CHAPTER II

REVIEW OF LITERATURE

2.1 Therapeutic role of conventional neurotrophins and neurotrophic factors (NTFs) derived from natural resources for treating neurodegenerative diseases

The therapy that can avoid the death of the neuronal cell either by inhibiting or intervening in various pathogenetic cascades that initially result in the dysfunction of the cell and eventually lead to the cell's death is defined as neuroprotection [1]. The theory of neuroprotection preserves some of the damage after administering the agent or prevents further adverse effects. Since the discovery of neurotrophins, their crucial role in regulating numerous essential neuronal functions, such as promoting neurite regeneration, preventing neuronal degeneration, and increasing synaptic plasticity, has been elucidated by various researchers both in *in vitro* laboratory studies and in *in vivo* experimental models [2-4].

Anticipating the remarkable physiological activity of NTFs in neuroprotective function and restoration of neuronal damage, they hold enormous potential to treat NDs [5]. Such examples include the reduced level of BDNF (essential for memory and learning) reported in some regions of the brain, viz. substantial nigra in PD patients [6], and reduced level of NGF noted in AD patients [7] eventually leads to a withdrawal of neuronal function and decrease the number and size of neurons. Therefore, maintaining the level of neurotrophins in the related degenerating region of the brain is a tremendous therapeutic invention. Studies have shown that systemic administration of exogenous neurotrophin molecules exerts prominent effects on neuronal development, thus suggesting they have significant therapeutic potential in the treatment of NDs malignancies, inflammations, and neuronal injury [8-11]. Some examples of the therapeutic significance of NTFs are mentioned in the following section.

2.1.1 BDNF delivery as a therapeutic target for PD and HD

Numerous reports highlight the therapeutic activity of NTFs in *in vivo* models of NDs induced by different neurotoxins (such as paraquat, acrolein, heavy metals, rotenone, etc.), which alter motor functions [7]. BDNF over-expression following BDNF gene transfection in dopamine neurons associated with D3 receptor activation, emerging as an essential strategy to restore the function of dopamine neurons in the 6-hydroxydopamine (6-OHDA)-induced rat PD model [12]. Baydyuk and Xu (2014) have established the significant contribution of the decreased level of striatal BDNF in HD pathogenesis and

highlighted BDNF-TrkB downstream signalling pathway as a probable therapeutic target for the treatment of HD pathogenesis [13].

2.1.2 NGF delivery as a therapeutic target for AD

NGF treatment has immense potential to prevent the degeneration and dysfunction of cholinergic neurons in *the in vivo* AD model [14]. Tuszynski et al. (2005) performed a phase 1 clinical trial of ex vivo NGF gene delivery with AD patients and marked the restoration in the rate of cognitive decline [15]. Other studies demonstrated the first clinical trial (Registration no: NCT01163825) with NGF delivery via implantation of encapsulated and genetically modified NGF-producing human cell line (NsG0202 implant) to the cholinergic basal forebrain of AD patients. The implants were taken off smoothly at 12 months and continual NGF secretion was observed in half of the AD patients [16]. Therefore, experimental and clinical facts confirmed that NGF can be a promising candidate for treating AD pathogenesis. NGF delivery alleviates Aβ accumulation and recovers cognitive and behavioral activity [14,17].

2.2 The challenges associated with the therapeutic application of conventional neurotrophins in treating NDs

Despite all the therapeutic potential of neurotrophins or NTFs, some studies have reported various issues and challenges related to the clinical implementation of NTFs. The most significant impediments associated with the clinical use of NTFs are their poor pharmacokinetic properties, short *in vivo* half-lives, and poor penetration via BBB [11,18]. However, the proteolytic degradation, rapid clearance mechanism (fast excretion by kidneys), and different binding sites on the peripheral tissues restrict access of the NTFs to the neuronal targets [18]. Therefore, as summarised in Fig 2.1, clinical application for neurotrophic factors has to face multiple limitations regarding pharmacokinetic features of delivery, physiochemical characteristics, and physiological aspects of the CNS compartment, [5].

