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Modulation of neurotrophic factors in the treatment of dementia, stroke and TBI: Effects of Cerebrolysin

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Abstract

Neurotrophic factors (NTFs) are involved in the pathophysiology of neurological disorders such as dementia, stroke and traumatic brain injury (TBI), and constitute molecular targets of high interest for the therapy of these pathologies. In this review we provide an overview of current knowledge of the definition, discovery and mode of action of five NTFs, nerve growth factor, insulin-like growth factor 1, brain derived NTF, vascular endothelial growth factor and tumor necrosis factor alpha; as well as on their contribution to brain pathology and potential therapeutic use in dementia, stroke and TBI. Within the concept of NTFs in the treatment of these pathologies, we also review the neuropeptide preparation Cerebrolysin, which has been shown to resemble the activities of NTFs and to modulate the expression level of endogenous NTFs. Cerebrolysin has demonstrated beneficial treatment capabilities in vitro and in clinical studies, which are discussed within the context of the biochemistry of NTFs. The review focuses on the interactions of different NTFs, rather than addressing a single NTF, by outlining their signaling network and by reviewing their effect on clinical outcome in prevalent brain pathologies. The effects of the interactions of these NTFs and Cerebrolysin on neuroplasticity, neurogenesis, angiogenesis and inflammation, and their

relevance for the treatment of dementia, stroke and TBI are summarized.

KEYWORDS
Cerebrolysin, dementia, neurotrophic factors, stroke, traumatic brain injury

1 | INTRODUCTION: NEUROTROPHIC FACTORS (NTFS)

NTF are mainly extracellularly secreted and diffusible, soluble proteins, which play pivotal roles as signaling molecules in the promotion of neuronal cell survival, proliferation, migration, differentiation and regeneration for the processes of neurogenesis, neuroplasticity and neuroinflammation.[1] The search for NTFs began in the 1930s, an era when tissue extracts were intensively studied for their cell proliferation and survival promoting effects, leading to the discovery of the nerve growth factor (NGF), the first known NTF, by Rita Levi-Montalcini in the 1950s. The observation that NGF influences neuronal cell survival, proliferation, migration, synaptogenesis and regeneration triggered a rethinking away from the paradigm of the limited and unchangeable number of neurons in the human brain to the possibility for neurogenesis and neuroplasticity. Consequently, Rita Levi-Montalcini's discovery of the NGF was earning her the Nobel Prize of Medicine and Physiology in 1986 and launching a huge new area of cell biology.[2] However, neuronal survival and differentiation (formation of axons, dendrites, synapses, and muscle innervation) by NGF turned out to be restricted to a very small group of neurons: sympathetic neurons and subpopulations of neural-crest-derived sensory neurons in the peripheral nervous system (PNS) plus the striatal and basal forebrain cholinergic neurons in the central nervous system (CNS).[3] Further NTF research was stimulated by the expectation that NTFs with different, non-NGF-responsive neuronal targets may exist covering neurons such as cranial sensory, enteric, parasympathetic or spinal motor neurons of the PNS as well as other CNS neurones.[4] This research was fruitful with the discovery of brain-derived NTF (BDNF) as second NTF in the 1980s. Since then, the number of new NTFs has been continuously growing, showing for each NTF their proper neurotrophic effects such as a distinct tropism of specific neuronal subpopulations in the PNS and CNS.[5,6] Consequently, NTFs are classified into superfamilies according to their structural and functional features.[7] In this article, we will use the term "neurotrophic factors" or "NTFs" in its broad sense, thus including all peptides that promote survival and repair of the cells of the nervous system.

1.1 | NTF structure and its receptors

NGF and BDNF were the first peptides with neurotrophic like activity to be discovered; they belong to the classical NTF family called neurotrophins. Structurally they are highly similar with 50% identity in amino acid sequence[7] and consequently they both can stimulate p75 receptor (Figure 1) signaling which is responsible of controlling cellular processes such as apoptosis.[8–10] BDNF and NGF form homodimers composed of two 14 kDa noncovalently linked monomeres[8,11] and dimerization is crucial for the stimulation of signal transduction. NGF, also stimulates signaling via the TrkA receptor (Figure 1) thereby controlling processes such as cell survival and growth.[8] BDNF can stimulate tropomyosin receptor kinase B (TrkB) receptor signaling, which is involved in the regulation of neuronal survival and differentiation, synaptic plasticity, electric potential and fear behavior.[12]

Other proteins that have been classified as NTFs were originally discovered in different biological contexts, but were later integrated into the NTF family. One of these is the Insulin-like growth factor (IGF-1). Although this 8 kDa sized protein has already been discovered in 1957,[13] its' neurotrophic properties were unraveled from the 1990s

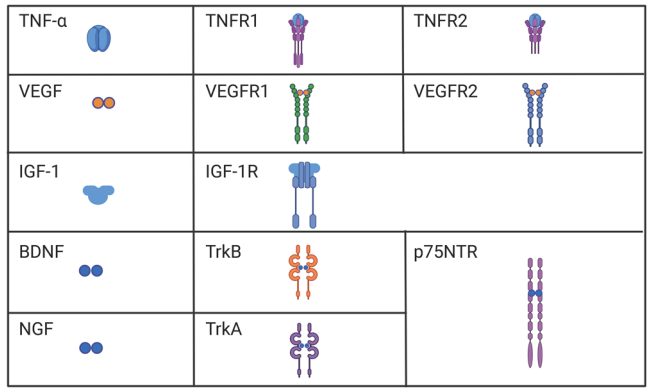

FIGURE 1 NTFs bound to their receptor structures. TNF-α signals through the TNFR1 and TNFR2 receptors. VEGF binds to the two receptors VEGFR1 and VEGFR2. IGF-1 is the ligand for the 320 kDa IGF-1R receptor. BDNF and NGF can both bind the p75NTR receptor; while BDNF represents the specific agonist for the TrkB receptor, and NGF also binds to its specific TrkA receptor. See Section 1.2 for more details. IGF-1, insulin-like growth factor 1; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor. [Color figure can be viewed at wileyonlinelibrary.com]

onwards.[14] Note that during early days of NTF characterization studies, when proteins' identity could not be easily determined in living cell experiments, NTFs' corresponding receptors played a pivotal role. Thus, to assure that the protein under observation really represented the NTF that should be investigated, receptors were used as validation system. Briefly, proteins' correct identity was checked by analyzing the protein's receptor binding preferences. This widely used and practical receptor-tropism-based NTF identity check might explain common practice today of NTFs and their receptors still often being discussed together as ligand-receptor pairs. IGF-1 binds via disulfide bonds to the IGF-1R receptor (Figure 1).[15] This binding event then induces autophosphorylation[16] of the cytoplasmic domain of IGF-1R, which then initiates growth, differentiation, proliferation, and survival responses of the neuronal cells.[17]

Another peptide that was originally discovered for different biological functions and later included in the list of molecules with neurotrophic properties is the vascular endothelial growth factor (VEGF). VEGF was first described in 1989, originally classified as angiogenic factor.[18] Further research investigating the strong impact of VEGF's on neuronal cells, leading to the additional classification of VEGF as new NTF.[19,20] VEGF forms homodimers comprising two 23 kDa peptides that can bind two receptors VEGR-1 and VEGFR-2 (Figure 1).[21] Both receptors are mediating cell migration, dendritic cell function, proliferation, cellular permeability, vasculogenesis and angiogensis.[21] Opposite effects of the two receptors have been demonstrated in lymphocyte development: Here VEGFR-1 affects precursor B-cell mobility in transiting between immune niches needed for full maturation, whereas VEGFR-2 is more involved in cell differentiation, survival and lymphangiogenesis.[22]

Some cytokines were demonstrated to exert neurotrophic effects[23,24] and were therefore also referred to as neuropoietic cytokines or neurokines.[23,25] Due to their properties neurokines can be classified as a subgroup of NTFs. These neurokines can modulate neuronal processes via the regulation of gene expression and cell numbers in the nervous and hematopoietic systems. This subgroup of cytokines plays an important role in normal brain development, as well as following injury during the healing process they act in their role as NTFs. Consequently, elevated levels of neuropoietic cytokines are associated with many neurologic disorders.[26]

The homotrimeric cytokine[27] tumor necrosis factor alpha (TNF-α) belongs to this neurokine family.[23,26,28] It can be present in a 3 × 17 kDa soluble and a 3 × 26 kDa transmembrane form and binds to the TNFR1 as well as the TNFR2 receptor (Figure 1).[27] Although TNF-α was first discovered in 1975,[29] it was only in the late 1990s[30] that its neurotrophic properties were revealed and that TNF-α was classified as neurokine. Thus, TNF-α is locally produced

by Schwann Cells,[31] exhibits pleiotrophic effects on glia cells and neurons, regulates homeostasis of the peripheral, central, and autonomic nervous system and has a role in peripheral nerve regeneration and apoptosis.[27] Here, the two receptors are the link to different functions for TNF-α[32,33]: While binding to the TNFR1 receptor mediates inflammation and proapoptotic signaling, the attachment of TNF-α to TNFR2 initiates neuroprotective and tissue regeneration processes.[32]

