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Review

Neurotrophic Factors in Stroke, Traumatic Brain Injury, and Neurodegeneration: A Convergent Pathophysiological and Translational Perspective

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Abstract

Neurotrophic factors (NTFs), including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), and vascular endothelial growth factor (VEGF), play a central role in neuronal survival, plasticity, and regeneration. Despite their distinct etiologies and temporal profiles, stroke (both ischemic and hemorrhagic), traumatic brain injury (TBI), and neurodegenerative diseases (NDDs), including Alzheimer's disease (AD) and Parkinson's disease (PD), converge on a common pathophysiological phenotype characterized by excitotoxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, blood-brain barrier (BBB) disruption, and neuronal apoptosis. Neurotrophic factors modulate these pathological cascades through tropomyosin receptor kinase (Trk) receptors, p75 neurotrophin receptor (p75NTR), and related signaling pathways, thereby supporting neuroprotection, neurogenesis, and synaptogenesis. Experimental evidence from preclinical models demonstrates robust beneficial effects of neurotrophin-based interventions in stroke, TBI, AD, and PD across protein, gene, and cell-based strategies. However, clinical translation remains severely limited. Early-phase clinical trials of adeno-associated virus (AAV)-mediated GDNF and neurturin gene therapy for PD, *ex vivo* NGF gene therapy for AD, and BDNF gene therapy for AD have confirmed acceptable safety profiles but yielded modest or inconsistent efficacy, largely due to constraints in brain delivery, the need for invasive neurosurgical procedures, restricted target coverage, suboptimal control of expression, and marked patient heterogeneity. Consequently, the principal barrier to clinical success is not biological validity, but the lack of safe, effective and scalable delivery platforms capable of bypassing or functionally modulating the BBB. In this review we synthesize shared pathophysiological mechanisms linking stroke, TBI and NDDs; examine the biology, receptor systems, and signaling pathways of key neurotrophic factors; summarize preclinical evidence for their therapeutic potential; and critically evaluate current delivery strategies, including viral vectors, lipid nanoparticles, exosomes, cell-based therapies, small-molecule mimetics, and intranasal administration. We conclude that overcoming delivery barriers through development of improved viral and non-viral platforms, minimally invasive administration routes, controllable expression systems, and rational patient stratification based on disease stage and biomarkers will be essential to fully realize the neuroprotective and neuroregenerative potential of neurotrophin-based therapies for acute and chronic brain disorders.

Keywords: neurotrophic factors; stroke; traumatic brain injury; neurodegenerative diseases; Alzheimer's disease; BDNF; NGF; gene therapy; neuroprotection

1. Introduction

The study of mechanisms that enhance neuronal survival is highly relevant because the central nervous system (CNS) is particularly vulnerable to stroke, traumatic injury, and neurodegenerative disorders, all of which are major causes of death, disability, and long-term reduction in quality of life [1]. In contrast to many other tissues, the adult CNS has a limited regenerative capacity, which makes recovery after injury especially difficult and contributes to persistent neurological and cognitive deficits [2]. This problem is becoming increasingly important in the context of population aging and the growing prevalence of chronic diseases, which together increase the burden of stroke, traumatic brain injury (TBI), and neurodegenerative diseases (NDDs), including Alzheimer's disease and Parkinson's disease. Despite their distinct etiologies and temporal profiles, these disorders converge on common pathophysiological mechanisms, including excitotoxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, blood-brain barrier disruption, and neuronal apoptosis, thereby supporting the search for unified neuroprotective strategies [3,4,5,6,7,8]. Within this framework, therapeutic approaches aimed at preserving neuronal viability, enhancing endogenous repair, and restoring synaptic and cellular plasticity are of particular interest.

Neurotrophic factors (NTFs), including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), glial cell line-derived neurotrophic

factor (GDNF), ciliary neurotrophic factor (CNTF) and vascular endothelial growth factor (VEGF), play a central role in neuronal survival, plasticity maintenance and regeneration [9]. These molecules are increasingly regarded as universal therapeutic targets for CNS pathologies [3]. Despite compelling preclinical evidence of the neuroprotective effects of NTFs, clinical implementation of neurotrophin-based approaches remains limited.

This review was conducted with the following objectives: (1) to summarize the shared pathophysiological mechanisms linking ischemic and hemorrhagic stroke, TBI and major NDDs; (2) to analyze the biology and signaling pathways of key NTFs; (3) to synthesize evidence of their role as biomarkers and therapeutic agents; (4) to critically evaluate strategies for NTF delivery to the brain and existing limitations. We hypothesize that overcoming delivery barriers will substantially enhance the realization of the therapeutic potential of neuroprotective strategies based on modulation of the neurotrophic system in these pathologies. The review included original research articles, systematic reviews and meta-analyses published predominantly over the last 10 years, as well as seminal works in the field of NTF discovery and biology.

Importantly, emerging evidence suggests that the translational failure of neurotrophin-based therapies may not reflect insufficient biological relevance of NTFs, but rather inadequate spatial and temporal control of their signaling in the injured brain. Dysregulation of receptor balance (tropomyosin receptor kinase (Trk) versus p75 neurotrophin receptor (p75NTR)), impaired retrograde transport, inflammatory microenvironmental shifts and restricted anatomical target coverage may critically determine therapeutic outcome [3,4]. From this perspective, neurotrophic modulation should be viewed not merely as replacement of deficient trophic support, but as precise systems-level regulation of interconnected survival, plasticity and repair pathways. Addressing these mechanistic and delivery-related constraints may therefore represent a prerequisite for bridging the persistent gap between robust experimental efficacy and modest clinical benefit.

To address this integrative framework, we first examine the shared molecular and cellular mechanisms that underlie stroke, traumatic brain injury and major neurodegenerative disorders. Establishing this common pathophysiological ground is essential for understanding why neurotrophic signaling represents a unifying regulatory system across these seemingly distinct conditions. We then analyze the biology and receptor-specific signaling of key neurotrophic factors within this convergent cascade, followed by a critical evaluation of preclinical and clinical evidence and the translational constraints that shape therapeutic outcomes.

2. Literature Review

2.1 Commonality of Pathologies: Neurodegeneration, Neurotrauma and Acute Cerebrovascular Disorders

The paradigm of modern neurology is increasingly shifting from disease-specific frameworks toward a convergent model of brain injury, emphasizing shared pathogenetic mechanisms across stroke, TBI and NDDs [10]. Despite differences in triggering events (acute disruption of blood supply in stroke, mechanical impact in TBI, slow accumulation of pathological proteins in NDDs), the subsequent cellular processes demonstrate remarkable similarity.

The key component unifying the pathogenesis of stroke, TBI and NDDs is a cascade of interrelated pathobiochemical reactions (oxidative stress, excitotoxicity, mitochondrial dysfunction, inflammation) leading to neuronal death [9].

At the cellular level, ischemia occurring during stroke induces excitotoxicity, oxidative stress and neuroinflammation. This critically impairs adenosine triphosphate (ATP) synthesis and ion pump function, leading to neuronal depolarization and massive glutamate exocytosis [10]. Excessive glutamate activates its receptors, particularly N-methyl-D-aspartate (NMDA) receptors, causing intraneuronal calcium overload. This leads to activation of proteolytic enzymes (calpains), lipases (phospholipase A2) and endonucleases, resulting in degradation of the cytoskeleton, cell membranes and DNA. Consequently, nitric oxide synthase (NOS) is activated, leading to excessive production of nitric oxide (NO). NO, combining with superoxide anion (O_2^-), forms peroxynitrite ($ONOO^-$), a substance toxic to cells. In parallel, mitochondrial function is disrupted, exacerbating oxidative stress and excessive generation of reactive oxygen species (ROS). ROS damage cellular components: lipids, proteins and DNA. Damaged neurons release signals that attract immune cells (microglia). Microglia become activated and release proinflammatory cytokines (tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6), which in turn amplify oxidative stress, excitotoxicity and blood-brain barrier (BBB) damage [11]. Ultimately, the triggered cascade of pathological reactions leads to neuronal death via two pathways: necrosis (in the ischemic core) and apoptosis (in the penumbra) [4].

In hemorrhagic stroke, in addition to ischemic injury, direct toxic effects of blood on brain tissue are observed, mediated by hemoglobin degradation products. Hemorrhage also causes elevated intracranial pressure, leading to secondary ischemia due to vascular compression. The inflammatory response in hemorrhagic stroke is generally more pronounced [5]. Regardless of stroke type, the ultimate outcome is neuronal death and impairment of brain function.