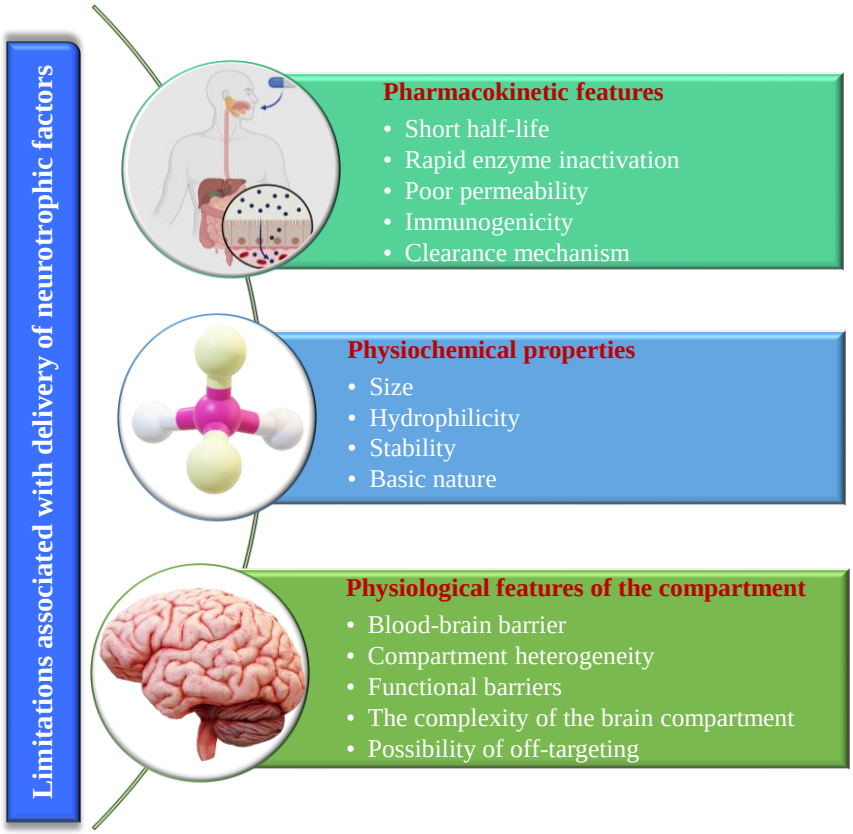

Fig 2.1 Limitations associated with the clinical application and delivery of neurotrophic factors. Created with BioRender.com.

2.3 Advantages of neurotrophin mimetic molecules over parent neurotrophins as therapeutics

There is an urgent requirement to resolve these impediments for the successful therapeutic application of neurotrophins. Several strategies focusing on the better pharmacokinetics of native neurotrophins, such as a small molecule or synthetic peptide (peptidomimetic) development that binds to specific receptors or neurotrophins mimetic have been suggested [19-21]. A peptidomimetic is a compound with pharmacophore similarity that mimics natural protein-fragment, peptide, or whole protein and which also possesses the ability to interact with the specific target and generate similar biological effects [22,23]. Peptide mimetics provides an obvious way to tackle the disadvantages of natural peptides. The molecule that mimics the biological activity of a natural peptide and has a molecular weight of less than 700 Da is referred to as a peptide mimetic. Peptide mimetics have significantly improved patient compliance and cost savings [23].

Moreover, peptide mimetics are far less expensive to produce than natural peptides. Also, natural peptides not encountered with peptide mimetics have issues with peptide storage, stability, and immunoreactivity [24]. In recent years, peptide mimetics have emerged as a new generation of promising drugs due to the rapid screening of small molecule libraries and rational design approaches [21,25].

The pharmacological benefits of peptidomimetics over protein therapeutics comprise favourable pharmacokinetic profiles, low molecular mass, absence of immunogenicity, and low cost [26,27].

2.4 Trends in the discovery of therapeutic peptide

The journey of peptide drugs started more than 100 years ago (Fig 2.2) when benzoylglycylglycine, the first dipeptide, was discovered by Theodor Curtius in 1881 [28]. Shortly, Emil Fischer (1901) synthesized the first unprotected dipeptide glycylglycine, and in 1902, he got a Nobel Prize for chemistry [28,29]. In the 1920s, since the emergence of insulin therapy, curiosity about peptide-based drugs has extensively increased [30]. du Vigneaud (1953) synthesized oxytocin as the first synthetic polypeptide that emerged as a therapeutic agent.