1.2 | NTFs bound to their receptor structures (Figure 1)

TNF-α signals through the TNFR1 and TNFR2 receptors both composed of an extracellular, an α-helical transmembrane and a cytoplasmic domain.[34] TNF-α trimerizes and activates the TNFR1 and TNFR2 receptors by binding to the N-terminal extracellular domain. This binding induces a recruitment of three TNFR molecules and furthermore a clustering of these TNFR trimeric receptor complexes in the cell-to-cell contact zone leading to full TNFR activation.[35] The extracellular domain is quite homologous between 55 kDa TNFR1 and 75 kDa TNFR2 receptor.[36] However, the two receptors' intracellular regions functionally diverge, as only TNFR1 but not TNFR2 is endowed with a death domain.[34,37]

VEGF binds to the two receptors VEGFR1 and VEGFR2. Both receptors, VEGFR1 and VEGFR2, belong to the tyrosine kinase receptor family, and dimerize to become activated following ligand binding.[21,38] VEGF binding may promote not only homodimeric receptor compositions but also a VEGFR1–VEGFR2 heterodimeric set-up.[39] As monomers, VEGFR1 is composed of 1312 amino acids of 180 kDa,[40] while the slightly longer 1337 amino acid sequence of the VEGFR2 monomer coincides with a higher molecular weight of 200 kDa.[39] Both receptors carry seven Ig-like domains in the extracellular region plus a tyrosine kinase domain with a long kinase insert.[21,40] There is however a binding affinity difference measurable, as VEGF binds with up to 100-fold more affinity to VEGFR1 than it does when binding to VEGFR2.[39]

IGF-1 is the ligand for the 320 kDa IGF-1R receptor.[15,41] The IGF-1R is a homodimeric transmembrane receptor with tyrosine kinase activity.[41] Each of the 180 kDa[41] monomers are composed of one extracellularly located α-chain and one membrane to cytoplasm spanning β-chain building an $\alpha_2\beta_2$ chain structure with 320 kDa molecular weight.[41,42] When IGF-1 ligand binds to the extracellular ligand binding domain on the α-chain, autophosphorylation on IGF-1R's cytoplasmic β-chain domain is induced via the tyrosine kinase located within the β-chain.[16]

BDNF and NGF can both bind the p75NTR receptor. P75NTR is a 75 kDa[43] transmembrane receptor containing extracellular cysteine-rich domains, a single transmembrane domain and an intracellular region comprising a juxtamembrane domain (Chopper-domain) and a death-domain (DD).[44] Although p75NTR's DD is lacking catalytic activity it is still forming an intracellular signaling hub.[45,46] Ligand recruitment induces conformational changes in the p75NTR extracellular domain and activation of the cytoplasmic DD.[47] One theory is that ligand recruitment triggers the dimerization to a symmetric non-covalently linked p75NTR 140 kDa sized homodimer. p75NTR trimers coexist with the monomeric and dimeric receptor versions on the cell membrane, and 200 kDa p75NTR trimers, however, seem not to be required for p75NTR activation.[46] p75NTR may also undergo two proteolytic cleavages[48]: (1) intramembrane cleavage performed by γ-secretase releases the intracellular cytoplasmic domain and (2) extracellular domain cleavage performed by α-secretase gives rise to the ectodomain.[45,49]

BDNF represents the specific agonist for the TrkB receptor.[15] TrkB is a single-pass transmembrane receptor composed of an extracellular, a transmembrane and an intracellular domain.[50,51] The TrkB receptor contains two extracellular immunoglobulin G (IgG) domains for ligand binding. There exist at least 2 isoforms of the TrkB receptor in humans, one full length 145 kDa[52] version comprising a tyrosine kinase domain at the intracellular tail and one truncated, shorter 95 kDa[50] isoform that is missing the catalytic kinase domain but terminating with an isoform-specific cytoplasmic sequence. These two isoforms may build non-covalently linked homoisodimers and hetero-isodimers. TrkB receptor monomers first dimerize into a preformed but inactive dimer in the cell membrane, a

process that is now considered to happen independently from ligand binding. Here, TrkB's extracellular juxtamembrane motif[53,54] seems to be involved in the repression of TrkB dimerization, that way regulating the amount of present but inactive TrkB predimers. Only upon BDNF binding, Y515 and Y816 TrkB autophosphorylation takes place which then induces conformational changes and Trk dimer activation.[55]

NGF can bind TrkA receptor's extracellular domain.[15] TrkA receptors exist as 280kDa[56] preformed, yet inactive, homodimers that are formed in the endoplasmic reticulum before they are being integrated into the cell membrane. In the absence of NGF ligands, TrkA proteins are present in the cell membrane as both, 140 kDa monomers and 280 kDa sized inactivated dimers.[56] Here, the homeostasis ratio represents 4:1, thus 80% monomers to 20% inactivated dimers.[57] This fraction of preformed dimer is kept stable, independent from NGF ligand presence or absence in the cytoplasmic environment.[56] While inactivated TrkA dimers are in dephosphorylated state,[56] NGF binding induces a conformational change and activation of TrkA's kinase activity. The prerequisite for any TrkA receptor activation is the dimerization of two TrkA monomers. This TrkA activation of the preformed dimers then happens via the rearrangement of TrkA's extracellular juxtamembrane region[57] and the cytoplasmic transphosphorylation of Y674 and Y675[57,58] sites. The binding of NGF was also shown to increase the number of the dimeric and oligomeric forms of this receptor.[57] NGF detachment pushes the TrkA receptor back into a resting state via dephosphorylation on the TrkA receptor.[59]

1.3 | Roles and interplay of NTFs (Figure 2)

NTFs are important stimuli for morphological changes of brain architecture and formation of new synaptic links. Thus, via their capacity of regulating the proliferation, survival, migration, and differentiation of cells in the nervous system, NTFs take over three main regulatory tasks: (1) Genesis tasks referred to as de novo neurogenesis and synaptogenesis, (2) Plasticity tasks like neuroplasticity, regeneration and angiogenesis and (3) Neuroinflammation.

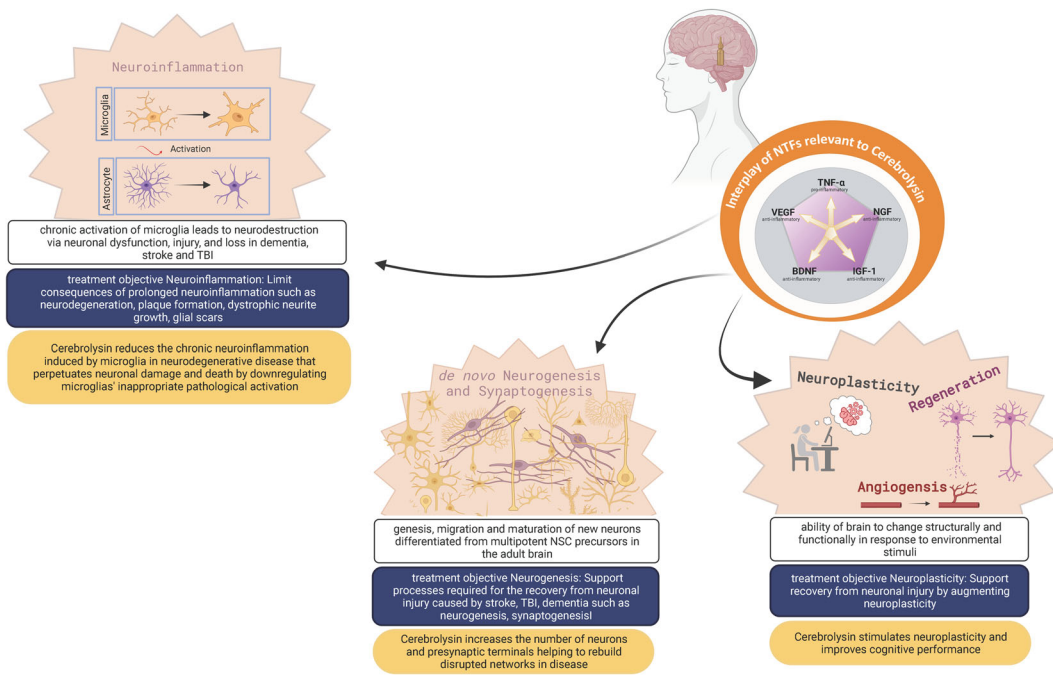

FIGURE 2 Roles and interplay of neurotrophic factors (NTFs): Modulation by Cerebrolysin. A comprehensive description is presented in Section 1.3. [Color figure can be viewed at wileyonlinelibrary.com]