Over the past decade, abundant new evidence has emerged confirming the similarity of TBI pathophysiology with pathological processes occurring during stroke. The primary and secondary phases of neuronal injury in TBI

are also associated with disruption of cellular homeostasis caused by BBB damage, osmotic shifts, inflammatory reactions, oxidative stress, excitotoxicity and apoptosis [6]. These processes collectively lead to impaired functional activity of neural tissue.

Analogous pathobiochemical pathways, albeit extended over years, underlie the pathogenesis of NDDs such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS) [7]. Although the trigger in NDDs is not an acute damaging event but rather a slow accumulation of pathological protein aggregates (beta-amyloid and tau protein in Alzheimer's disease, alpha-synuclein in Parkinson's disease, etc.), the subsequent cellular response is remarkably similar to that in stroke and TBI. The same excitotoxicity, oxidative stress, neuroinflammation and apoptosis are observed [8].

Thus, despite different etiologies and time scales, stroke, TBI and NDDs converge on a unified pathophysiological phenotype. This conceptual commonality paves the way for the development of universal neuroprotective strategies targeting not a specific cause but common key elements of neuronal death, representing an extremely promising direction for therapy of a wide spectrum of nervous system disorders [4,8,12].

2.2 Rationale for NTF Application

Therapeutic strategies aimed at enhancing endogenous reparative processes appear quite promising in light of the commonality of pathological mechanisms. NTFs—a family of proteins that ensure neuronal survival, development and plasticity—occupy a central place in such strategies.

The ischemic cascade, excitotoxicity and neuroinflammation are associated with a significant reduction in the expression and/or availability of endogenous NTFs [13]. The limited amount of secreted NTFs prevents the survival of all neurons that could, however, be rescued by administration of exogenous NTFs or stimulation of their synthesis. Activation of these components provides multifaceted therapeutic action. They can prevent cell death by stimulating synthesis of anti-apoptotic proteins. Furthermore, they improve synaptic plasticity and promote neurogenesis, which is critically important for restoration of lost functions. They also regulate microglial activity, shifting its profile from proinflammatory to neuroprotective, and exert antioxidant effects [14,15]. Thus, therapeutic strategies modulating neurotrophic support represent a promising multifaceted approach to correcting neurodegenerative processes associated with various cerebral pathologies, targeting common pathophysiological mechanisms and activating endogenous reparative processes in neural tissue.

2.3 History of NTFs

NTFs constitute a family of proteins that play a critical role in the survival, differentiation and functional activity of nerve cells. They support neurons by modulating various aspects of their physiology [16].

The first NTF to be identified was NGF. This discovery belongs to Rita Levi-Montalcini and Viktor Hamburger, whose work began in the 1950s. Their research started with an intriguing observation: a mouse tumor placed in chicken embryos induced vigorous nerve fiber outgrowth. Further experiments confirmed that a factor released by the tumor was responsible for stimulating nerve growth. For this groundbreaking discovery, Rita Levi-Montalcini was awarded the Nobel Prize in Physiology or Medicine in 1986 [17].

The NTF hypothesis was further developed following isolation of the second NTF—BDNF [14]. Molecular cloning of the *BDNF* gene [15] revealed its structural similarity to NGF, leading to the formation of the NTF family concept. Subsequent research led to identification of two additional family members: NT-3 and neurotrophin-4 (NT-4) [18]. Later, neurotrophin-6 and neurotrophin-7 were discovered in fish, with no mammalian homologs [19].

The identification of NTFs opened new horizons in studying fundamental processes of neurogenesis and synaptic plasticity. Their functions encompass formation of precise neural circuits, modulation of synaptic plasticity underlying learning and memory, regulation of affective states and nociception, as well as stimulation of regeneration after injury.

2.4 Biology of NTFs

2.4.1 The NTF Family and Their Structure

NTFs control various aspects of neuronal survival, development and function in both the central and peripheral nervous systems [9]. Individual neurons may be responsive to more than one neurotrophin depending on their developmental stage.

Mature NTFs are protein dimers assembled from two identical molecules. Their three-dimensional structure is stabilized by a characteristic "cysteine knot"—a robust construction of three disulfide bonds, which is also characteristic of other growth factors (e.g., transforming growth factor-β (TGF-β)). Regions of the molecule responsible for core functions are highly conserved, while other areas are more variable and determine the specificity of each NTF [19,20,21].

In addition to classical neurotrophins, a number of other polypeptide factors possess neurotrophic activity. CNTF [22], GDNF [23], insulin-like growth factor (IGF) [24], basic fibroblast growth factor (bFGF) [25], VEGF [26], TGF-β [27] and Sonic Hedgehog protein (Shh) [28] are also capable of supporting the survival of specific CNS neuronal populations and protecting these cells from damage.

2.4.2 NTF Receptors and Signaling Mechanisms

NTFs interact with two main classes of receptors: Trk and the low-affinity p75 receptor (p75NTR/CD271) [15,29].

Trk receptors are receptor tyrosine kinases activated upon binding of specific neurotrophins. NGF binds to TrkA [30,31], BDNF and NT-4 bind to TrkB [15,21], and NT-3 predominantly binds to TrkC [32] but can interact with TrkA and TrkB with lower efficiency [33]. Ligand-induced dimerization of Trk receptors leads to their autophosphorylation and activation of intracellular signaling cascades such as Ras-mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt) and phospholipase C gamma (PLCγ)1, which regulate neuronal survival, differentiation, synaptic plasticity and metabolism [33].

Unlike the selective Trk receptors, p75NTR, a member of the tumor necrosis factor receptor (TNFR) superfamily, is recognized as a receptor for all neurotrophins, as it binds all neurotrophins with similar affinity [34]. Its signaling mechanism is also fundamentally different: lacking intrinsic kinase activity, p75NTR acts through co-receptors and intracellular mediators (adaptor proteins), leading to activation of signaling pathways such as nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK). p75NTR can modulate Trk receptor signaling by promoting formation of high-affinity binding sites for NGF, facilitating endocytosis and retrograde transport of neurotrophin-Trk complexes [35]. However, in certain contexts, particularly in the absence of Trk receptors, p75NTR activation can initiate pro-apoptotic signals [35].

Trk receptor function is modulated by p75NTR at multiple levels—by enhancing ligand binding, increasing neurotrophin availability through stimulation of axonal growth and target innervation, and by promoting endocytosis and retrograde transport [36,37]. For example, p75NTR inhibits activation of Trk receptors by non-preferred NTFs both *in vivo* and *in vitro* [36]. It has been demonstrated that deletion of exon III of p75NTR in senescence-accelerated mouse prone 8 (SAMP8) mice leads to pronounced degeneration of cholinergic neurons of the basal forebrain and cognitive impairment [38].

The study [39] also indicates that integrin α9β1 may serve as a third receptor for NGF, BDNF and NT-3. Integrin α9β1 is a multifunctional receptor whose engagement leads to activation of the MAPK pathway, resembling the interaction of NGF with TrkA.

Furthermore, mechanisms of Trk receptor transactivation by G protein-coupled receptors (GPCRs) in the absence of neurotrophins have been demonstrated [40]. Adenosine and pituitary adenylate cyclase-activating polypeptide (PACAP) can activate Trk receptors, enhancing neuronal cell survival through stimulation of Akt activity [41].

Collectively, the data on the receptor profile, cross-activation of the Trk and p75NTR systems, and involvement of integrins and GPCRs demonstrate that NTFs form a tightly interconnected signaling network influencing neuronal survival, plasticity and circuit remodeling. For further exposition, it is appropriate to summarize the key characteristics of the major NTFs in tabular form. Table 1 (Ref. [9,14,15,17,18,20,21,23,26,29,30,31,32,33,34,39,40,42,43,44,45,46,47]) presents the main cellular targets, receptors, signaling pathways and principal functional effects of NGF, BDNF, NT-3, GDNF, CNTF and VEGF in the CNS.

2.4.3 Age- and Sex-Dependent Regulation of Neurotrophic Factor Expression and Function

The expression and bioavailability of NTFs in CNS tissues are not static properties—they undergo systematic, region-specific changes across the lifespan and are substantially modulated by biological sex [48,49,50]. These two factors represent major sources of biological variability that critically influence both the baseline neuroprotective capacity and the responsiveness of neural tissue to injury and must be considered when evaluating the translational potential of neurotrophin-based therapies.