The commercial interest of an industrial group increased in peptide therapeutics, and peptides became more studied as an essential future for drug candidates in the 1960s. However, during that time, peptide synthesis by solution-phase method required years of effort. In 1963, the discovery of solid-phase peptide synthesis (SPPS), along with the advancement in the purification methods, gained significant focus from the pharmaceutical industry [31], and in 1984 Bruce Merrifield received the Noble Prize in Chemistry for his achievements [32]. The 1970s saw the progression in molecular biology techniques like recombinant DNA technology that facilitated the industrial-scale production of therapeutic peptides. Furthermore, human insulin was the first accepted therapeutic peptide produced in 1974 [33].

Over the last few decades, great progress in peptidomimetics technology has taken place, which has promoted researchers and industries to identify peptides of therapeutic utility, and various peptides (natural and synthetic analogues) are undergoing clinical studies [34]. Since insulin was the first accepted therapeutics, around 80 peptide therapeutics or more are available in markets for a range of diseases such as cancer, diabetes, multiple sclerosis, chronic pain, HIV infection, and osteoporosis [32].

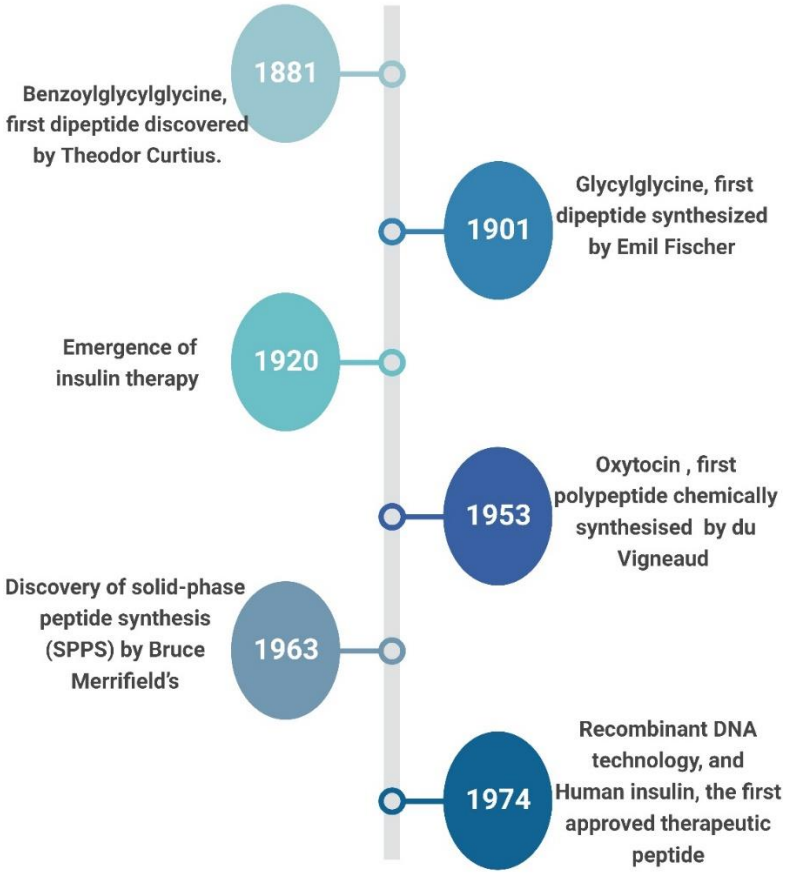

Fig 2.2 Trends in peptide therapeutic development. Created with BioRender.com

2.5 Application of peptidomimetics as drug prototypes to treat NDs

2.5.1. Peptide mimetics to NGF and TrkA receptor: Longo et al. (1990) were the first to show that NGF mimetics, which is a small cyclized dimeric peptide, P7 (KGKE amino acid residues) exerts p75NTR-dependent neurotrophic activity and inhibits neuronal death [35]. The first cyclic dimeric peptide P7 (CATDIKGAEC amino acid residue) mimetic to NGF domain was verified to trigger a neurotrophic response after binding through p^{75NTR} receptor (p^{75NTR} antagonist) and protect neurons from beta-amyloid (Aβ) induced cell death [36]. The study persistent with the site-directed mutagenesis revealed that the NGF residues Lys32, Lys34, and Lys95 are crucial for the interaction of NGF to p^{75NTR} [37].