1.3.1 | NTFs: De novo neurogenesis and synaptogenesis

In the adult rat brain, up to 10.000 new neurons are created on a daily basis by multipotent neuronal precursor cells (NPCs). NPCs derive from NSCs and have the ability to proliferate and differentiate in the presence of NTFs into neurons, also called neurogenesis. During neurogenesis NPCs transition from the proliferative, multipotent state to fully differentiated neurons, which then become incorporated into existing circuits of the adult brain. The whole process is governed by the extracellular signaling of NTFs to regulate intracellular pathways and changes in gene transcription. The two major regions in the postnatal brain for neurogenesis are the subventricular zone of the lateral ventricle (SVZ) and the hippocampal dentate gyrus (DG) of the adult brain. After neurogenesis has completed, NTFs promote the de novo formation of synapses of these newly born neurons. This process, also named synaptogenesis, describes the formation and maturation of first synaptic contacts of the newly formed neurons with the existing nervous system. Synaptogenesis occurs all over the lifespan of a healthy person and is favored by learning processes which induce dendrite formation and the integration of young neurons into the neuronal network. Strikingly, neurogenesis is not needed for learning and memory acquisition.[60]

1.3.2 | NTFs: Neuroplasticity, regeneration and angiogenesis

The embryonic, young and adult nervous system is capable of adapting in response to endogenous and exogenous stimuli like training, new experience or injury by a structural (e.g. changes in axon, dendrites and synaptic placement) and functional (e.g., changes in synaptic strength and transfer of brain function from one brain area to another) reorganization. For this process of neuroplasticity and synaptic plasticity neuronal structure, cell functions as well as neurotransmitter profiles need to be modified. NTFs provide a decisive impact on neuroplasticity as they modulate receptor trafficking, neurotransmitter release as well as the placement of whole axons and dendrites. Furthermore, NTFs regulate the formation of new capillaries out of existing vessels in the brain for angiogenesis. Angiogenesis is critical for the neuroplastic processes of learning and memory acquisition.[60]

1.3.3 | NTFs: Neuroinflammation

Neural injury and neurodegenerative diseases induce an inflammatory response. The inflammatory response includes the activation of microglia, the resident immune cells of the CNS, which normally respond to neuronal damage and remove the damaged cells by phagocytosis and are also capable of releasing a large variety of potentially noxious substances exerting cytotoxic effects. These activated microglial cells then express various NTFs. Activation of microglia is a hallmark of brain pathology. Thus, inflammatory process in the CNS is believed to play an important role in the pathway leading to neuronal cell death in a number of neurodegenerative diseases by becoming chronic. Microglia can become chronically activated by either a single stimulus (e.g., Lipopolysaccharide or neuron damage) or multiple stimuli exposures to result in a cumulative neuronal loss with time. The chronic activation of microglia may in turn augment neuronal damage through the release of potential cytotoxic molecules. Therefore, suppression of microglia-mediated inflammation has been considered as an important strategy in neurodegenerative disease therapy. Several anti-inflammatory drugs have been shown to repress the microglial activation and to exert neuroprotective effects in the CNS following different types of injuries.

1.3.4 | Modulation of NTFs interplay by cerebrolysin

Cerebrolysin is a pleiotropic drug that is capable of modulating the endogenous expression of NTFs amongst other factors. The five NTFs TNF-α, NGF, IGF-1, BDNF, and VEGF (drawn in the pentagon) have already been amply confirmed as Cerebrolysin targets in preclinical and clinical studies. To get a general idea about Cerebrolysin's mode of action one has to consider that NTFs influence each other's expression as well as the activity and expression of further Cerebrolysin relevant targets like Caspase 3, T-cells or the MAPK. This complex network of influencing factors points out Cerebrolysin's unique treatment strategy based on its pluripotent modulatory capacity.

1.4 | NTFs in dementia, stroke, and TBI pathologies

NTF profiles are imbalanced across various CNS pathologies, which is why pharmacological interventions with the ability to modulate NTF expression are of particular interest. One such drug is Cerebrolysin, which has been reported to influence the expression of TNF-α,[61,62] NGF,[63] IGF-1,[61] BDNF,[64,65] and VEGF.[66] Intriguingly, these five NTFs are also demonstrably imbalanced in brain pathologies such as dementia,[67–71] stroke[72–76] and traumatic brain injury (TBI)[77–81] (Supporting Information: Figure S1). The therapeutic potential of modulating these NTFs will be discussed in this review.

TNF-α, NGF, IGF-1, BDNF, and VEGF differ in their mode of action:

1. the expression profile within brain tissue: Whereas IGF-1,[82] BDNF,[83] and NGF[84] are continuously expressed in normal healthy brain, TNF-α,[85] and VEGF[86] are only produced in injured brain during the healing process. Interestingly, expression profiles of NTFs are highly interdependent (Figure 2).
2. the capacities of inflammatory repression: Although TNF-α[85,87] operates as proinflammatory messenger, NGF,[88] IGF-1,[89] BDNF,[90] and VEGF[91] have anti-inflammatory characteristics.
3. the penetration of the blood brain barrier (BBB): TNF-α,[92] IGF-1,[93] and BDNF[94] show a relatively good BBB penetration compared to VEGF[95] and NGF[96] that are not capable of passing the BBB themselves easily.
4. the permeating effect on the BBB: TNF-α[97] and VEGF[98] are known to increase BBB permeability while BDNF and IGF-1 rather support BBB barrier functions.[99]

2 | NTFS AND NEUROGENESIS

Throughout a human's life and influenced by day-to-day activities like learning or physical activity, approximately 700 new neurons are generated each day,[100,101] however, neuroinflammation, stress, depression, anxiety, sleep deprivation or aging processes can counteract these neurogenetic activities.[102–104] For neurogenesis, NTF stimuli by e.g. NGF,[105] IGF-1,[106] BDNF[107] or VEGF[108] induce neural stem cell (NSC) proliferation, migration and differentiation.[102] NSC stocks are prominent in the ventricular-subventricular zone (V-SVZ) and the subgranular zone (SGZ) of the DGs in the hippocampus but were also found in the neocortex, spinal cord, tegmentum, substantia nigra, amygdala, and brainstem.[102] Furthermore, NSCs are able to migrate along blood vessels, which enlarges their sphere of action to the striatum.[109,110] Although NSCs and astrocytes are present in brain regions outside the V-SVZ and DG, like in the cortex, the unfavorable extracellular environment restrains their ability to differentiate into neurons.[109–112]

Injuries and NTFs stimulate NSC differentiation into neuroblasts and astrocytes, consequently, neurogenesis is modified under pathological conditions. For instance, neurogenesis is upregulated in the V-SVZ and DG upon brain tissue injury and impaired in neurodegenerative (Parkinson's, Alzheimer's and Huntington's disease) and mental disorders (depression or schizophrenia).[113] Here, NTF profiles do not only serve as disease biomarkers that can be

applied for diagnosis and treatment monitoring (Supporting Information: Figure S1),[114,115] but represent also for themselves accessible treatment targets, as disease symptoms that are caused by NTF imbalances can also be expunged with the re-establishment of a healthy NTF equilibrium.[116,117] Several drugs that affect NTF signaling have been shown to promote neurogenesis, like sildenafil, lithium, metformin, coenzyme Q10,[118] and Cerebrolysin.[119] Furthermore, also therapeutic interventions like transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS)[120] and the (auto-)transplantation of exogenous stem cells have shown to boost neurogenesis.[118]

2.1 | Neurogenesis in dementia

Impaired neurogenesis has been shown to precede alzheimer's disease (AD)-related pathologies.[121,122] Accordingly, negative neurogenesis regulators like aging, stress,[123] inflammation,[124] nutrient deficiency,[123] alcohol,[125] and cocaine[126] are thought to have a negative impact on the cognitive performance in AD patients.[127,128] On the NTF level, TNF-α[67,68,129] and VEGF[71] are overrepresented in dementia, IGF-1[68] is scarce, and BDNF is imbalanced[70,130] (Supporting Information: Figure S1). Establishing a neuron-friendly environment by therapeutic adjustment of NTFs for extrinsic reinduction of neurogenesis may therefore have a beneficial impact on cognitive performance in AD.[128]

2.2 | Neurogenesis in stroke

The ischemic area is characterized by an unfavorable environment and a lack of adequate neurotrophic support for brain cells, which also affects neuronal connectivity. Immediately post-stroke, expression is upregulated for TNF-α[67,73] and VEGF[47,71] and downregulated for IGF-1[76] (Supporting Information: Figure S1), whereas after this first modification impulse the NTF profile is subject to complex changes[76,131–133] (Figure 3).