2.4.3.1 Age-Related Changes in NTF Availability.

BDNF. BDNF exhibits the most thoroughly characterized age-related trajectory among the neurotrophins. Study [48] employing microarray and quantitative polymerase chain reaction (qPCR) analysis of human postmortem orbitofrontal cortex tissue (n = 209; ages 16–96 years) demonstrates a progressive, age-dependent downregulation of *BDNF* mRNA that co-segregates with decreased expression of 78 genes associated with both excitatory and inhibitory synaptic function. In parallel, TrkB full-length receptor (*TrkB-TK+*) mRNA in the human temporal cortex and hippocampus declines significantly across the lifespan [49], and *TrkB.T1* (truncated) transcript levels in the hippocampus similarly decrease between young adult and aged groups [50]. This receptor downregulation is functionally critical: blockade of TrkB activity in adult mice reproduces the age-like pattern of synaptic gene expression changes observed in aging humans, indicating that receptor loss—rather than ligand loss alone—drives the functional deficit [51].

Beyond receptor downregulation, a shift in the BDNF/proBDNF balance compounds the problem of aging. In aged rodents, elevated hippocampal proBDNF levels relative to young controls activate p75NTR-dependent cofilin phosphorylation and dendritic spine loss, leading to progressive memory impairment [52]. Furthermore, systemic neuroinflammatory challenges (including surgically induced sepsis) suppress hippocampal TrkB phosphorylation and BDNF protein specifically in aged animals but not in young controls, illustrating that the age-impaired neurotrophic axis is disproportionately vulnerable to superimposed inflammatory insults [53].

Clinically, a study [54] in patients with acute ischemic stroke has confirmed that BDNF levels in individuals over

Table 1. Major neurotrophic factors, their targets and signaling pathways in the CNS.

Neurotrophic factor	Major cellular targets in the CNS	Principal receptors	Key signaling pathways	Primary functional effects	Reference
NGF	Cholinergic neurons of the basal forebrain, sympathetic neurons, oligodendrocyte precursors	TrkA, p75NTR, integrin α9β1	Ras-MAPK, PI3K-Akt, PLCγ, NF-κB-JNK	Neuronal survival, maintenance of cholinergic phenotype, neuritogenesis, myelin protection, modulation of neuroinflammation	[9,17,30,31,34,39]
BDNF	Pyramidal neurons of cortex and hippocampus, striatal neurons, GABAergic interneurons, glia	TrkB (full-length and truncated isoforms), p75NTR	Ras-MAPK, PI3K-Akt, PLCγ, transactivation via GPCRs	Synaptic plasticity and LTP, neurogenesis, dendritic remodeling, regulation of excitation/inhibition balance, antidepressant effects in experimental models	[9,14,15,20,21,29,32,40,42]
NT-3	Spinal and cortical neurons, proprioceptive sensory neurons, oligodendroglial lineage cells	TrkC (high affinity), TrkA-TrkB (low affinity), p75NTR	Ras-MAPK, PI3K-Akt	Axon growth and guidance, support of proprioceptive pathways, remyelination, participation in CNS tract repair	[9,18,32,33,34]
GDNF	Midbrain dopaminergic neurons, spinal motor neurons, striatal neurons	GFRα1-RET complex, NCAM	MAPK-ERK, PI3K-Akt, Src-family kinases	Survival and functional support of dopaminergic neurons, motor neuron protection, modulation of synaptic transmission, improvement of motor recovery	[9,23,32]
CNTF	Motor neurons, retinal ganglion cells, astrocytes, oligodendrocytes	CNTFRα-LIFRβ-gp130 complex	JAK-STAT, PI3K-Akt, MAPK-ERK	Neuroprotection of motor neurons and retinal cells, glial trophic support, modulation of inflammatory response	[9,43,44,45]
VEGF	Endothelial cells, neural stem/progenitor cells, neurons, astrocytes	VEGFR-1, VEGFR-2, neuropilins	PI3K-Akt, MAPK-ERK, PLCγ	Angiogenesis, BBB modulation, neurogenesis, activity-dependent neuroprotection; under certain conditions—enhanced vascular permeability and risk of cerebral edema	[26,46,47]

Trk, tropomyosin receptor kinases; CNS, central nervous system; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin-3; GDNF, glial cell line-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; VEGF, vascular endothelial growth factor; p75NTR, p75 neurotrophin receptor; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; PLCγ, phospholipase C gamma; NF-κB, nuclear factor kappa B; JNK, c-Jun N-terminal kinase; LTP, long-term potentiation; GFRα1, GDNF family receptor alpha 1; RET, rearranged during transfection receptor; NCAM, neural cell adhesion molecule; ERK, extracellular signal-regulated kinase; CNTFRα, ciliary neurotrophic factor receptor alpha; LIFRβ, leukemia inhibitory factor receptor beta; JAK, Janus kinase; STAT, signal transducer and activator of transcription; VEGFR, vascular endothelial growth factor receptor; BBB, blood-brain barrier.

55 years of age are significantly lower both at baseline and following injury compared to younger patients, providing translational validation that the age-related BDNF deficit observed in animal models has direct clinical relevance.

NGF. NGF undergoes a functionally critical shift from neuroprotective to potentially neurotoxic signaling during aging [55]. In aging rats (19–22 months), proNGF levels in the prefrontal cortex and hippocampus increase by 1.8–1.9 times, while mature NGF decreases by 36–44%, leading to an age-related deficit in neurotrophic support. Concurrently, p75NTR expression increases by 1.6–1.8 times, and sortilin by 1.8–2.1 times, transforming p75NTR into a high-affinity proapoptotic receptor for accumulated proNGF [56]. Due to decreased plasmin-mediated cleavage and increased neuroserpin activity, proNGF accumulates in aging brain tissue where it forms the proNGF–p75NTR–sortilin signaling complex in basal forebrain cholinergic neurons and substantia nigra dopaminergic neurons, inducing apoptosis not observed in young animals [57]. Postreceptor signaling is manifested by a significant decrease in MAPK phosphorylation via TrkA in the basal forebrain in response to exogenous NGF in aged rats, despite adequate TrkA protein levels [58]. Thus, age-related changes in the NGF system represent the combined effects of proNGF accumulation, postreceptor dysfunction, and a shift in the balance toward proapoptotic signaling via p75NTR–sortilin, making cholinergic and dopaminergic neurons particularly vulnerable to age-related degeneration. This mechanism confirms that age-related deficiency of neurotrophic NGF support is not simply an age-related correlation, but an active driver of neurodegenerative processes that can be potentially reversible with targeted modulation of p75NTR activity [59].

GDNF. Age-related changes in GDNF expression show a tissue-dependent pattern. In the rat frontal cortex, GDNF mRNA and protein appear to increase with age, potentially reflecting compensatory upregulation, whereas hippocampal levels remain relatively stable [60]. A study [61] using mice with a twofold increase in endogenous GDNF expression (Gdnf hypermorphs) demonstrate that maintaining elevated baseline GDNF preserves cholinergic marker expression and cognitive function with aging and, importantly, elevates NGF levels in multiple brain regions of old animals—indicating that GDNF and NGF cooperatively buffer age-related cholinergic decline. In peripheral neurotrophic models of Parkinson's disease, the neuroprotective efficacy of GDNF against 6-hydroxydopamine (6-OHDA)-induced dopaminergic loss is preserved in aged rats, supporting the relevance of GDNF-based interventions in older subjects [62].

NT-3. NT-3 undergoes pronounced developmental regulation that directly constrains the neuroplasticity capacity of the CNS across age. In the normal rat spinal cord, *NT-3* mRNA is highly expressed during the early postnatal period (P3–P10) and decreases sharply between P10 and P17, coinciding with the progressive restriction of CNS axonal growth capacity. Following spinal cord injury, this developmental pattern is recapitulated in the injury response: neonatal tissue displays significantly higher *NT-3* mRNA levels compared to adult tissue, a differential that correlates with the superior axonal regenerative potential of the immature spinal cord [63]. In parallel, NT-3 expression declines in peripheral target tissues—including skeletal muscle—during normal postnatal development and advancing age, contributing to impaired neuromuscular junction integrity and sarcopenia [64]. In the adult CNS, the efficacy of exogenous NT-3 delivered via adenoviral vectors is tightly dependent on injury phase: NT-3 overexpression promotes robust corticospinal tract (CST) axonal sprouting when administered during the acute phase (2 weeks post-injury), but fails to do so when applied 4 months after injury [65]. This temporal constraint is likely mediated by co-inducing signals from Wallerian degeneration products that are present acutely but absent from chronically injured tissue [66]. Together, these data indicate that the therapeutic window for NT-3 in repair is defined not only by the age of the subject, but critically by the injury phase, limiting the translational applicability of NT-3-based strategies to acute interventions.