Scientists further expanded their findings and showed that peptide P7, NGF peptidomimetic blocked amyloid β (Aβ) binding to the p^{75NTR} receptor and protected from the cell death caused by Aβ [36]. Mutagenesis studies have indicated that the NGF loop 4 domain is one of the domains crucial for the binding of TrkA; hence peptide mimetics

of the NGF loop 4 domain plays a significant role in interacting with TrkA receptor [37,38]. LeSauteur et al. (1995) reported cyclic peptide mimetics to NGF β-loop [24] inhibited the NGF-induced growth of neurite in PC-12 cells, acting as a potent 'antagonist' of TrkA receptor [39]. However, they exhibited no neurotrophic potential without NGF, implying their 'agonist' activity [39].

On the other hand, a monomeric peptide C (92-96) maintained the survivability of PC-12 and other cells when monoclonal antibodies bound the p^{75NTR} receptor, signifying a 'partial agonist profile' [40]. Cyclized dimeric peptide, C (92-97) of β-turn appears to mediate TrkA binding, is responsible for *in vitro* activation of TrkA, and encourages the survival of neuroblastoma and PC-12 cells [40]. The NGF-like neurotrophic activity demonstrated by cyclic dimeric peptide loop4 mimetics P92 induces TrkA-dependent ERK and Akt signal transduction pathways [41]. A Series of functional peptides mimetics to the C-D loop of NGF were designed to understand their bioactivity [42,43]. Another peptide mimetic to NGF named LIL4 established NGF agonist activity in PC-12 cells and a rat model of neuropathic pain [44].

Estenne-Bouhtou and team (1996) combined various NGF areas in one molecule [45]. Two β-hairpin loops, L1 and L4, were united by them to produce active peptide mimetics of NGF. It has been reported that a synthetic chimeric peptide NL4, including the NGF loop 4 hairpin motif linked to the nucleic acid binding domain, shows a potential advantage for targeted gene delivery to cells or tissue expressing TrkA receptors [46]. Peptide mimetics to two linear sequences of N-cadherin extracellular domain 1 (INPISGQ and HAVDI) act as an antagonist [47]. In contrast, a cyclic peptide N-Ac-CHAVDINGHAVDIC-NH2 consists of a tandem repeat of individual motifs. It acts as an N-cadherin agonist capable of stimulating the outgrowth of neurites in a comparable way to native N-cadherin [48].

Another TrkA selective peptide mimetic to NGF named D3 (TrkA partial agonist) is homologous to the β loop of the NGF side chain, inducing TrkA dimerization and supporting dorsal root ganglion neurons to survive [49]. Compound D3 has been found to protect root ganglion neurons from degeneration, improve memory in aged rats after the administration by intracerebroventricular minipump [40,50], and rescue short-term memory deficit [51]. Furthermore, MIM-D3, a TrkA agonist peptidomimetic, enhanced the secretion of glycoconjugate and significantly improved corneal injury in a rat with dry eye syndrome [52,53].

The design of dimeric dipeptide mimetic of NGF loop4 named GK- 2 (bis(N-succinyl-Lglutamyl-L-lysine) hexamethylenediamine) indicated therapeutic impact in *in vitro* neuronal cells and an *in vivo* rat model of neurodegenerative disorders like PD and AD, diabetes mellitus and brain ischemia with no side effects [2]. Gk-2 dimeric peptide completed the pre-clinical trials as a therapeutic drug for healing poststroke situations without adverse side effects [21,54]. In 2021, Tarasyuk et al. reported synthesizing two analogues of the peptide mimetics to NGF loop1 bis-(N-aminocaproic-glycyl-L-lysine)hexamethylenediamine (GK-6) that are bis-(N-acetyl-glycyl-L-lysine)hexamethylenediamine (GTS-611) and bis-(N-aminocaproyl-glycyl-glycine)hexamethylenediamine (GTS-613). The GTS-613 analogue of GK-6 showed neuroprotective effects in oxidative stress induced-HT-22 neuron cells *in vitro* at concentrations of 106 and 105 M, whereas GK-6 and GTS-611 induced distinction in PC-12 cells [55].

