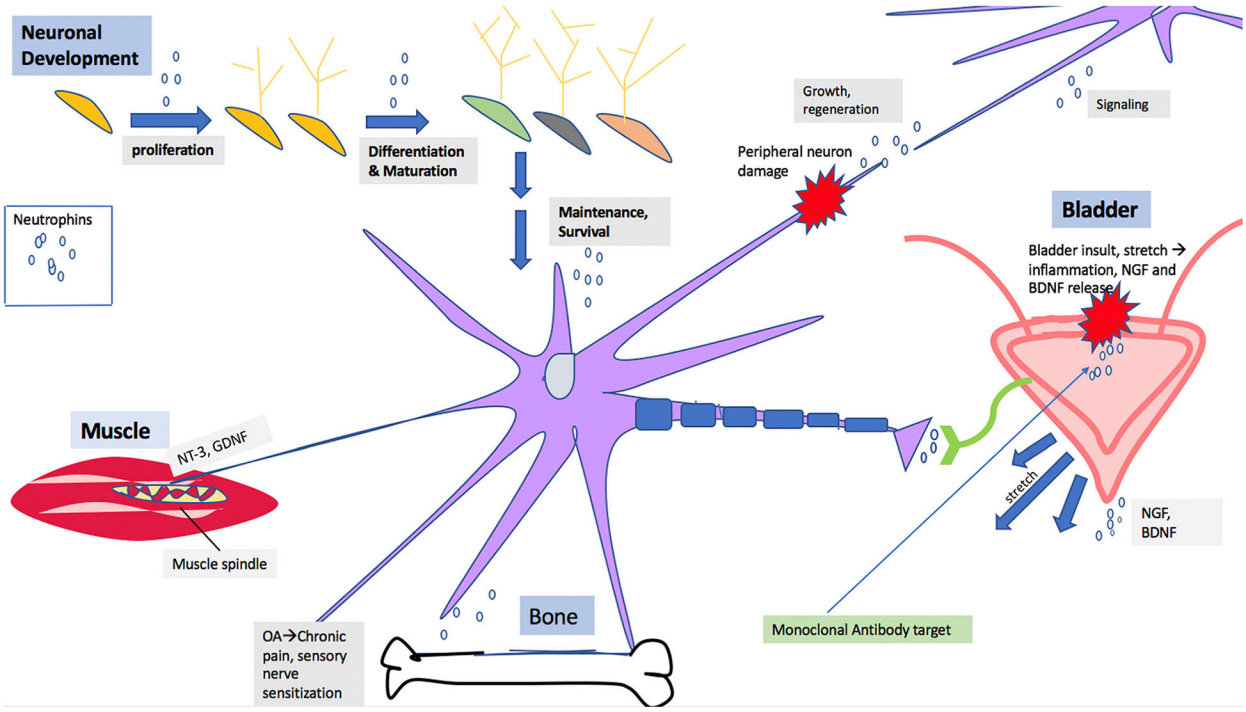

Fig. 1.

Schematic diagram showing role of neurotrophins in neuronal development and in disease pathology

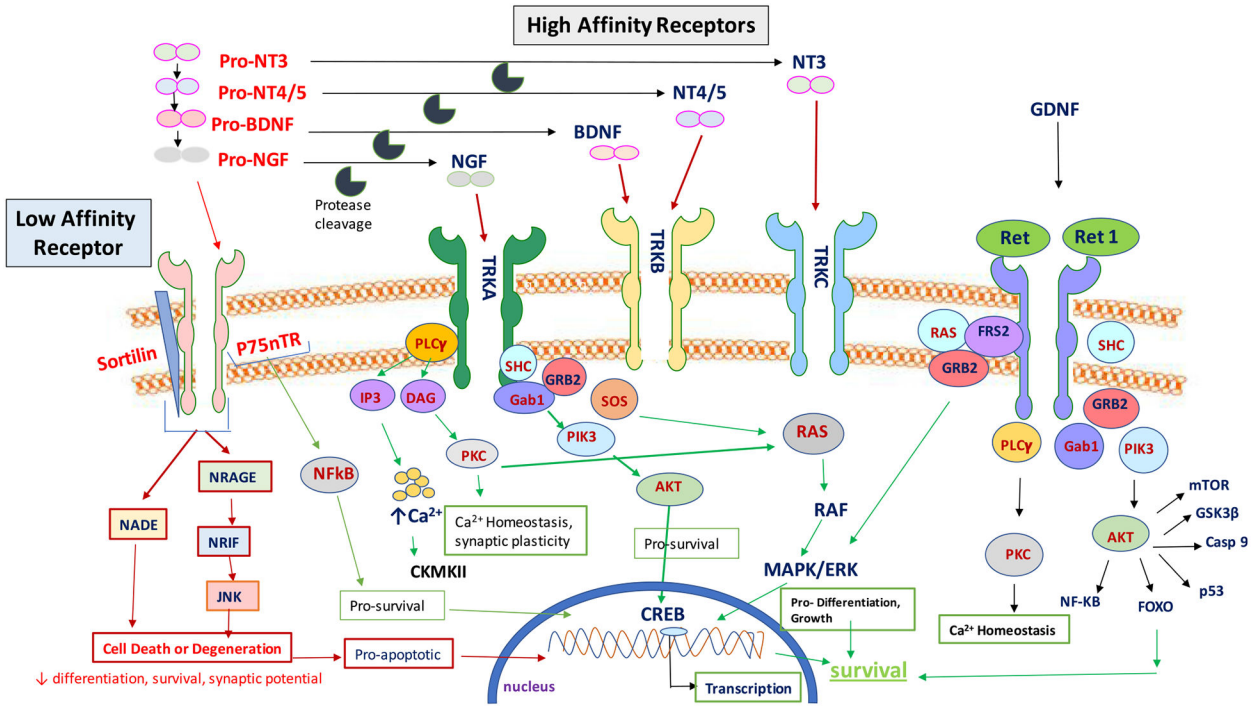

Fig. 2.

Schematic illustration of neurotrophin signaling. (NT = neurotrophins, BDNF = brain-derived neurotrophic factor, TRK = tyrosine receptor kinase, GDNF = glial-derived neurotrophic factor, PLC = phospholipase C, RAS = Ras proteins, GRB = growth factor receptor-bound protein 2, PIK3 = phosphatidylinositol-4,5-bisphosphate 3-kinase, AKT = AKT serine/threonine–protein kinases, FOXO = The forkhead box O transcription factor, PKC = protein kinase C, CREB = the cAMP-responsive element-binding protein)

Table 1

NTs involved in different diseases and their targets

Disease	Neurotrophic factor(s)	Targets
Alzheimer's disease	NGF, BDNF, and GDNF	Cholinergic neurons
Parkinson's disease	GDNF/neurturin	Striatal neurons
Huntington's disease	BDNF	Striatal neurons
Spinal cord injury	BDNF and NT-3	Site of injury
Supranuclear palsy	GDNF	Several in CNS
Amyotrophic lateral sclerosis (ALS)	NGF and BDNF	Motor neurons
Down syndrome	NGF	Cholinergic neurons
Sensory neuropathy	NGF	Sensory and sympathetic neurons
Overactive bladder (OAB)	NGF and BDNF	Bladder
Bladder pain	NGF	Bladder