CNTF. Unlike classical neurotrophins, *CNTF* mRNA in the spinal cord increases significantly between P10 and P17, reflecting a post-developmental role in glial trophic support and myelination [63]. Following acute injury, CNTF expression is upregulated in reactive astrocytes and activates Janus kinase (JAK)–signal transducer and activator of transcription (STAT)3 signaling in a paracrine/autocrine manner, which is critically important for neuroprotection of motor neurons and retinal ganglion cells [67]. However, neuroinflammatory activation of JAK–STAT3 in astrocytes and microglia contributes to the proinflammatory glial phenotype that predominates in aged brain tissue, creating a bidirectional regulatory context in which trophic JAK–STAT3 signaling may be progressively co-opted by inflammatory pathways with advancing age [68].

VEGF. Circulating VEGF rises acutely following ischemic stroke onset and remains elevated for at least 90 days, but this acute response is attenuated in older patients with vascular comorbidities [69]. The functional output of VEGF signaling decreases with age due to progressive endothelial dysfunction and reduced vascular endothelial growth factor receptor (VEGFR)-2 responsiveness, limiting angiogenic and neuroprotective effects per unit of VEGF protein [70]. Moreover, age-related BBB compromise shifts the net effect of VEGF toward enhanced vascular permeability and cerebral edema rather than neuroprotection, a phenomenon of direct clinical relevance when considering VEGF-based therapies for elderly patients [71].

2.4.3.2 Sex Differences in NTF Expression and Function. Biological sex substantially influences NTF expression, receptor sensitivity and downstream signaling through hormonal, genetic and epigenetic mechanisms that have direct implications for disease susceptibility and the efficacy of neurotrophin-based therapies.

BDNF. The *BDNF* gene contains a functional estrogen-response element (ERE)-like sequence, and estrogen receptor α (ERα) co-localizes with BDNF in hippocampal CA3 pyramidal neurons [72]. Neonatal gonadectomy in male rat pups significantly reduces hippocampal *BDNF* mRNA on P7, and a single injection of estradiol benzoate on P0 restores levels to those of intact animals across all ages examined, demonstrating a direct estrogen-dependent transcriptional regulation of *BDNF* during development. In adult ovariectomized rats, 14-day estradiol treatment increases BDNF immunolabeling and mRNA in the CA1 and CA3 hippocampal subfields and in the medial and basomedial amygdala [73]. Female rodents show higher BDNF expression in limbic structures compared to males, and this advantage is abolished by ovariectomy [74]. These sex differences have clinical correlates: lower BDNF levels are associated with impaired general cognitive function specifically in older women but not in age-matched men [75].

Testosterone, or its metabolites, may influence adult neurogenesis by altering levels of neurotrophic factors within the brain. For example, female canaries given testosterone implants showed increased levels of BDNF. Male rats have higher levels of BDNF within the dentate gyrus than do females, suggesting that BDNF levels may be regulated by sex hormones. Testosterone also modulates BDNF in a region- and age-dependent manner. Castration reduces hippocampal BDNF in male rats, whereas testosterone implants increase hippocampal BDNF in transgenic male SAMP8 mice, indicating androgen-sensitive regulation of BDNF. However, neither testosterone nor dihydrotestosterone alters hippocampal BDNF levels in aged male rats, consistent with the idea that testosterone may act predominantly via aromatization to estradiol and activation of the well-characterized estrogen-response element in the *Bdnf* gene rather than via direct androgen receptor binding. Moreover, testosterone effects on BDNF are subregion-specific: castration increases BDNF in mossy fibers projecting from the dentate gyrus to CA3 but decreases BDNF in CA1, which is rich in androgen receptors, suggesting that androgen-dependent enhancement of adult neurogenesis may be mediated indirectly through increased CA1 plasticity rather than a simple increase of BDNF in the dentate gyrus [76].

NGF. In peripheral tissues, NGF shows clear sex- and hormone-dependent regulation. In cardiac tissue of young adult Sprague–Dawley rats (12 weeks), males exhibit significantly higher NGF content than females, and this sex difference is attenuated in older animals in parallel with an age-related decline of neurotrophic support, particularly in sedentary females [77]. In limbic regions, aging is associated with a shift toward a less trophic NGF profile. Experimental and clinical data suggest that the loss of ovarian estrogens after reproductive senescence further enhances vulnerability of NGF-dependent hippocampal circuits in females, creating a sex-specific window of risk for cholinergic dysfunction and cognitive decline [78].

GDNF. Emerging evidence suggests that GDNF signaling is also modulated by sex and hormonal milieu. In experimental models of cerebellar ischemia–reperfusion, male rats show more pronounced shifts in GDNF expression in Purkinje cells than females, indicating sex-dependent regulation of endogenous GDNF responses to acute injury [79]. In experimental models of global and focal brain ischemia, exogenous GDNF confers robust neuroprotection of vulnerable neuronal populations, but the magnitude and durability of this effect differ between males and females, consistent with sex-dependent regulation of endogenous GDNF responses to acute injury. At the molecular level, GDNF is strongly upregulated in activated astrocytes and microglia in response to neuroinflammatory and ischemic stimuli, positioning glia-derived GDNF as a key stress-responsive trophic factor in the injured brain [80]. Given well-documented sex differences in hypothalamic–pituitary–adrenal (HPA) axis reactivity and neuroinflammatory profiles [81], these glial GDNF responses are likely to be differentially engaged in males and females, adding another layer of sex specificity to neurotrophin regulation in the CNS [82].

These findings carry direct translational consequences. First, preclinical efficacy data generated predominantly in young adult male rodents may substantially overestimate the neuroprotective effects achievable in elderly patients of both sexes, as target tissue receptor density, signaling competence and neuroinflammatory tone differ profoundly from experimental conditions. Second, the age-related shift toward proBDNF and proNGF signaling raises the concern that exogenous NTF administration may paradoxically activate p75NTR-sortilin-dependent proapoptotic pathways in elderly patients if cleavage and receptor specificity are not controlled. Third, the hormonal dependence of NTF expression indicates that menopausal status and androgen levels should be considered as stratification variables in clinical trials of neurotrophin-based therapies, particularly those targeting BDNF-dependent or dopaminergic circuits. Collectively, these considerations underscore the need for age- and sex-stratified experimental designs in both preclinical and clinical neurotrophin research and support the development of delivery strategies capable of bypassing or correcting the age-associated impairments in NTF signaling.

2.5 Effects of NTFs in Target Pathologies

2.5.1 NGF

NGF—as previously mentioned, the first NTF to be discovered. The role of NGF is attracting increasing attention due to its involvement in neuronal survival, repair and plasticity after injury. Astrocytes and pericytes produce NGF in response to inflammatory mediators, which reduces neuronal apoptosis and plays an important role in the neuroprotective response: in the regulation and trophic support of neuronal development, differentiation and maturation, particularly for cholinergic neurons of the basal forebrain [83]. NGF also demonstrates pronounced protective properties toward glial and vascular endothelial cells, as well as other cell populations under various pathological conditions [83,84].

Experimental data indicate the ability of exogenous NGF to reduce apoptotic cell death, decrease infarct volume, prevent delayed neuronal death, induce a neuroprotective microglial phenotype, stimulate angiogenesis and promote neuronal regeneration and functional recovery [85,86]. Clinical studies [87,88] have shown that serum NGF concentrations are significantly lower in patients with ischemic stroke compared to healthy individuals. Statistical correlation analysis demonstrated a strong inverse relationship between NGF levels and National Institutes of Health Stroke Scale (NIHSS) scores, indicating that lower NTF levels are associated with more severe neurological deficits. Furthermore, significant correlations were found between NGF levels and functional outcome measures including the Barthel Index, supporting the hypothesis that reduced neurotrophic support contributes to impaired recovery of activities of daily living [87]. Luan et al. (2019) [88] demonstrated that patients with higher NGF levels at 3 months after stroke showed more significant recovery of motor function and speech.

Experimental studies have shown that NGF administration stimulates neurogenesis and improves functional recovery after TBI [84,89]. A clinical study demonstrated that endogenous NGF levels in cerebrospinal fluid correlate with TBI severity and outcome in children [90].