A synthetic peptide consisting of N-terminal encoding amino acid 1-14 of human NGF (hNGF 1-14) has been reported to induce TrkA-dependent cascade in PC-12 cells, comparable with native NGF [3]. Peptide derivative hNGF1-14 (TrkA agonist) triggered neuronal activity in the CNS and PNS, signifying that peptide hNGF1-14 can retain the neurotrophic potency of parent NGF [4]. The acylated form of hNGF1-14 (Ac-hNGF1-14) has prospected to show even better potency in inducing TrkA signaling that signifies the increasing stability of the peptide, which in turn might influence the ligand-receptor complex formation [4].

Previously, *in vitro*, studies have demonstrated that hNGF 1-14 mimics the whole NGF activating TrkA-dependent downstream pathways catalyzed explicitly by the Zn^{2+} and Cu^{2+} metal ions [56]. Peptide mimetics of NGF-mediated phosphorylation of cyclic AMP response element-binding protein (CREB) transcription factor ensued in the enhanced appearance of BDNF [4,57].

2.5.2. Peptide mimetics to BDNF and TrkB receptor: BDNF specifically binds to TrkB and encourages synaptic function, neuronal survival, and differentiation [58]. In recent years, research focus has intensified toward peptide mimetics to BDNF loops 2 and 4 as a therapeutic agent for treating neurodegenerative diseases like AD [20,59]. Cyclic monomeric peptides analogous to BDNF Loop 2 that may acquire BDNF-like antagonist activity had no intrinsic activity [60]; however, cyclic dimeric peptides analogous to loop

2 promoted neuron survival with lesser efficacy than native BDNF and some possessed pro-survival properties [61].

Linear, monomeric, synthetic tetra peptides (B-1 to B-5) developed from the loop 4 carboxy-terminal region of BDNF-induced TrkB phosphorylation. They (peptides B-3 and B-5) displayed a neurotrophic effect in cultured hippocampal neuronal cells [62]. Active dipeptide GSB-106 mimetics of BDNF loop 4 was designed that exhibited in oxidative stress (H_2O_2-induced) model of rat hippocampal cell line HT22 and *in vivo* neuroprotection activity in Balb/c male mice model and provided the basis for the development of anti-depressant drug under preclinical studies (https://4science.ru/project/14- N08- 12- 0086) [54,63]. Neuroprotective activity of GSB-106 was found *in vitro* neurotoxin 6-hydroxy dopamine (6-OHDA) induced-SH-SY5Y human neuroblastoma cells [64].

To explore the receptor binding role of the BDNF loop, Fletcher and Hughes designed a total of five monomeric monocyclic peptides mimetics, loop1 analogue (L1), loop 2 analogues (L2a and L2b), and loop 4 analogues (L4a and L4b) [8]. All designed peptides were discovered to inhibit BDNF neurotrophic effect; however, interestingly, one peptide mimetics of BDNF loop 4(L4a-L4b) acted as a partial BDNF-like agonist [65]. In addition, cyclized pentapeptide2 (cyclo(-D-Pro-Ala-Lys-Arg-) derived from BDNF loop 4 binding regions to p^{75NTR} showed neurotrophic activity without Trk B activation [66]. Further, it was investigated that this pentapeptide cyclo-D PAKKR promoted neuronal myelination *in vitro* dorsal root ganglion sensory neurons and *in vivo* rat model via p75NTR receptor [9,66].

The therapeutic role of cyclo-D PAKKR was further studied in experimental autoimmune neuritis (EAN), demyelinating peripheral neuropathy rat model [67]. The most bioactive peptide, tricyclic dimeric peptide 6 (TDP6), a small polycyclic peptide that mimics the BDNF region that binds TrkB to act as a TrkB agonist, significantly inhibits *in vitro* TrkB-dependent oligodendrocyte myelination [68].

Using a peptidomimetic approach, scientists developed a cyclic peptide cyclotraxin-B derived from BDNF, a highly variable region III, a TrkB inhibitor that inhibited both BDNF mediated and BDNF independent activities [69,70]. Recently, peptide mimetics of neurotrophin molecules have found use in several clinical trials [54,71]. Some small peptides function as inhibitors and mimetics of BDNF pair of loops

appropriate for therapeutic use [61,65]. BDNF tetrapeptides were identified that mimic the neurotrophic effect of BDNF in mouse hippocampal cell culture [62].