On the cellular level, stroke triggers astrocytes and microglia to change morphology, to proliferate,[143] and to migrate toward the lesion in response to various upregulated extracellular matrix (ECM) proteins.[110] At this proneurogenic stage[144] the brain tissue shows characteristics of the embryonic brain. Four days poststroke, microglial inflammation decreases[145] and a window of increased neurogenesis opens for about 10 days in the ventricular-subventricular and the SGZ.[146] NSCs proliferate and differentiate into neuroblasts, which migrate within an astrocyte tunnel from the V-SVZ along concentration gradients of secreted morphogens[110,146] into the peri-infarct striatal region to differentiate into neurons and to integrate into the neural network. However, the success rate of endogenous neurogenesis is low. The migration of neuroblasts into the target area is nondirectional and thus time-consuming due to their divert course and detours.[110] Furthermore, about 80% of the newly formed neurons die within 2 weeks, and 6 weeks after the insult only 0.2% of apoptotic neurons have been replaced in the striatal stroke area.[112,146] Cortical strokes do not even trigger neurogenesis. Overall, and although astrocytes already on site may also transdifferentiate into neurons,[147] the potential of endogenous neurogenesis for tissue repair and functional recovery is limited.[112]

All the more important are thus therapeutic interventions that enhance neurogenesis and induce neuronal repair,[148] such as task-specific rehabilitation measures or exogenous stimulation via therapeutic modification of NTFs.[109,145,146,148-150] Shifting NTF expression into an improved neurogenic profile promotes NSC survival and causes SVZ-derived neuroblasts to continue their migration and to connect injured cortical areas outside the striatum.[145]

2.3 | Neurogenesis in TBI

Similar to ischemia, NTF expression is modified after TBI with consequences for neurogenesis: the expression of TNF-α,[67,78] VEGF,[77] and NGF[80,151] is upregulated while BDNF[79,152] and IGF-1[81] levels are decreased (Supporting

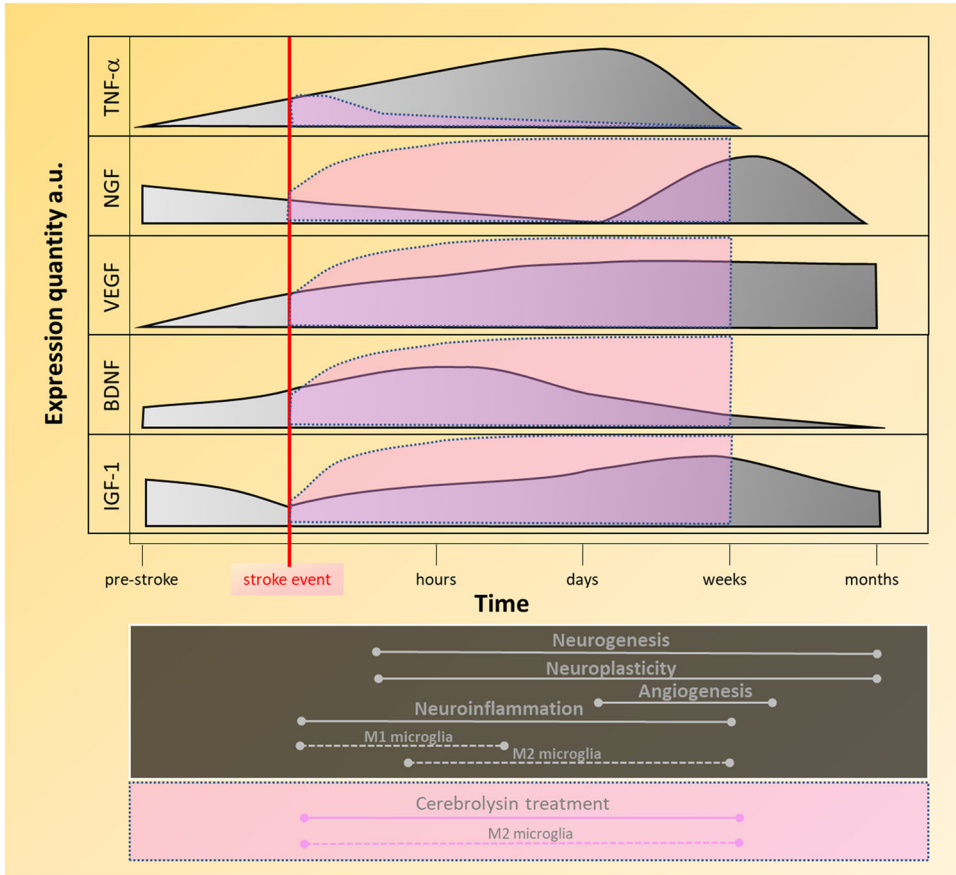

FIGURE 3 Temporal pre- and post-stroke NTF secretion profile. This figure summarizes (in gray) the temporal NTF expression profiles of IGF-1, BDNF, VEGF, NGF, and TNF-α before, during and after a stroke event. Furthermore, the time windows for neuroinflammation, neurogenesis, neuroplasticity and angiogenesis processes are depicted as well as the timely distribution for microglial M1 and M2 types. In pink, Cerebrolysin's impact on NTF expression patterns have been overlaid. The pink box sets the treatment window for Cerebrolysin. Cerebrolysin is capable of shifting the proinflammatory activated M1 microglia type into the anti-inflammatory activated state (M2 microglia) which is crucial for brain tissue repair, as it promotes extracellular matrix deposition and angiogenesis. a.u., arbitrary units. References: TNF-α[134]; NGF[135,136]; VEGF[137,138]; BDNF[139]; IGF-1[76,131–133]; Neuroreaction (Neurogenesis, Neuroplasticity, Neuroinflammation)[138,140,141]; Cerebrolysin effects on TNF-α,[61,142] NGF,[63] VEGF,[66] BDNF,[64,65] and IGF-1.[61] [Color figure can be viewed at wileyonlinelibrary.com]

Information: Figure S1). Whereas NSC proliferation and neuronal differentiation is enforced in multiple areas of the adult mammalian brain, seizures may counteract the migration of NSCs.[153] Furthermore, the DG region within the hippocampus is particularly affected, even when not directly by the TBI itself, with signs of injury up to 12 months after the brain accident.[153,154] However, neurogenesis response in the DG rises with TBI severity and lasts for at least several weeks. While mild TBI does not even induce NSC proliferation in the DG, moderate TBI shows intensified NSC proliferation, and severe TBI fortifies the whole neurogenesis spectrum from NSC proliferation to survival of immature neurons and their maturation.[155] TBI-induced neurogenesis in the hippocampus is generally more accepted by the scientific community than in the cerebral cortex and even optimistic estimations for cortical neurogenesis suggest that only 1% of the neurons in the cortical network are replaced by young, recently generated

neurons.[156,157] It is striking that classic clinical TBI interventions such as anesthetics and anti-epileptics hinder the self-repair process through neurogenesis.[153] However, neurogenesis has been shown to contribute to functional TBI recovery,[154,158] thus NTF modulating agents are expected to support neurogenesis.

3 | NTFS AND NEUROPLASTICITY

The human brain has throughout life the ability to regenerate, adapt, and learn from environmental inputs such as emotions, physical activity, social interaction, and novelty.[159] This ability of neuronal modulation, also known as neuroplasticity, is under the biochemical command of NTFs.[160] Neuroplasticity requires low levels of TNF-α[161,162] and high levels of NGF,[163] IGF-1,[164] BDNF,[165,166] and VEGF.[167] The initiated neuroplastic process intervenes both structurally and functionally: it is characterized by a temporary volume expansion in the gray matter as well as by the rewiring of neuronal circuits, the relocation of synapses, and modulation of synaptic transmission strength in the branched human brain network, consisting of 10^{11} neurons[168,169] and 10^{15} synapses.[170] Apart of these daily adjustments, neuroplasticity also happens upon dramatic situations, such as brain injuries, when complete functional neuronal networks are transferred from injured to undamaged regions to restore lost functions.[171–175] As many brain and mental diseases, such as epilepsy, migraine, Alzheimer's disease, fronto-temporal degeneration, stroke, schizophrenia, depression, bipolarity as well as post-traumatic stress disorder (PTSD)[15,176] are associated with malfunctioning neuroplasticity, a successful therapy needs to be capable of restoring the neuroplastic repair mechanisms that got out of hand in disease. It seems possible to intervene in the patients' neuroplastic abilities of the brain by shifting NTF levels with medication and other therapeutic interventions. Medications having a positive effect on neuroplasticity include histone deacetylase inhibitors,[177] anti-depressant drugs,[160] drugs modulating the dopaminergic, cholinergic, serotonergic, and noradrenergic transmission systems,[176] and NTF-modulating drugs[15] like the immunosuppressive fingolimod, the selective serotonin reuptake inhibitor (SSRI) fluoxetine,[178] and the neuropeptide preparation Cerebrolysin.[142,179] Positive effects on neuroplasticity have also been reported from new techniques such as neurofeedback,[180] tDCS,[181] repetitive TMS,[182,183] and constraint induced movement therapy.[184] The combination of these techniques with medication could even have a synergistic treatment effect,[175] with the drug acting permissively to enhance plasticity and rehabilitation, and providing guidance for appropriate wiring of the plastic network. Interventions with a positive effect on neuroplasticity are thought to provide therapeutic benefit in stroke, brain injury, autism, attention-deficit/hyperactivity disorder, learning disabilities, depression, anxiety, and addictions.[177] In contrast, the anxiolytic β-blocker propranolol is used in PTSD therapy as neuroplasticity blocker. Propranolol decreases NGF,[185] IGF-1,[186] BDNF,[187] and VEGF[188,189] levels and increases that of TNF-α.[190,191] Under the medication of propranolol, the PTSD patient's brain can no longer maintain and thus cuts off its fatal wiring between flashback content and correlated emotions, a process that relieves the patient from the typical an unbearable emotions popping up during flashbacks.[192]