Systematic reviews indicate considerable promise of NGF as a neuroprotective and neuroregenerative agent [91]; however, its therapeutic potential remains unrealized due to the lack of effective strategies for delivering bioactive NGF to damaged neural tissue across the blood-brain barrier [84,92].

2.5.2 BDNF

BDNF is a well-characterized protein that plays an important role in the development and maintenance of neuronal health. It is widely expressed in the brain and promotes neuronal survival, particularly under hypoxic conditions, through activation of TrkB and p75NTR receptors and subsequent signaling cascades [93,94]. It contributes to proper development and adaptation of glutamatergic and GABAergic synapses and also influences serotonergic and dopaminergic neurotransmission [42,95,96].

In neurodegenerative pathologies and stroke, a statistically significant reduction in BDNF levels is observed [97]. Administration of drugs that stimulate BDNF synthesis, such as antidepressants, promotes post-stroke recovery [22]. BDNF administration itself promotes motor function recovery, reduces infarct size and stimulates neurogenesis in the injury zone [84]. Preclinical study [98] in animal models demonstrates the potential to stimulate formation of new neurons after intracerebral hemorrhage through BDNF by increasing proliferation and differentiation of stem cells into neuroblasts. BDNF administration can also counteract the process of ischemic cell damage and improve sensorimotor recovery after stroke and TBI [99]. Recently, growing evidence points to the significance of BDNF in post-stroke recovery, particularly in improving motor skills and reducing post-stroke depression. Therefore, rehabilitation techniques aimed at optimizing the influence of BDNF on neuroplasticity appear promising for effective neural function restoration [100].

2.5.3 NT-3

NT-3 plays a key role in the development and function of locomotor circuits, including descending axons of the serotonergic and corticospinal tracts, as well as afferent pathways from muscles and skin [101]. Neurotrophins NT-3 and NT-4, by binding to p75NTR, TrkA, TrkB and TrkC receptors, regulate a wide range of neuronal processes [102]. According to research data, patients who have suffered stroke exhibit a significant decrease in NT-3 concentrations, suggesting its potential use as a diagnostic biomarker [103]. Experimental evidence indicates that delayed (48 hours) intramuscular injection of adeno-associated virus (AAV) delivering NT-3 (AAV-NT3) after severe spinal cord injury leads to improvement of motor function, manifested as recovery of walking skills and coordinated swimming. This supports the hypothesis of a therapeutic role for NT-3 in spinal cord injuries, likely mediated by modulation of somatosensory feedback [104]. Furthermore, a study [105] demonstrates that delayed peripheral administration of NT-3 can restore sensorimotor functions after ischemic stroke. Clinical trials of NT-3 (for constipation treatment) confirmed the safety and good tolerability of high peripheral doses [106,107], making it a promising candidate for therapy of degenerative nervous system pathologies.

2.5.4 GDNF

GDNF is classified as a member of the TGF-β superfamily. This factor exhibits pronounced neurotrophic activity, supporting neuronal viability, stimulating differentiation of precursor cells and participating in synapse formation [108]. It was initially characterized as a trophic factor for midbrain dopaminergic neurons, but subsequently its

spectrum of action was found to be significantly broader, encompassing other neuronal subpopulations [109].

Stimulation of GDNF synthesis, enhancement of its bioavailability or simulation of its effects represents a promising approach for therapeutic intervention in acute cerebrovascular disorders (stroke). It has been shown that prophylactic administration of a lentiviral vector expressing GDNF (Lv-GDNF) exerts a pronounced stimulatory effect on the expression of the transcription factor Nurr1, critical for dopaminergic neurons, and the growth-associated protein 43 (GAP43) protein, which plays a role in growth and plasticity, under conditions of striatal ischemia. Treatment with Lv-GDNF led to a significant reduction in the number of damaged neurons. Furthermore, increased GDNF expression induced expression of the transcription factor NF-κB and the nitric oxide synthase enzymes iNOS and nNOS in the contralateral hemisphere [110].

GDNF has been shown to influence the production of key enzymes that support neuronal viability and participate in neuronal development. It is hypothesized that this property of GDNF may reduce the likelihood of post-stroke epilepsy. GDNF exerts pleiotropic effects on the motor neuron system, stimulating neurogenesis, neuronal differentiation and neuromuscular junction function [111]. This suggests that increased GDNF expression after stroke or TBI may improve motor function recovery. Moreover, given the established correlation between GDNF levels and conditions such as depression and chronic pain, increasing its levels may also contribute to psychoemotional recovery [103]. Owing to its trophic role toward dopaminergic neurons, GDNF is potentially capable of exerting preventive effects against parkinsonism and modifying its progression [112,113].

2.5.5 CNTF

CNTF plays an important role in astrocyte-mediated effects. It induces gene expression, enhances viability and promotes differentiation of diverse neuronal subpopulations, including sensory, sympathetic and motor neurons [43]. Application of genetic constructs promoting increased CNTF levels has shown encouraging results in experimental models of ischemic brain infarction [44]. Its main function involves activation of the JAK-STAT cascade, which promotes maintenance of neuronal health and stimulates neurogenesis, which is particularly important in pathologies such as Alzheimer's disease [114]. In one study, peptide 6c (GDDL), corresponding to amino acid sequence 147–150 of the CNTF protein, demonstrated the ability to stimulate neurogenesis in the dentate gyrus and modulate neuronal plasticity, which correlated with improved cognitive performance in mice [45]. Moreover, CNTF, as a factor supporting oligodendrocyte viability, is capable of initiating remyelination [115] and, together with other factors, participates in the process of neuronal recovery after TBI.

2.5.6 VEGF

VEGF, a key regulator of angiogenesis, possesses a broad spectrum of biological effects, making it a promising candidate for treatment of neurological disorders. Beyond its vascular effects, VEGF exerts neuroprotective action, promotes neurogenesis and regulates neuronal activity [46]. It has been established that stroke onset, regardless of type, is accompanied by an immediate increase in plasma VEGF levels, which remain elevated for at least 90 days after stroke [47,116]. This finding points to the potential application of VEGF as a biomarker and also makes it attractive for investigation as a therapeutic agent. *In vivo*, VEGF plays a significant role in neurodegenerative processes, both in acute neural tissue injury and in chronic diseases. Consequently, VEGF can be considered a factor modulating neurodegenerative processes: its increased expression may exert protective effects, while decreased expression may exacerbate injury. The influence of VEGF is particularly important because it simultaneously affects both the nervous and vascular systems [26].

2.6 Challenges in NTF Delivery to the Brain and Promising Approaches

Thus, NTFs represent a significant therapeutic resource for correcting a wide spectrum of neurological disorders. The concept of their application assumes that modulation of NTF levels or enhancement of their signaling pathways may lead to increased neuronal survival, induction of axonal regeneration, improvement of synaptic plasticity and, consequently, reduction of clinical symptoms and slowing of disease progression. However, practical implementation of such a strategy faces substantial obstacles related to NTF delivery to the CNS.

The BBB is a critical factor limiting the penetration of macromolecules, including large proteins, from the systemic circulation into the brain parenchyma [117]. Given that NTFs are relatively large polar molecules, their transcytosis across the BBB is impeded [118]. In existing studies, direct intracerebral injection is used for neurotrophin delivery, the negative aspects of which include a high degree of brain tissue traumatization during the injection procedure [119]. Intranasal NTF administration has also been shown to facilitate effective substance delivery, suggesting the feasibility of applying this method as a delivery route [120,121]. Other routes of administration demonstrate even lower delivery rates to target cells.

Cumulative preclinical data on current strategies for BBB circumvention and NTF delivery are presented in Table 2 (Ref. [23,104,122,123,124,125,126,127,128,129,130,131,132]), enabling comparison of the efficacy, limitations and translational potential of major platforms (AAV vectors, *LNP* mRNA, exosomes, cell therapy, etc.).

Table 2. Approaches to NTF delivery in preclinical studies of stroke, traumatic injuries of the CNS and NDDs (2016–2026).