In 2010, a study described two mimicking peptides, Betrofin-3(RGI, RGIDKRHWNSQ) and Betrofin-4 (SYVRALTMDSKKRIGWR), were obtained from the loop-3 and loop-4, respectively, of BDNF, which interacted with BDNF receptors, TrkB and p75NTR to induced neurite outgrowth as well as to increase the neuron survival through MAPK and Akt pathways [72]. These pathways are also activated by native BDNF post-binding to TrkB and p^{75NTR} [59].

Zhan et al. (2013) reported a novel self-assembling nanofibre scaffold (SAPNS) named RADA16-I to uphold peripheral nerve regeneration in a sciatic nerve injury model [73]. Because peptide mimetics to BDNF alone were not sufficient to activate the receptor, scientists developed a functionalized self-assembling peptide that was produced by BDNF-derived neurotrophic peptide (RGI) to the self-assembling peptide RADA16-I C-terminal (Ac-(RAD)4-CONH2) that promoted nerve regeneration with increased re-myelination and recovered motor function [74].

2.5.3. Peptide mimetics to NT-3 and Trk-C receptor: β- turn peptidomimetics are produced to mimic the NT-3 hot spot that binds to TrkC receptor subtype and NT-3 like neurotrophic function [75-77]. A Peptidomimetics mini-library has also been designed based on the β-turn of NGF and NT-3 [78]. Some peptide mimetics elicited neuritogenesis and survival, whereas others caused either survival or neurite outgrowth [78]. This group also described the design and synthesis of bivalent TrkC peptide mimetic ligands that promoted neuritogenesis or potentiated phosphorylation of TrkC [79].

The list of neurotrophins mimetics-based treatment of NDs is summarised in Table 2.1.

Table 2.1. Peptidomimetic-based treatment of NDs with neurotrophin

Neurotrophins	**Sequence**	**Neurodegenerative diseases (NDs)**	**Model**	**Mechanism of action**	**References**
NGF loop 1 mimetics	IPenKGKEVCT NGF partial agonists	Neoplasia	*In vitro* Dorsal root ganglia chick embryos, mice	Encourage neuronal survival via p75 dependent mechanism	[35,39]
NGF loop 4 mimetics, P92	TDEKQ, NGF partial agonist	Neurodegenerative disease	*In vitro* Dorsal root ganglia chick embryos	TrkA-dependent ERK and Akt signaling. Promote both survival and neurotrophic activity.	[41,80]
NGF β turn	Peptidomimetic	Neurodegenerative disease, pain, neoplasia	*In vitro*		[40]
NGF mimetics containing KGA amino acid sequence	CATDIKGAEC p75NTR antagonist	Alzheimer's disease	*In vitro* p75 NTR- and p140trkA-NIH-3T3 cell and E17 foetal rat cortical neurones	Block the Aβ-mediated p75 NTR signaling and arresting the Alzheimer's disease progression	[36]
NGF loop 1 and 4 mimetics, LIL4	CTDIKGKCTGACDGKQC NGF agonist	Neuropathic pain	*In vitro* in chick dorsal root ganglia, PC-12 cells, and; *in vivo* rat model of peripheral neuropathic pain	Induced tyrosine phosphorylation of TrkA, but not TrkB, receptor and restore neuropathic behavior in a rat model of peripheral neuropathic pain	[44]
NGF mimetics, C(92-97)$_{dimer}$	Cyclized dimer C(92-97)$_{dimer}$ *N*-Ac-YCTDEKQACY	Neoplasia, pain	*In vitro* neuroblastoma and PC-12 cells	Induced TrkA dimerization, phosphorylation, and internalization	[40]
NGF loop C-D mimetics,	N-acetyl-YCTDEKQCY		*In silico*	An essential constituent of induced-fit ligand binding between the NGF C-D loop and TrkA.	[42,43]
NGF loop 4 mimetics	NL4 and NL4-10K Synthetic peptide for targeted gene delivery	Neurodegenerative disease	*in vitro* in PC-12 cells and NIH3T3 cells	Act through TrkA to trigger the same signal	[46]