Functional plasticity takes place at the synaptic level (synaptic plasticity) and describes the activity-dependent change in the strength of synaptic transmission by dendritic spine thickness, the amount of neurotransmitters released and the receptor density on the recipient neuron. Persistent enhancement (long-term potentiation; LTP) and reduction (long-term depression; LTD) of synaptic transmission are deemed to be the underlying principle of the brain's ability to create, retrieve and selectively forget memory. NTFs are major players in neuroplasticity. It has been shown that induction of LTP requires the presence of NTFs like BDNF,[178] IGF-1,[193] VEGF,[194] or TNF-α[195] but not NGF.[178] In experimental studies exogenous NTF administration has shown to enhance LTP, however, several NTFs, such as VEGF or NGF, show poor blood–brain barrier penetration and a short half-life in plasma; small NTF mimetics are thus under discussion as an alternative treatment approach.[15,178]

3.1 | Neuroplasticity in dementia

Neuroplasticity is still available at an early stage of dementia, although to a less degree than in healthy, aging people, which still allows the patient's brain to compensate for a disease-related, disabled neuronal signaling pathway and to relearn previously forgotten competences.[196] As dementia progresses, the patient's neuroplasticity and associated cognitive abilities worsen. In addition, accumulating Aβ suppresses LTP and enhances LTD.[196–198]

3.2 | Neuroplasticity in stroke

A 3-month window of hyperplasticity opens within the first days after stroke with unique genetic, molecular, physiological, and structural events,[199] including remapping of local and long-distance neuronal connections. Furthermore, over-activation of the glutamate receptor NMDA (N-methyl-D-aspartate),[200,201] triggered by acute oxygen and glucose deprivation,[202,203] induces LTP and probably also LTD.[200,204] The peri-infarct zone is characterized by an increased expression of growth promoting factors, while growth inhibiting factors are downregulated[205] within the first 2 weeks after stroke.

The brain's endogenous repair mechanism allows a stroke patient to recover spontaneously up to 70% within 3 months.[206] Initiation of appropriate neurorehabilitation techniques within the hyperplastic window takes advantage of an increased responsiveness to the training to further increase the recovery rate.[207,208] Such techniques include the experience of an enriched environment as well as physical, occupational, speech, neuropsychological, and constraint-induced movement therapies.[199,205] When the hyperplastic window is closed, compensation processes can still occur by training healthy brain areas to take over the functions of the injured area.[209] Pharmaceutical interventions like Cerebrolysin,[208] fluoxetine[210] or autologous cortical cell transplantation[149] have been reported to prolong the therapeutic window of hyperplasticity, paving the way for full recovery. The growing evidence for the role of pharmacological agents in neuroplasticity is also supported by the endorsement of international neurological societies for compounds such as Cerebrolysin.[211]

3.3 | Neuroplasticity in TBI

The neuroplastic response after brain trauma is often not sufficient for full recovery, not even after mild trauma. Recent research suggests the involvement of different neuroplastic mechanisms, depending on the time point of training initiation. Whereas immediate activity triggers structural reorganization,[212] the brain rather launches a functional transfer from the damaged to healthy brain areas upon later onset. However, this relearning leads to a longer recovery time for the patient.[213] In terms of synaptic plasticity, LTP is impaired for up to 8 weeks while LTD may even be enhanced.[214]

4 | NTFS AND NEUROINFLAMMATION

Neuroinflammation is induced by activation of microglia, which promotes the expression of the proinflammatory NTFs and cytokines (TNF-α, IL-6, and IL-1β) and concurrently suppresses anti-inflammatory NTFs such as BDNF, NGF, IGF-1, and VEGF.[105,215]

The proinflammatory, activated microglia (M1 microglia) kills invaded organisms and phagocytizes damaged neurons to prevent secondary neuronal damage.[216] Within this process, neurogenesis and neuroplasticity processes are restricted.[102,172] Once phagocytosis is complete M1 microglia shifts to an anti-inflammatory activated state (M2 microglia), expressing NTFs and cytokines of the anti-inflammatory and

pro-neurogenic type (BDNF, IGF-1, NGF, VEGF, and IL-10).[215,217] Shifting the microglial phenotype from M1 to M2 triggers ECM deposition by fibroblasts to promote capillary-like tube formation and angiogenesis. This shift is a crucial step as maintenance of the M1 phenotype leads to chronic brain inflammation, excessive neuronal death and brain disease.[99]

A reduction of M1 microglia in dysfunctional brain tissue provides a reasonable target for an effective treatment strategy (see Figures 2 and 3 for roles and interplay of NTFs). Hyperbaric oxygen therapy (HBOT) is an off-label approach to tackle chronic neuroinflammation and is claimed to achieve significant cognitive improvements even years after brain injury.[218–221] HBOT decreases the level of inflammatory TNF-α[220] and increases production of anti-inflammatory cytokines and NTFs (IL-10,[220] VEGF,[222] NGF,[223] IGF-1,[224] and BDNF[225]). Cerebrolysin has also been shown to stem neuroinflammation[226–229] and to be safe and well tolerated in clinical studies,[230–237] whereas many antineuroinflammation drugs and therapies, such as minocycline,[238] etanercept, SSRI, SNRI, simvastatin, resveratrol, CHPG, VU0360172, Gp91ds-tat, rosiglitazone, azithromycin, nAchR, IL1ra, and NPC transplantation, showed severe side effects and have failed in their translation to clinics.[239,240]

4.1 | Neuroinflammation in dementia

AD involves a chronic inflammatory component, and the strength of the systemic inflammation has been shown to coincide with the level of cognitive decline.[241] In AD, proinflammatory factors like IL-6, IL-1, and TNF-α are produced in excess, microglia becomes activated to the M1 phenotype, and microglial-mediated Aβ clearance is compromised.[241,242] Genome-wide association studies have shown a specific spectrum of gene polymorphisms to be associated with microglial clearance in AD.[243–246] Experimental studies in a rodent model have shown that ablation of microglia prevented the onset of AD, suggesting that microglia are triggering AD pathology.[247]

4.2 | Neuroinflammation in stroke

Stroke causes damaged cells and debris and increases the amount of reactive oxygen species.[248,249] Within minutes and dependent on stroke severity, these pathologic stimuli activate proinflammatory M1 microglia,[250] which produce proinflammatory cytokines. Within 2–3 h after stroke these cytokines trigger the permeability of the BBB,[249] which is maintained for up to 1 week. During this time, CNS-specific antigens attract peripheral leukocytes (e.g., neutrophils, macrophages, and lymphocytes) to migrate through the permeated BBB and infiltrate brain tissue.[251] Over time brain damaging M1 microglia may transition after stroke in brain or blood into beneficial M2-like phenotypes.[252]

This transition from M1 to M2 phenotype has been shown to depend on several factors:

1. age: M2 phenotypes decline with age, while M1 phenotypes increase[250,253];
2. gender: the inflammatory response of M1 is milder in females than in males[254];
3. stroke type: the M1/M2 ratio differs between ischemic and hemorrhagic stroke[253]; and is never static but changes continuously over time poststroke.[253]

Although this dualistic M1/M2 differentiation model recently turned out to be too simplistic, it laid the ground for the development of pharmaceutical treatment interventions that aim pushing M1 phenotypes into M2 polarized microglia.[252,253]

4.3 | Neuroinflammation in TBI

TBI is the result of excessive force on the head that may cause contusion of neurons, glia, and blood vessels including injury of the BBB, which leads to functional decline, cognitive impairment, and affective disorders of the patient.[255,256] A few hours after TBI, increased cytokine production and excitotoxicity, oxidative stress, and mitochondrial impairment lead to further permeation of the BBB so that non-CNS molecules may penetrate the brain tissue and provoke activation of microglia, triggering their migration towards the damaged tissue. Six hours after the insult, microglia have adapted their transcriptomic profile and 24 h postinjury a microglial community has accumulated in the injured brain area. After another 24 h, activated microglia start to proliferate and form the glial scar,[257,258] a dense cellular interface with the lesion,[259] which increases with the extent of BBB damage. Although the glial scar seals the BBB leak and isolates the damaged area to prevent the spread of apoptotic signals[216] and viral/bacterial infections, it comes with a drawback: the physical and biochemical barrier formed by the glial scar prevents neuronal regrowth in the context of neuroplastic regeneration.