Platform type	Route/method of delivery	NTF and form	Disease model	Species	Key results	Key limitations	Potential advantages	Reference
Viral vectors (AAV)	Direct intracerebral infusion, intrathecal delivery	AAVT42-BDNF	Alzheimer's disease	Mice (APP/PS1; rTg4510; 3× Tg), cynomolgus macaques	Improved neuronal structure; improved learning and memory	Invasive delivery; no effect on pathological protein deposition	High efficiency of local CNS transduction	[122]
Viral vectors (AAV)	Intramuscular injection	AAV1-NT-3	Spinal cord injury (thoracic contusion)	Rats	Improved locomotor function and hindlimb coordination; sensorimotor reorganization	No pronounced neuroprotection at epicenter; dose optimization needed	Minimally invasive route; possible clinical translation in "delayed window"	[104]
Exosomes/EVs	Stereotactic injection (BDNF-hNSC-Exo)	BDNF-loaded NSC-derived exosomes	Ischemic stroke (MCAO)	Rats	Enhanced neuronal survival; inhibited microglial activation; promoted differentiation of endogenous NSCs into neurons; improved neurological recovery	Invasive delivery route; loading heterogeneity; difficulty of standardization and scaling	High biocompatibility; BBB permeability; low immunogenicity; combines neuroprotective properties of NSC-Exo with BDNF	[123]
Exosomes/EVs	Intranasal delivery (MSC-EVs with neuropeptides)	MSC-EV + BDNF peptides	Ischemic stroke (photothrombosis)	Mice	Reduced infarct size; improved neuronal survival	High production cost; limited range of therapeutic molecules	Non-invasive route; low immunogenicity; clinically scalable approach	[124]
Intranasal protein delivery	Intranasal recombinant protein administration	Recombinant NGF	TBI (closed head injury)	Rats	Reduced motor deficit; decreased neuroinflammation and glial activation; neuroprotection in acute period	Limited therapeutic window; need for dose standardization	Non-invasive route of administration	[125]
Nanoparticles/LNP, mRNA gene therapy	Lipid nanoparticles (DA6-LNP), IV injection	DA6-LNP-mRNA BDNF	TBI (closed head injury)	Mice	BDNF overexpression in brain; reduced cognitive impairment	Short-duration expression; need for repeated doses	Minimally invasive route; targeted mRNA delivery to CNS	[126]
Hydrogels/local delivery	Plasmid DNA in biocompatible hydrogel, intracerebral injection	Plasmid-BDNF	Intracerebral hemorrhage (ICH)	Rats	Local BDNF elevation; enhanced neurogenesis; decreased lesion volume; improved neurological function	Invasive stereotaxic injection; local effect; dose optimization required	Targeted delivery to lesion; sustained release; compatibility with surgical hematoma evacuation	[127]
Cell therapy + hydrogel	MSC-BDNF in hydrogel, intracerebral injection	BDNF-MSC	Ischemic stroke (photothrombosis)	Mice	Stimulation of neurogenesis; white matter repair and angiogenesis; reduced neuroinflammation; improved neurological function	Limited therapeutic effect; need for repeated injections	Favorable safety profile; low immunogenicity	[128]

Table 2. Continued.

Platform type	Route/method of delivery	NTF and form	Disease model	Species	Key results	Key limitations	Potential advantages	Reference
Hydrogels/local delivery	Recombinant protein in hydrogel, intracerebral injection	BDNF (protein)	Ischemic stroke (photothrombosis)	Mice, cynomolgus macaques	Elevated BDNF levels in peri-infarct tissue; stimulation of axonal growth and neurogenesis; improved neurological function	Invasive stereotaxic injection; no effect on infarct size	Sustained release; MRI-visualizable hydrogel; high clinical translation potential	[129]
Small molecules/mimetics	TrkA agonist, intraperitoneal injection	Gambogic amide (GamAm)	Ischemic stroke (MCAO)	Rats	Enhanced corticorubral plasticity; improved motor and coordination functions	Systemic administration; possible side effects	Minimally invasive route; pharmacological simplicity	[130]
Small molecules/mimetics	NGF dipeptide mimetic, intraperitoneal injection	Dipeptide mimetic of NGF loop 4	Ischemic stroke (MCAO)	Rats	Stimulation of neurogenesis and synaptogenesis; decreased infarct volume	Systemic administration; need for confirmation by additional methods	Minimally invasive route; no hyperalgesia; broad therapeutic window	[131]
Nanoparticles/LNP	Terpolymer-based nanoparticles, IV injection	BDNF-TPN	Alzheimer's disease	TgCRND8 mice	Increased BDNF expression; reduced apoptosis and neuroinflammation; improved cognitive function	Systemic administration; need for repeated doses	Minimally invasive route; favorable safety profile; high bioavailability	[132]
Focused ultrasound	Focused ultrasound + plasmid, IV injection	GDNF plasmid	Parkinson's disease (6-OHDA model)	Rats	Restored GDNF expression; preservation of dopaminergic neurons; improved motor function	Need for repeated procedures; systemic plasmid administration	Non-invasive targeted delivery; favorable safety profile	[23]

NTF, neurotrophic factors; TBI, traumatic brain injury; NDDs, neurodegenerative diseases; AAV, adeno-associated virus; MCAO, middle cerebral artery occlusion; SVZ, subventricular zone; APP, amyloid precursor protein; PS1, presenilin 1; EVs, extracellular vesicles; IV, intravenous; RVG, rabies virus glycoprotein; NSC, neural stem cell; LPS, lipopolysaccharide; MSC, mesenchymal stem cell; LNP, lipid nanoparticle; MRI, magnetic resonance imaging; TPN, terpolymer nanoparticle; 6-OHDA, 6-hydroxydopamine.

Table 3. Clinical studies of NTF delivery to the CNS (2001–present).

Delivery method	NTF (dosages)	Disease	Phase	Results	Limitations	Advantages	Reference
Direct AAV2-BDNF infusion into entorhinal cortex and hippocampus	AAV2-BDNF	Alzheimer's disease (mild/moderate)	I	Ongoing study (patient enrollment); safety and tolerability assessment; planned evaluation of cognitive functions and tau pathology biomarkers over 12–24 months; preliminary data show increased entorhinal cortex metabolism on FDG-PET	Invasive stereotaxic procedure; gene therapy risks in critical memory regions	First clinical trial of *BDNF* gene therapy in AD; direct delivery to hippocampal formation regions; potential for neuroprotection and synaptic plasticity restoration	[136] NCT05040217
Bilateral intraputaminal AAV2 infusion	AAV2-GDNF (3.3×10^{12} vg/mL, up to 1800 µL/putamen)	Parkinson's disease (mild to moderate)	Ib–II	Good tolerability; GDNF expression in dopaminergic neurons; stable motor scores	Invasive neurosurgery; no statistically significant efficacy on primary endpoints	Potentially long-lasting GDNF expression; targeted striatal delivery	[112,137,138] NCT06285643
Chronic intermittent infusion via implant (10 study treatments at 4-week intervals)	Recombinant GDNF (protein) (120 µg/putamen for each introduction)	Parkinson's disease (moderate)	II	Favorable safety profile; drug delivery to target areas; some signs of improvement in individual patients; no statistically significant difference from placebo on primary and secondary endpoints	Highly invasive procedure with delivery system implantation; no proven clinical efficacy; high cost	Direct local delivery to striatum bypassing BBB; possibility of dose modulation; good tolerability	[139]
Intraputaminal AAV2 infusion (total volume of 40 µL per hemisphere)	AAV2-neurturin (CERE-120) (5.4×10^{11} vector genomes)	Parkinson's disease (moderate)	I → II/IIb	Phase I: favorable safety profile, possible motor improvement; Phase II: questionable safety profile; no significant efficacy on UPDRS motor assessment at 12 months vs. sham surgery group	Invasive procedure; limited neurturin expression in putamen; high rate of serious adverse events; probable association with oncogenesis; no clinical efficacy	First proof of targeted neurotrophic protein expression in brains of patients with neurodegeneration; demonstration of AAV2 safety as gene therapy vector	[140] NCT00985517
Ex vivo gene therapy (fibroblast implantation) (5–10 µL into each of sites)	NGF (autologous genetically modified fibroblasts) (2.5×10^6–1.0×10^7 total cells)	Alzheimer's disease (mild stage)	I	Favorable safety profile; reduced rate of cognitive decline (MMSE, ADAS-Cog); statistically significant increase in cortical glucose metabolism on PET; postmortem—dense penetration of cholinergic axons into transplant	Neurosurgical cell implantation; *ex vivo* approach requires individual production; small sample (n = 8 phase I)	Proof of concept: *NGF* gene therapy is safe and can stimulate cholinergic modulation of cortical processes and metabolism in AD patients	[141] NCT00017940
Injections AAV2 (at the caudal two-thirds of the NBM)	AAV2-NGF (1.2×10^{10}–1.2×10^{11} vector particles)	Alzheimer's disease (mild and moderate stages)	I → II	Favorable safety profile; sustained NGF expression; signs of cholinergic activation (neuronal hypertrophy, axonal sprouting); activation of canonical trophic signaling	Neurosurgical implantation; absence of clinical assessment results and disease progression rate data	Sustained NGF expression; convincing cholinergic activation data across all patient categories	[142] NCT00087789 and NCT00017940

FDG-PET, fluorodeoxyglucose positron emission tomography; AD, Alzheimer's disease; CERE-120, Adeno-Associated Virus Serotype 2-Neurturin; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; NBM, nucleus basalis of Meynert.