				transduction pathways that NGF activates.	
N-Cadherin mimetics	*N*-Ac-CHAVC-NH2 N-cadherin antagonists	Axonal regeneration	*In vitro* 3T3 cells		[47,48]
D3	Peptidomimetics, Trk A agonist	Neurodegenerative disease, rescue short-term memory deficit	*in vitro* PC-12 cells and; *in vivo* cognitively impaired aged rats	Induce dimerization and activation of TRK Receptor. Inhibits loss of dorsal root ganglion neurons.	[50,51]
MIM-D3	TrkA agonist	Dry eye treatment	Phase III clinical trial (https://clinicaltrials.gov/ct2/show/study/NCT03925727)	Promotes secretion of glycoconjugate from cultured conjunctival cells and improved concentration of glycoconjugates in the tear fluid of normal rats	[52,53]
GK-2 mimetics to NGF loop4	The beta-turn sequence of NGF loop 4, GK-2	Neurodegenerative disease, brain ischemia, diabetes mellitus	Pre-clinical studies *in vitro* mouse hippocampal neurons (line HT-22), primary culture of rat hippocampal neurons (HN), PC-12 cells of rat pheochromocytoma, and; *in vivo* in rats model	Crossed the blood-brain barrier without any toxic effect. Binds with TrkA receptors and specifically triggers PI3K/ Akt signaling pathway. Neuroprotective with no side effects.	[2,54]
NGF mimetic hNGF 1-14, Ac-hNGF1–14, hNGF1–15 dimer	human NGF 1–14 sequence (SSSHPIFHRGESFV-NH2); Ac-hNGF1–14 (Ac-SSS H4PIFH8RGESFV-NH2); hNGF1–15 dimer (SSS HPIFHRGESFC-S)$_2$ TrkA agonist	CNS diseases	*in vitro* PC-12 cells, Dorsal Root Ganglion Dissociated Culture and	hNGF1–14 peptide has shown full NGF-mimetic potential; Survival and differentiation of dissociated dorsal root ganglia (DRG)	[3,4,56]
BDNF loop 2 mimetic	Cyclic peptide partial BDNF-like agonist	Neurodegenerative disease	*in vitro* dorsal root ganglion sensory neurons	TrkB dimerization, Neuron survival	[61]
BDNF mimetics tetra peptides B3 and B5	Peptide B-5 (Ac-I-K-R-G-CONH2), B-3 (Ac-S-K-K-R-CONH2), BDNF partial agonist and antagonist	Neurodegenerative diseases, depression,	*in vitro* mouse primary hippocampal neuronal culture	Increase the expression of BDNF and TrkB	[62]

		stress,s and anxiety			
BDNF loop 4 mimetics dipeptide GSB-106	GSB-106 [28], TrkB agonist	Psychiatric disorders, cerebral ischemia	Preclinical studies *in vitro* hippocampal cells of the HT22, SH-SY5Y human neuroblastoma cells and *in vivo* Balb/c male mice	Activation of TrkB-dependent pro-survival.	[54,63,64,81 ,82]
BDNF loop 4 mimetics Penta peptide cyclo-D PAKKR	cyclo-DPAKKR	Demyelinating diseases	*in vitro* dorsal root ganglion sensory neurons and *in a vivo* rat model	Promote NF- B pathway via a p75NTR-dependent manner. Enhances NRG1-typeIII expression in developing sciatic nerve.	[8,9,61,65-67]
BDNF mimetic multicyclic peptide TDP6	$(Ac\text{-}CVPVCKGQLCE\text{-}NH_2)_2$ dimerize by E-K amide bond TrkB agonist	Oligodendrocyte myelination	*in vitro* dorsal root ganglion sensory neurons	TrkB-dependent oligodendrocyte myelination, ERk1/2 activation	[68]
BDNF mimetic cyclic peptide cyclotraxin B	CNPMGYTKEGC (Disulfide bridge: Cys1-Cys11), TrkB antagonist	Brain disorders	*in vitro* Cortical neurons, PC-12cells, and *in vivo*	Allosterically alters the TrkB conformation and inhibits both BDNF-dependent and basal activities	[69,70]
Betrofin 3 and Betrofin 4 mimetics of BDNF loop 3 and 4	Betrofin 3 RGIDKRHWNSQ, Betrofin 4 (SYVRALTMDSKKRIGWR) partial agonist	Neurodegenerative diseases	*in vitro* Cortical neurons	Induce signaling Through TrkB and p75NTR-mediated Akt and MAPK pathways. Enhanced neurite outgrowth and survival	[72]
NGF loop 1 mimetics GK-6 and their analogs GTS-611 and GTS-613	bis-(N-aminocaproyl-glycyl-L-lysine) hexamethylenediamide(GK-6),bis-(N-acetyl-glycyl-Llysine)hexamethylenediamide (GTS-611) and bis-(N-aminocaproyl-glycyl-glycine)hexamethylenediamine (GTS-613)	Neurodegenerative diseases	*in vitro* oxidative stress-induced HT-22 neuron cells	GTS-613 shown neuroprotective effect, GK-6 and GTS-611 induce differentiation in PC-12 cells	[55]