Acute primary inflammation is a fundamental factor for efficient CNS repair and functional recovery. However, in a subset of TBI patients, neuroinflammation does not subside within the first weeks and is still evidenced even after decades.[97] Microglial activation that remains chronically activated has a maladaptive character[256] with detrimental cognitive, functional and affective consequences for the patient. Chronically deregulated NTF profiles, such as elevated TNF-α levels secreted by activated M1 microglia and induced by chronic neuroinflammation, have been shown to worsen neuropsychiatric disorders.[140] This may explain the evidence that pharmacological suppression of chronic neuroinflammation relieves brain damage and improves functional recovery.[256] Interestingly, exogenous NTF administration also gives the brain more regeneration capacity by allowing the axons to cross the barrier of the glial scar.[257]

5 | NTFS AND ANGIOGENESIS

During cerebral angiogenesis endothelial cells of blood vessels migrate within brain tissue, proliferate, and form new capillaries. The initiation of this vascularization process requires upregulation of VEGF,[260] IGF-1,[260,261] NGF[262] and BDNF[260] and/or downregulation of TNF-α.[263] In adults, human blood vessel networks are generally static, dividing once in 3 years,[264,265] however, angiogenesis can be actively induced in patients with vascular damage from ischemic stroke or brain injury.[266–269] This expanded cerebral vascular network supports the migration of neuroblasts in the direction of the injured brain area and ensures the neurotrophic support of the newly generated neurons with NTFs[267] (Figure 2).

5.1 | Angiogenesis in dementia

Blood vessel formation is disturbed in AD brains. The typical Aβ deposits and pathological NTF levels, such as an increased VEGF and TNF-α expression profile, lead to excessive cerebral angiogenesis with a concomitant disturbance of the BBB integrity.[270,271]

5.2 | Angiogenesis in stroke

While the blood supply in the ischemic core is completely interrupted, the blood and oxygen supply in the penumbra is still detectable, but impaired.[272] This hypoxic state leads to an upregulation of VEGF[273] and subsequently to angiogenesis within a time frame of 3 days to 3 weeks after the stroke.[267] The newly formed

microvessels normalize the exchange of blood and oxygen in the penumbra and facilitate macrophage-mediated clearance of the necrotic tissue.[274] The extent of angiogenesis in the penumbra has been shown to correlate with the patient's life expectancy.[275] In contrast, an inadequate angiogenic reaction leads to the spread of the injured tissue, which in turn causes damage of primary unaffected brain tissue and may lead to dementia.[269] Therapeutic interventions that stimulate angiogenesis have been shown to be beneficial to the patient's outcome by promoting blood supply, reducing infarct size, and promoting the restoration of vascular-neural interactions in the penumbra.[269,276]

5.3 | Angiogenesis in TBI

In the area of a TBI, severe vascular injuries occur, which are characterized by a marked decrease in the total vessel length and the vascular connections.[277] This loss of capillaries leads to a restriction of cerebral blood flow which affects the integrity of the BBB, and may further lead to ischemia, hypoxia, hemorrhage, and edema formation.[272] Endogenous repair mechanisms start within the first hours by rising proangiogenic NTFs like VEGF to induce angiogenesis.[265] Premature capillary structures form within 2 days after the injury and blood flow is gradually restored within 2 weeks.[272] Expression level of VEGF peaks 2 weeks after injury.[265] There is also evidence that mortality decreases and functional recovery improves with increasing cerebral angiogenesis.[265,277] Because of the proangiogenic potential, drugs such as erythropoietin,[278] thymosin β-4,[279] statins,[280] NTFs[265] and Cerebrolysin,[62,66,281] all of which are involved in the VEGF pathway, are investigated for their therapeutic effects in TBI.

6 | MODULATION OF NTFS TO TREAT *DEMENTIA, STROKE AND TBI* PATHOLOGIES

Modulation of NTF expression has been shown to be effective in the treatment of brain pathologies like stroke, TBI and AD.[282,283] Modulating a single NTF by individual, purified NTFs or NTF inhibitors aims to increase or decrease the availability of a specific NTF in the patient (Figure 4). However, neurological brain pathologies are complex and influenced by multiple genetic and/or environmental factors. Thus, modulating several NTFs simultaneously is expected to be more beneficial than a single-target approach, which is reflected by the increasing number of multi-target drugs that receive approval by the FDA.

One of these multi-target/pleiotropic drugs is Cerebrolysin[284] (Figure 5), a mixture of peptides with neurotrophic properties and free amino acids. Molecular biology data demonstrated that the peptide fraction of Cerebrolysin can either mimic the activity of NTFs or stimulate the biogenesis of endogenous NTFs.[63,285–287] The peptide composition of Cerebrolysin was demonstrated to be unique and essential for its pharmacological properties.[288] Cerebrolysin is registered for the treatment of stroke, TBI and dementia and shows an excellent clinical safety profile.[287,289] Cerebrolysin has been shown to upregulate VEGF,[66] BDNF,[64,65] IGF-1,[61] and NGF,[63] to downregulate TNF-α, and to induce pro-NGF/NGF conversion (Figure 3, 4, and 5).

The interaction of the NTFs, the effects of a pleiotropic therapeutic intervention with Cerebrolysin, and the consequences of an IGF-1 increase are shown in Figure 5.

6.1 | Modulation of NTFs and therapeutic outcome in dementia

Single modulators of TNF-α, BDNF, IGF-1, and NGF have shown beneficial effects in AD patients. These NTFs are modulated also by Cerebrolysin,[287] suggesting that this mode of action contributes to its clinical efficacy (Figure 5).

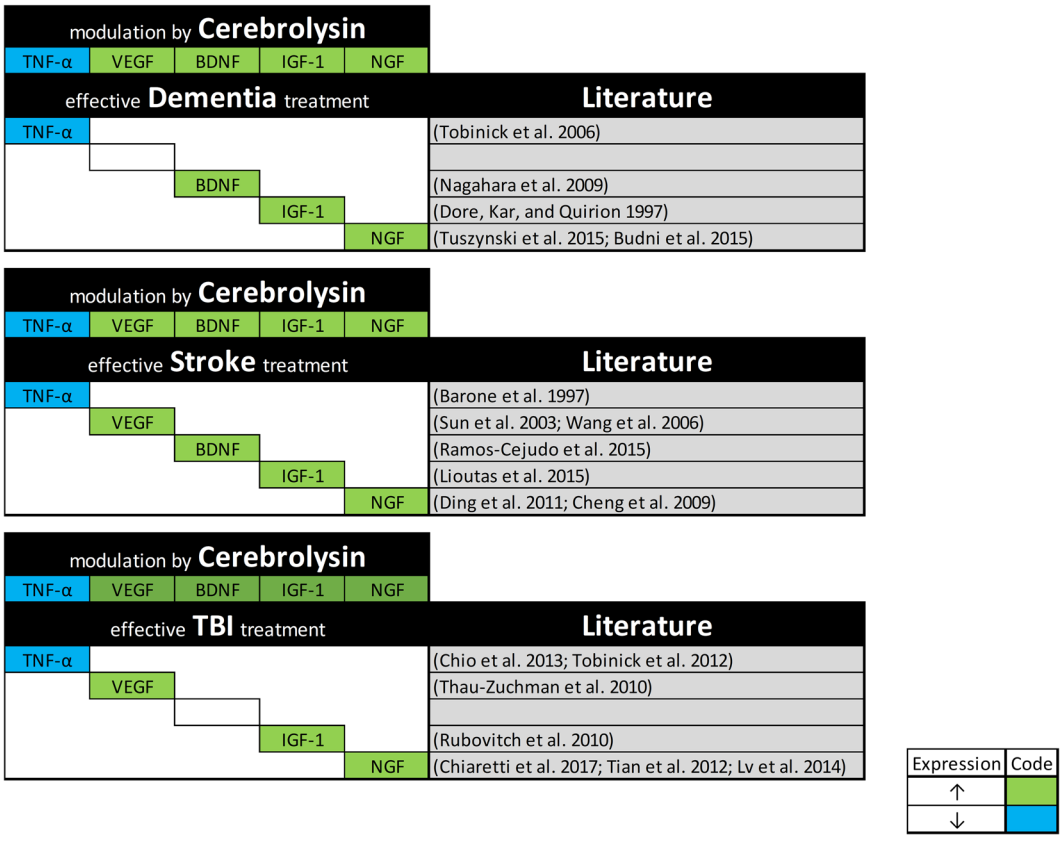

FIGURE 4 Modulation of NTFs by single substance drugs and Cerebrolysin. This graph recaps representative animal model and patient studies with positive therapeutic outcome for single substance drugs that modulate the expression of single NTF targets in the same direction as Cerebrolysin does. In contrast to such single substance drugs, Cerebrolysin is a multipeptide compound that exerts a multimodal treatment effect for dementia, stroke and TBI patients. Thus, its multi-target tropism may induce simultaneous upregulation of VEGF, BDNF, IGF-1 and NGF plus TNF-α downregulation, which should allow a broader, more efficient and stable treatment effect. [Color figure can be viewed at wileyonlinelibrary.com]

6.2 | Modulation of NTFs and therapeutic outcome in stroke

Single target compounds that down-regulate TNF-α or up-regulate VEGF, BDNF, IGF-1, or NGF were found to have good therapeutic potential in stroke. These NTFs are simultaneously modulated by Cerebrolysin and lead to an NTF profile, which is very beneficial for the structural changes in the context of the recovery of a stroke patient (Figure 3).