Comparison of preclinical data reveals that several fundamentally different NTF delivery platforms are used to overcome BBB limitations, each with its own advantages and risks. At the *in vivo* model level, the most convincing results have been obtained for viral constructs (primarily AAV-mediated gene therapy), nanoparticles (lipid nanoparticles with mRNA) and exosomal systems, as well as transplantation of cells stably secreting neurotrophic factors. Meanwhile, small molecular NTF mimetics demonstrate the possibility of BBB bypass but currently lag behind full-length proteins and gene therapy in selectivity and effect magnitude. Collectively, these data support the principle of using neurotrophic signaling as a therapeutic strategy but simultaneously underscore the gap between high experimental efficacy and the complexity of clinical translation due to invasiveness, immune risks, limited target coverage and challenges of scalable manufacturing.

Despite the growing body of preclinical data confirming the efficacy of these approaches, no commercial neurotrophin-based drugs for the treatment of NDDs, stroke sequelae and neurotrauma currently exist in clinical practice.

Translational limitations of preclinical research are already relevant at the stage of determining the prospects for selecting the most effective routes for administering therapy products. The intravenous route possesses the lowest efficiency of delivery to brain tissue: this is associated with the complexity of molecular penetration through the blood-brain barrier and a restricted spectrum of delivery vehicles. According to some authors, AAV9 and its modified forms (AAV-B1 and AAV-AS) remain the preferred options for this administration route [133]. Also, with this administration route, the risk of potential ectopic expression of neurotrophic factors increases [134].

Another method widely used in preclinical studies, but which has demonstrated clinical prospect limitations, is the intranasal route of administration. Thus, the authors describe variable delivery to central nervous system cells, rapid clearance from the nasal cavity, proteolysis, limitations on the volume of the agent administered, and short exposure time [135].

To overcome the blood-brain barrier and enhance transduction efficiency, attempts have been made to introduce therapy products into the cerebrospinal fluid system of the brain (intrathecal, subpial, intracisternal, and intracerebroventricular). Despite the prospects for distributing drugs to various regions of the brain, the method is limited by rapid elimination and the necessity for multiple repeated injections [133]. In this regard, the leading method for delivering promising candidates into neurons is the intraparenchymal route of delivery, which has been demonstrated in clinical trials.

Against this background, the narrow but instructive pool of early clinical studies in which specific neurotrophin delivery strategies have been tested in patients with Parkinson's disease and Alzheimer's disease is of particular interest. These studies allow assessment of which platforms (AAV2-GDNF, AAV2-neurturin, *ex vivo NGF* gene therapy, encapsulated CNTF-secreting cells) have maintained an acceptable safety profile upon clinical transition and what efficacy barriers have been identified at the Phase I–II level. Key parameters of these clinical trials (delivery method, neurotrophin type, dosages, disease, phase and main outcomes) are summarized in Table 3 (Ref. [112,136,137,138,139,140,141,142]).

In general, clinical trials testify to a favorable safety profile of therapeutic strategies directed at neurotrophic factors [112,136,137,138,141]. Recorded serious adverse effects were associated primarily with surgical intervention and included confusion, seizures, hemorrhages, cerebral edema, and infarction of the caudate nucleus, temporary psychiatric changes and urinary retention [140], as well as an episode of cerebral ischemia in the region located directly in front of the infusion site [112,137,138]. In all cases, the symptoms were transient, and no residual neurological deficit was observed. In another study, GDNF administration increased the frequency of development (difference of ≥3 patients between treatment groups) dyskinesia, paraesthesia, Lhermitte's sign, ON and OFF phenomena, and diplopia in comparison with placebo [139].

Collectively, the clinical trial results summarized in Table 3 demonstrate the typical gap between biological activity and clinically meaningful effect characteristic of novel therapeutic strategies. Although therapeutic approaches aimed at stimulating neurotrophic support of nerve cells have shown an acceptable safety profile and confirmed local NTF expression in clinical studies, most trials have not achieved statistically significant improvements on primary clinical endpoints. This reflects key unresolved issues: limited target coverage with local infusions, difficulty in selecting dose and administration regimen, variability of clinical phenotypes and neuroplasticity reserve among patients, and the risk of adverse effects.

Further progress will most likely be associated with several parallel steps: improvement of delivery systems (viral and non-viral systems, new capsids, promoters allowing regulation of expression levels), transition to less invasive routes of administration (intranasal, oral, intravenous), and more precise patient stratification by disease stage and biomarkers. A combined approach, where neurotrophic system modulation is combined with rehabilitation and standard pharmacotherapy, appears increasingly important. The resolution of these practical challenges—at the interface of preclinical and clinical research—will determine whether therapeutic strategies modulating neurotrophic support can assume a real place in the treatment of neurodegenerative, traumatic and vascular brain diseases.

The integrative relationships between convergent injury cascades, neurotrophic modulation and translational constraints are summarized in Fig. 1.