dimeric peptide analogs of two agonists	two agonists directed to the extracellular domain of TrkA: the peptide sequence of NGF itself, and the anti-TrkA monoclonal antibody 5C3	Neurodegenerative diseases	PC-12 cells	Binding competition, promoting TrkA phosphorylation and differentiation of cultured sensory neurons	[40]
small molecule peptidomimetics	based on β-turns of NT-3 and NGF	Neurodegenerative disease	PC-12 cells	Binding competition; promote neuron survival and/or neurite outgrowth	[78]
LM22A4	Small molecule non-peptide based on the loop 2 domain of BDNF	Traumatic brain injury	Rat model	promotes survival of hippocampal neurons in a TrkB-dependent manner	[58]
LM11A-24	Small molecule non-peptide p75NTR ligand	Neurodegenerative disease		prevents p75NTR – dependent cell death	[83]
Ac-CHAVDINGHAVDIC-NH2 (SW4)	cyclic peptide containing the HAVDI sequence of N-cadherin			Promotes neurite outgrowth and neuron cell survival	[27]

2.6 Snake venom derived peptidomimetics as therapeutics to treat neurodegenerative disorders

In previous studies, NGFs have been isolated and characterized from *Vipera lebetina* [84,85] and *D. russellii* snake venom [85-88]. Islam et al. (2020) have isolated and characterized Nn-α-elapitoxin-1 from Indian Cobra *N. naja* venom which exhibits neuritogenesis potency (similar to other neurotrophin molecules) but no sequence similarity to conventional nerve growth factor (NGF) [89]. Venoms also contain neurotropic factors that induce sympathetic and embryonic sensory neuron differentiation and regulate neurite outgrowth from rat PC-12 cells. The PC-12 cells are clonal cells that are derived from stem cells of rat pheochromocytoma and show the phenotypic characteristics correlated with pheochromocytomas as well as their nonneoplastic counterparts; adrenal chromaffin cells [90]. In response to different neurotrophins, the cell line PC-12 is a useful model system for neuronal differentiation [91,92]. NGF facilitates the transformation of these pheochromocytoma cells into cells that develop sympathetic neuronal features [93].

Snake venom contains a mixture of peptides and proteins with various biological roles [94]. In the envenomed casualty, these biomolecules disrupt fundamental processes, leading to morbidity and death. Conversely, they also elicit signaling pathways that show advantageous effects in particular diseases. Throughout the years, convincing attempts have been made to identify new molecules from snake venom and modify them into therapeutic tools [95]. Since the development of the first peptidomimetic drug 'Captopril' derived from snake venom, numerous other toxins have been investigated as naturally active with therapeutic potential that might signify a potential alternative [96,97].

A tripeptide (p-BTX-I) derived from *Bothrops atrox* venom shows neuroprotective and neurotrophic effect at the dose of 192 μM in PC-12 cell line treated with dopaminergic neurotoxin 1mM 1-Methyl-4-phenylpyridinium iodide (MPP+), active metabolite of the putative inducer of Parkinson's disease (PD), MPTP [98]. Further studies have reported that p-BTX-I (25 μg) also shows protection against acrolein (10 μM)-induced AD model of PC-12 cells and improves bioenergetics and synaptic plasticity [99]. Therefore, synthetic peptides derived from snake venom hold considerable potential as drug candidates for treating NDs.

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