6.3 | Modulation of NTFs and therapeutic outcome in TBI

TNF-α, VEGF, IGF-1, and NGF have been shown to individually improve TBI outcome. Cerebrolysin also modulates the expression of these NTFs and thus combines the positive effect of these single target drugs to improve recovery from TBI.

The complex cascade of molecular events associated with the etiology of brain pathologies demonstrate the limitation of monomodal drugs for long-lasting improvements in brain pathologies.[320,321] As a result, multimodal

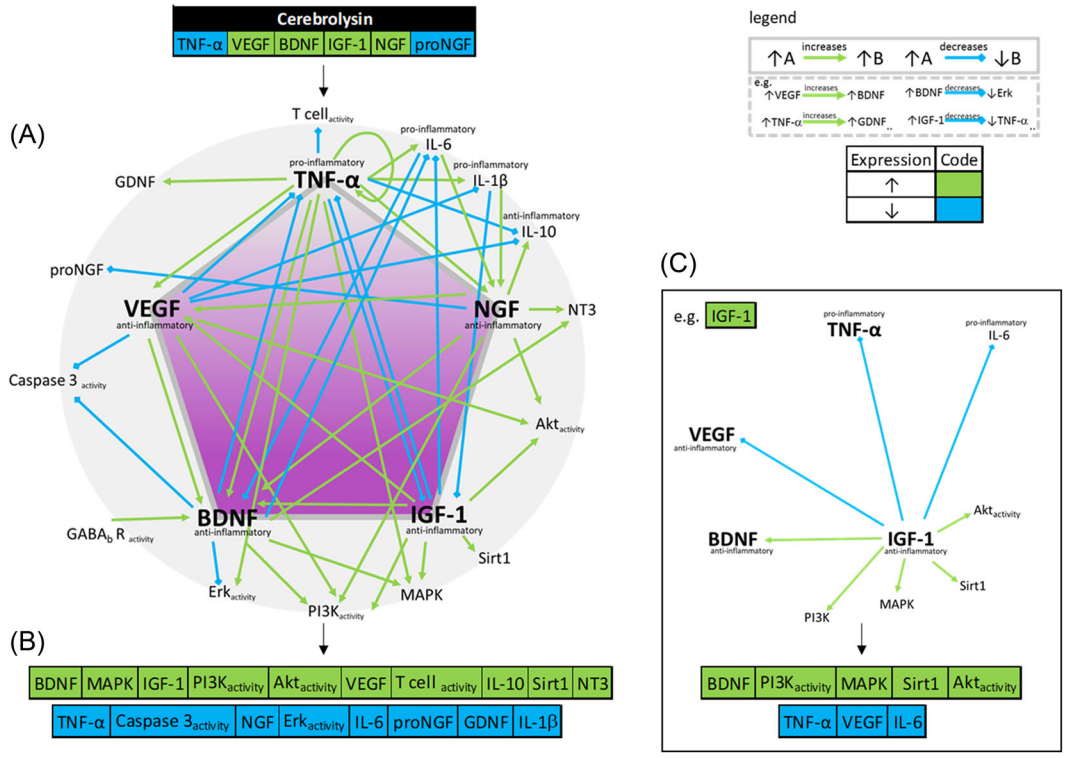

FIGURE 5 Interplay of clinically relevant NTFs and Cerebrolysin. This figure depicts the NTF-related modulation network of Cerebrolysin, a multifunctional drug. (A) Highlights the global network of NTF expression interdependencies with each other (green and blue arrows). Cerebrolysin treatment is known to downregulate TNF-α and proNGF, and to upregulate VEGF, BDNF, IGF-1 and NGF expression. Through the established Cerebrolysin modulated target network (target factors in pentagon and cycle) one can deduce a broader set of expected modulations in expression during Cerebrolysin treatment (lower green [upregulated factors] and blue bars [downregulated factors]). (B) Depicts the expected pleotropic outcome of modified NTF profiles when Cerebrolysin is used. (C) How to read the graph is shown by the example of IGF-1 increase in the black box. Following the arrows in the scheme starting from IGF-1, it can be deduced that an IGF-1 increase should also increase the expression or activity of BDNF, PI3K, MAPK, Sirt1 and Akt; while reducing TNF-α, VEGF and IL-6 expression at the same time. References: TNF-α influences GDNF,[290] VEGF,[291] BDNF,[292,293] NGF,[293] IGF-1,[294] IL-6/MAPK/Erk,[295,296] IL-1β,[295] IL-10,[297] T cell activity,[298,299] TNF-α[300]; NGF influences NT3,[301] IL-10,[88] VEGF,[260] pro-NGF,[302] BDNF,[303] PI3K,[304] Akt,[305] BDNF[306,307]; IGF-1 influences VEGF,[308] TNF-α,[294] IL-6,[309] Akt,[310] Sirt1,[311] PI3K,[312] MAPK[313]; BDNF influences NT3,[301] Caspase 3,[314] TNF-α/IL-6,[90] MAPK/Erk/PI3K[315]; VEGF influences Caspase 3,[316] BDNF,[317] Akt,[316] PI3K,[318] IL-10/IL-1β/TNF-α.[319] [Color figure can be viewed at wileyonlinelibrary.com]

drugs such as Cerebrolysin with its pleiotropic mechanism of action on neurogenesis, angiogenesis, neuroplasticity, and neuroinflammation come to the fore (Figure 2).

7 | PLEIOTROPIC MODULATION OF NTFS WITH CEREBROLYSIN: CLINICAL EFFICACY IN *DEMENTIA*, *STROKE*, *AND TBI*

The multimodal drug Cerebrolysin modulates the profile of several NTFs, which are relevant in cerebrovascular and neurodegenerative diseases such as dementia, stroke and TBI. Randomized, double-blind clinical trials have shown that Cerebrolysin is effective, safe, and well-tolerated in the treatment of these pathologies.

7.1 | Clinical outcome of pleiotropic modulation of NTFs with Cerebrolysin in dementia

The clinical efficacy and safety profile of Cerebrolysin for dementia syndromes has been assessed in 39 clinical trials with duration of up to 3 years. A total of 3624 patients have been enrolled in these trials, 1930 of them into double-blind, controlled trials, 1049 into open-label trials and 645 into a noninterventional study. For AD, Cerebrolysin is intended for long-term use, as AD is characterized by a progressive deterioration of the pathological condition over several years. Cerebrolysin has shown to induce symptomatic improvement in the patient's global functions as well as improvement and long-term maintenance of cognitive performance up to several months after treatment (Figure 6).

Two meta-analyses have been performed in AD by Wei et al.[322] and Gauthier et al.[323] and one meta-analysis in vascular dementia by Chen et al.[324] updated by Cui et al.[325] The meta-analysis published by Gauthier et al.[323] showed a statistically significant effect of Cerebrolysin on the clinical global assessment of change for 1 and 6 months of treatment. Furthermore, Cerebrolysin improved the cognitive outcome already after 1 month of treatment, a head start that sustained over time. This meta-analysis has shown an overall significant beneficial effect and a favorable benefit-risk ratio of Cerebrolysin in patients with mild-to-moderate AD. The Cochrane meta-analysis by Cui et al.[325] on six randomized controlled trials with a total of 597 patients reported a statistically significant beneficial effect of Cerebrolysin on general cognitive and global functions in elderly patients with vascular dementia of mild to moderate severity. The magnitude of the effect of Cerebrolysin is similar to that in AD or higher. This is of particular relevance for the clinical situation especially as no alternative medication is approved for vascular dementia pointing to a high clinical relevance of effects observed with Cerebrolysin.