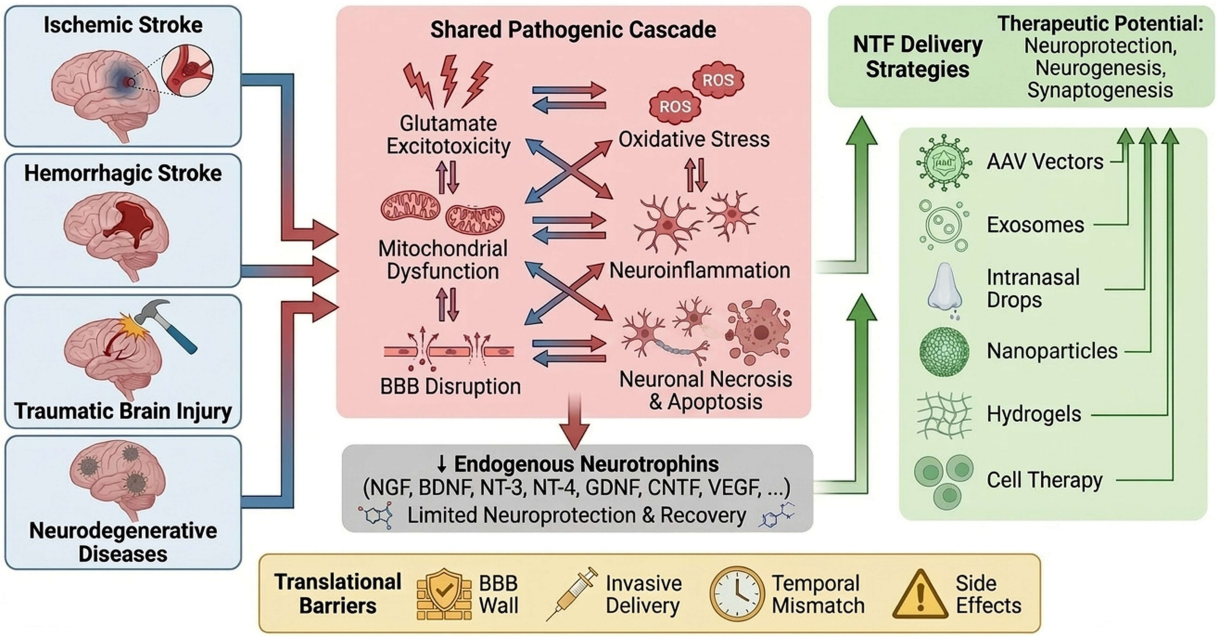

Fig. 1. Convergent pathophysiological cascade and neurotrophic modulation across acute and chronic brain disorders. Distinct etiological triggers of acute and chronic brain disorders—ischemic stroke (brain with thrombotic occlusion), hemorrhagic stroke (intracerebral blood accumulation), traumatic brain injury (mechanical impact), and neurodegenerative diseases (accumulation of pathological protein aggregates)—initiate parallel pathological processes that converge on a shared cascade of secondary brain injury mechanisms. The central red zone illustrates key interrelated events comprising glutamate excitotoxicity, oxidative stress with reactive oxygen species generation, mitochondrial dysfunction, neuroinflammation with microglial activation, blood-brain barrier disruption, and neuronal necrosis/apoptosis, interconnected by bidirectional feedback loops amplifying tissue damage. These convergent cascades downregulate endogenous NTFs, including NGF, BDNF, NT-3, NT-4, GDNF, CNTF, VEGF, and others (...), thereby limiting endogenous neuroprotection and recovery potential. The green zone illustrates principal NTF delivery platforms with therapeutic promise—AAV vectors, exosomes/extracellular vesicles, intranasal administration, lipid nanoparticles, hydrogel-based sustained release systems, and cell-based therapies—collectively converging toward restoration of neuroprotection, neurogenesis, synaptogenesis, and angiogenesis. Despite the convincing results of preclinical studies, the clinical efficacy of the developed approaches is limited. Translational barriers to NTF therapy application are depicted in the gold zone: blood-brain barrier impermeability, requirement for invasive delivery procedures, temporal mismatch between intervention timing and disease progression, and risk of adverse effects. Abbreviations: ROS, reactive oxygen species.

3. Conclusions

Neurotrophic factors occupy a central and well-supported position in the pathogenesis and potential therapy of stroke, TBI and NDDs. Their expression profiles, receptor systems and downstream signaling pathways are intimately linked to excitotoxicity, neuroinflammation, neuronal survival, synaptic plasticity and regenerative remodeling—properties that collectively justify the sustained interest in NTFs as both prognostic biomarkers and therapeutic targets. Critically, the available evidence indicates that the persistent translational gap in this field reflects not insufficient biological rationale, but rather the complexity of delivering, controlling and contextualizing neurotrophic signaling within the injured human brain.

Several limitations inherent to the existing literature warrant explicit acknowledgment. The preponderance of preclinical data has been generated in young adult male rodents under highly controlled experimental conditions that inadequately capture the biological heterogeneity of clinical populations [48,49,50]. Age-related downregulation of Trk receptor signaling, progressive accumulation of pro-apoptotic proNGF and proBDNF, impaired retrograde axonal transport and persistent neuroinflammatory priming all fundamentally alter tissue responsiveness to exogenous neurotrophins in ways that are not recapitulated in standard animal models [48,52,57,59]. Sex-dependent hormonal modulation of NTF expression and receptor sensitivity represents an additional source of variability that remains insufficiently incorporated into experimental design and may contribute to overestimation of treatment effects when extrapolating to diverse patient populations [75,77,78]. These constraints are particularly consequential in stroke and neurodegenerative diseases, where advanced age, vascular comorbidity and polypharmacy define the dominant clinical phenotype [54,69,70,71].

At the clinical level, two categories of pitfalls are especially salient. First, delivery remains the primary un-

resolved barrier: systemic administration is limited by poor BBB penetration and off-target peripheral expression, whereas intranasal, intrathecal and intracerebroventricular routes are constrained by variable distribution kinetics, rapid clearance and the requirement for repeated invasive procedures [133,134,135]. Direct intraparenchymal delivery, which remains the dominant strategy in clinical trials, achieves high local concentrations but is inherently invasive, provides restricted anatomical target coverage and carries non-negligible procedural risk [112,136,137,138]. Second, the temporal dimension is equally critical: acute injuries such as ischemic stroke and TBI demand intervention within narrow time windows during which most gene therapy platforms have yet to reach stable expression, while neurodegenerative diseases are typically diagnosed after substantial irreversible neuronal loss has already occurred [8,112]. Compounding these issues, dysregulated receptor balance in the aged or injured brain—characterized by upregulated p75NTR and sortilin alongside impaired ligand processing—raises the clinically significant concern that uncontrolled exogenous neurotrophin delivery may paradoxically activate proapoptotic rather than pro-survival signaling cascades [56,57].

Early-phase clinical trials of *GDNF*-, *NGF*- and *BDNF*-based gene therapy have collectively demonstrated acceptable safety and confirmed target engagement, yet have yielded modest and inconsistent functional benefit [112,137,141,142]. This dissociation between molecular efficacy and clinical outcome underscores that the principal barrier is no longer biological validity, but the absence of safe, scalable and temporally controllable delivery systems capable of achieving appropriate spatial resolution of trophic signaling across the diseased CNS [117,118,132,135].

Future progress will require coordinated advances on multiple fronts. Preclinical models must incorporate aged animals of both sexes, clinically relevant comorbidity profiles and realistic treatment timing to generate data with greater predictive validity [50,73,78,82]. On the delivery side, next-generation AAV capsids with enhanced CNS tropism, engineered exosome-based vectors, lipid nanoparticle platforms for mRNA delivery and focused ultrasound-assisted BBB modulation represent the most promising near-term candidates for minimally invasive administration [23,124,132,143]. Inducible expression systems and patient stratification based on disease stage, circulating NTF biomarker levels and receptor genotyping will be essential to maximize the therapeutic index and identify the populations most likely to respond. Integration of neurotrophic modulation with rehabilitation and neuromodulatory approaches may further amplify functional gains through synergistic plasticity mechanisms, while small-molecule Trk agonists and NTF mimetics offer a pharmacologically tractable complementary strategy where full-length protein delivery is impractical. Collectively, these directions point toward a conceptual reorientation: the objective of future NTF-based therapy should be not the simple replacement of deficient trophic factors, but the precise, spatiotemporally calibrated modulation of neurotrophic signaling networks adapted to disease stage, individual biology and delivery context [118,120,122,143,144].

Resolution of these challenges will determine whether neurotrophins can transition from the category of promising experimental tools to a sustainable clinical technology of neuroprotection and neuroregeneration for stroke, TBI and NDDs.

Abbreviations

AAV, adeno-associated virus; AD, Alzheimer's disease; Akt, protein kinase B; ALS, amyotrophic lateral sclerosis; ATP, adenosine triphosphate; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CNS, central nervous system; CNTF, ciliary neurotrophic factor; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; EVs, extracellular vesicles; FDG-PET, fluorodeoxyglucose positron emission tomography; GAP43, growth-associated protein 43; GDNF, glial cell line-derived neurotrophic factor; GFRα1, GDNF family receptor alpha 1; GPCR, G protein-coupled receptor; ICH, intracerebral hemorrhage; IGF, insulin-like growth factor; IL, interleukin; iNOS, inducible nitric oxide synthase; IV, intravenous; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LNP, lipid nanoparticle; LPS, lipopolysaccharide; LTP, long-term potentiation; Lv, lentivirus; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; mRNA, messenger ribonucleic acid; MSC, mesenchymal stem cell; NCAM, neural cell adhesion molecule; NDDs, neurodegenerative diseases; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NIHSS, National Institutes of Health Stroke Scale; NMDA, N-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; NT-3, neurotrophin-3; NT-4/5, neurotrophin-4/5; NTFs, neurotrophic factors; PACAP, pituitary adenylate cyclase-activating polypeptide; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinase; PLCγ, phospholipase C gamma; p75NTR, p75 neurotrophin receptor; RET, rearranged during transfection receptor; ROS, reactive oxygen species; RVG, rabies virus glycoprotein; Shh, Sonic Hedgehog; STAT, signal transducer and activator of transcription; SVZ, subventricular zone; TBI, traumatic brain injury; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; TPN, terpolymer nanoparticle; Trk, tropomyosin receptor kinase; UPDRS, Unified Parkinson's Disease Rating Scale; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Author Contributions

OVS conceived and designed the review and drafted the manuscript. DAK performed the analysis and synthesis of clinical studies and contributed to data interpretation and drafting of relevant sections. MVP and MVK contributed to the interpretation of data, participated in drafting specific sections, and critically revised the manuscript for important intellectual content. All authors contributed to literature review, editorial revisions. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used the AI-assisted tool Perplexity (GPT-based large language model) to improve readability and style, and to ensure that the texts are free of errors in grammar, spelling, punctuation and tone. Fig. 1 was independently conceived, designed, and scientifically structured by the authors; Perplexity was used solely to assist with suggestions for visual style, and the final figure was created and edited by the authors. All AI-assisted content was thoroughly reviewed, corrected, and approved by the authors, who take full responsibility for the accuracy, originality, and integrity of the final manuscript.

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