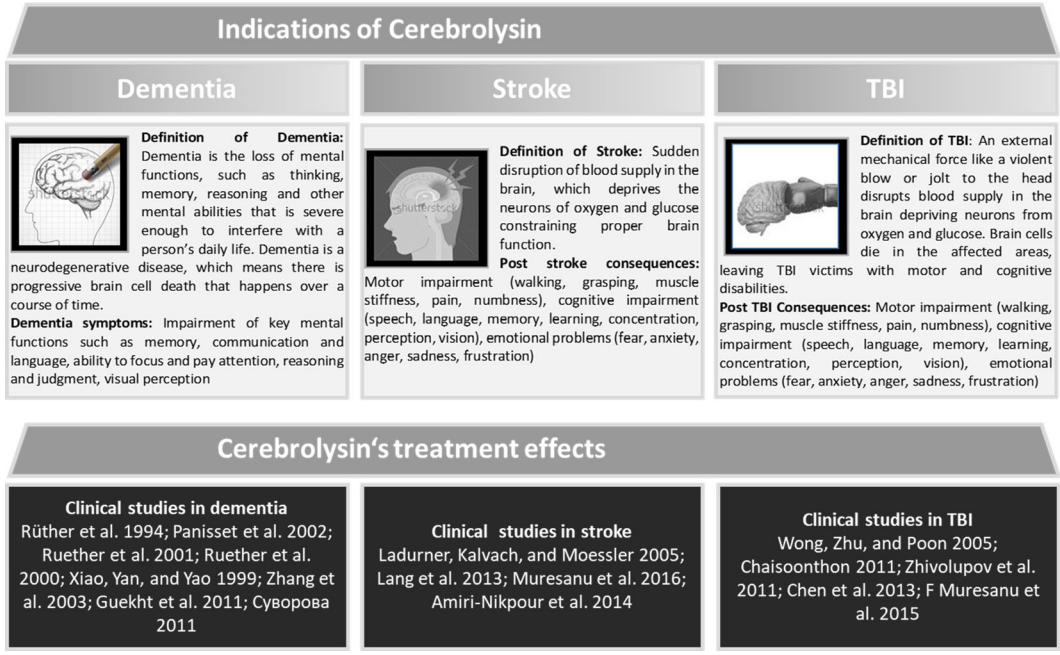

FIGURE 6 Therapeutic Indications of Cerebrolysin. In the upper box the three main indications of Cerebrolysin dementia, stroke and TBI are defined. In the boxes in the middle a summary of the main outcomes of clinical trials with Cerebrolysin in dementia, stroke and TBI are listed. The lower black boxes cite some representative clinical studies for Cerebrolysin in the three main indications.

7.2 | Clinical outcome pf pleiotropic modulation of NTFs with Cerebrolysin in stroke

The clinical efficacy and safety profile of Cerebrolysin in stroke has been assessed by 68 clinical trials with duration of up to 1 year (Figure 6). A total of 8950 subjects have been enrolled in these trials, 3369 of them into 23 double-blind, controlled trials, 4640 into open-label trials and 941 into noninterventional studies. A recently published meta-analysis by Bornstein et al.[237] combined the results of nine ischemic stroke trials, assessing efficacy of Cerebrolysin on global neurological improvement early post-stroke. All included studies had a prospective, randomized, double-blind, placebo-controlled design. The patients were treated with 30–50 ml Cerebrolysin once daily for 10–21 days, with treatment initiation within 72 h after onset of ischemic stroke. The nonparametric Mann –Whitney (MW) effect size for the NIHSS on day 30 (or 21) demonstrated superiority of Cerebrolysin as compared with placebo (MW 0.60, $p < 0.001$, $N = 1879$). The combined number needed to treat for clinically relevant changes in early NIHSS was 7.7 (95% confidence interval [CI] 5.2–15.0). The additional full-scale ordinal analysis of modified rankin scale at day 90 in moderate to severe patients resulted in MW 0.61 with statistical significance in favor of Cerebrolysin (95% CI 0.52–0.69, $p = 0.012$, $N = 314$). This meta-analysis confirms the beneficial effect of Cerebrolysin on global neurological deficits in patients with acute ischemic stroke. Analyses of individual study results indicate that beneficial treatment effects with Cerebrolysin occur early, that is, between Days 5 and 21, and were shown in the stroke deficit level, the global disability, activities of daily living, mental status, motor functions, reduction of infarct volume, and post-stroke depression[142,326–333]. These early effects were characterized by an accelerated recovery up to 3 weeks after stroke, thus potentially allowing a more efficient early rehabilitation. In line is the observed reduction of the mortality rate in patients treated with Cerebrolysin. The trial performed by Heiss et al.[334] reported a mortality rate from all causes of 5.3% in Cerebrolysin treated patients and of 6.6% in the placebo group receiving standard treatment, corresponding to a relative reduction in mortality of 20% (hazard ratio 1.26; 97.5% conficence interval lower bounds [CI-LB] 0.75; $p = 0.19$). In more severely affected stroke patients (NIHSS > 12) the reduction in cumulated mortality was even more pronounced: 11% in the Cerebrolysin group compared to 20% in the placebo group, resulting in a 48% reduction of mortality (hazard ratio 1.97; 97.5% CI-LB 1.00; $p = 0.02$). Safety and tolerability of Cerebrolysin in acute ischemic stroke patients was also shown in the meta-analysis by Bornstein et al.[237]

7.3 | Clinical outcome of pleiotropic modulation of NTFs with Cerebrolysin in TBI

The clinical efficacy and safety profile of Cerebrolysin in TBI has been assessed in 27 clinical studies with a duration of up to 6 months. A total of 9752 patients have been enrolled in these trials, 261 of them into three double-blind controlled trials, 1457 into open-label trials and 8034 into noninterventional studies. Trials have shown beneficial effects of Cerebrolysin in both, the acute treatment of TBI as well as in the treatment of long-term sequelae in the sub-acute phase (Figure 6). This finding is of importance since it is generally considered that the time period for a successful therapeutic intervention in TBI patients is limited to the first 6–12 months after brain injury.[335,336] Cerebrolysin improved the level of consciousness and the global, cognitive and neurological performance of the patient. These findings were in line with beneficial changes in neurophysiological parameters. Cerebrolysin was effective in patients regardless of whether they underwent surgery after TBI. Most importantly, Cerebrolysin led to a marked and faster recovery as compared to placebo or basic therapy only and to earlier discharge from hospital.[337] Cerebrolysin was safe and well tolerated. In the recently published CAPTAIN trials[338,339] Cerebrolysin improved global outcome, cognitive speed, attention and depression in moderate to severe TBI patients in comparison to placebo, 90 days post-stroke. The meta-analysis of Ghaffarpasand et al.[340] reported a significant increase in functional outcome versus controls as observed by the Glasgow Outcome Scale (SMD = 0.30; 95% CI: 0.18–0.42; $p < 0.001$; I^2: 87.8%) and the modified Rankin Scale (SMD = −0.29; 95% CI: −0.42 to 0.16; $p = 0.05$; I^2:89.6%).

8 | OUTLOOK ON FUTURE DIRECTIONS

Neurological brain pathologies are complex in their NTF profile deregulations. In consequence, to improve current therapeutic outcomes in brain pathologies, treatments need to become complex too. Multimodal drugs, that can modulate several deregulated NTFs simultaneously, are expected to have stronger therapeutic impacts than drugs with single targets. This means pluripotent and combinational treatments will need to be much more considered in medical practice. To support this goal, more pluralistic biochemical knowledge of brain pathologies needs to be provided for the physician. This biochemical complexity is however only starting to be approached in research by in vitro, in vivo and clinical studies. Most of the time single NTF targets are being studied without looking at the whole picture, missing an interactive view of related expression events. Underlying interconnective data are still missing to a large extent. Data on the interplay of NTFs are urgently needed. So future preclinical and clinical studies of brain pathologies will need to add a set of NTF biomarkers in their screening protocol. Multiomics data need to be better harnessed for this aim; data- and text-mining projects aiming to correlate single NTF study results should be extensively pursued. Why are these pluralistic research projects still rare? The quest to develop highly selective compounds was surely driven by: (1) the fear to see an increased number of side-effects when a drug had more targets it interacted with; (2) the complexity in experimental design and data analysis of a multifunctional drug; ands (3) the missing regulatory paths for such drugs to get approved in an epoch of single-compound/single-target drugs. Nevertheless, there is accumulating evidence that due to biochemical disease complexity neurodegenerative and brain diseases single target drugs are unlikely to offer sufficient improvement. Cerebrolysin as multimodal drug also proves the "bigger side-effect hypothesis" of multi-modal drugs wrong, as it has been extensively proven to be safe.[289] In the future, further in vitro, in vivo and clinical multi-target studies are indicated to integrate the multimodal drug approach in the medical community. Probably supported by modern AI driven experimental design and data analysis. Research strategies that will help explain the multiple levels of mode of action of such multimodal drugs like Cerebrolysin. These new insights will pave the way for a broader understanding of multimodal drugs in the future and for significant improvement in the standard of care for various neurological diseases.

AUTHORS CONTRIBUTION

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Medical writing, editorial, and other assistance: Editorial assistance in the preparation of this manuscript was provided by Dr Eleanor Roberts, Beeline Science Communications, Ltd, Support for this assistance was funded by EVER Pharma GmbH.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

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