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INVITED REVIEW

Synthetic microneurotrophins: Neurotrophin receptors for therapeutics of neurodegenerative diseases

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Neurodegenerative disorders are characterised by the chronic progressive degeneration of specific neuronal subtypes, neuroinflammation, myelin damage and synaptic loss. Despite their growing incidence, advancements in effective treatments remain limited, because of lack of knowledge for the aetiology of the diverse pathophysiology to design systematic therapies. Several studies highlight the role of neurotrophic factors (NTFs) as potential neuroprotective, regenerative therapies for these disorders. Although NTFs hold protective and regenerative potential for chronic neuroinflammatory and neurodegenerative conditions, major hurdles impair their clinical use, such as optimising the dosage of NTFs, minimising the invasiveness of delivery methods, overcoming blood-brain-barrier (BBB) impermeability and managing side effects. In the last two decades our group have synthesised and screened a large chemical library of steroidal analogues of **dehydroepiandrosterone** (DHEA), an endogenous steroid hormone, for their ability to mimic neurotrophin neuroprotective and neurogenic actions. Interestingly, DHEA was shown to interact with all neurotrophin receptors, acting most probably as an ancestral neurotrophin early in evolution. However, its chronic pharmacological use is questioned by its action as a major precursor of steroidogenesis. This review highlights the findings of numerous preclinical studies on these synthetic, non-toxic, BBB permeable DHEA derivatives, named microneurotrophins (MNTs), deprived of endocrine actions, activators of specific neurotrophin receptors. The multimodal actions of MNTs against neuronal death and activation of microglia, in addition to their beneficial effects in synaptogenesis and neurogenesis, place them as interesting lead molecules in the armamentarium of therapeutics for neurodegeneration.

KEYWORDS
Alzheimer's disease, amyotrophic lateral sclerosis, BDNF, diabetic retinopathy, microneurotrophins, multiple sclerosis, NGF, p75 neurotrophin receptor, Parkinson's disease, Trk receptors

Abbreviations: AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; APP, Amyloid precursor protein; DHEA, Dehydroepiandrosterone; DR, Diabetic retinopathy; EAE, Experimental Autoimmune Encephalomyelitis; GDNF, Glial cell-line derived neurotrophic factor; hNPC, human neural progenitor cell; MS, Multiple sclerosis; NGF, Nerve growth factor; NSC, neural stem cell; NT3, Neurotrophin 3; PD, Parkinson's disease; RGC, retinal ganglion cell; Trk, tropomyosin receptor kinase.

1 | INTRODUCTION

Neurodegenerative diseases are characterised by the progressive neuronal loss, resulting in significant impairment of nervous system function and represent a major global health challenge. Neurodegeneration and neuroinflammation are fundamental hallmarks of central nervous system (CNS) disorders (Ransohoff, 2016). Neurodegenerative diseases, including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and, in acute cases, spinal cord injury (SCI,) remain incurable and impose substantial costs on both individuals and society (Lindvall & Kokaia, 2010; M. Metcalfe et al., 2017; Przedborski et al., 2003). The most common are dementias, with AD and PD, with their incidence rising significantly as the world's population ages. Currently, an estimated 50 million people worldwide are affected by neurodegenerative diseases, and this number will rise to 115 million by 2050 ('The Challenge of Neurodegenerative Diseases in an Aging Population,' 2017).

At present, available therapeutic options are insufficient to reverse or even halt the progression of neurodegenerative processes (Frozza et al., 2018; Volkman & Offen, 2017). Additionally, the development of effective therapies is hindered by the complexity of the pathogenic mechanisms underlying neuronal loss and the conflicting pathological causes of these diseases. Furthermore, the aetiology of sporadic neurodegenerative diseases is unknown, rendering the design of effective systematic therapies for each one a daunting task. The challenge is further exacerbated by the significant limitations faced by most therapeutic agents, particularly their inability to effectively cross the blood–brain barrier (BBB) (Ebrahimi et al., 2020; Zlokovic, 2008).

Neurotrophins are polypeptide growth factors that regulate key neuronal functions during development and adulthood, including cell differentiation, proliferation, survival, axonal growth and synaptic plasticity. The neurotrophin family includes **nerve growth factor** (NGF), **brain derived neurotrophic factor** (BDNF), and **neurotrophins 3** and 4/5 (NT-3, and **NT-4/5**). They exert their effects via binding to their specific high-affinity membrane receptors: **TrkA** (for NGF), **TrkB** (for BDNF and NT4/5) and **TrkC** (for NT3). Additionally, all neurotrophins can bind with lower affinity to the pan-neurotrophin receptor, **p75NTR** (Barker, 2004; Bibel et al., 1999), while their immature, pro-apoptotic isoforms, pro-neurotrophins, present high affinity for the $p75^{NTR}$-Sortilin complex (Jansen et al., 2007). Released by target tissues, they prevent presynaptic neurons from undergoing apoptosis and promote the differentiation of progenitor cells into neurons (Allen & Dawbarn, 2006; Huang & Reichardt, 2001). Their complex signalling pathways play crucial roles in cell physiology and are essential for understanding various diseases (Chao et al., 2006; Numakawa & Odaka, 2022; Reichardt, 2006). Numerous studies have demonstrated that the processing and expression levels of neurotrophins are dysregulated in MS, AD, PD and ALS, contributing significantly to degenerative pathology (Budni et al., 2015; Jiao et al., 2016; Just-Borràs et al., 2022; Karimi et al., 2022; Lorigados Pedre et al., 2002). Hence, the specific role of neurotrophins in each of these disorders and their therapeutic potential has been extensively examined, showing promising results. However, natural neurotrophins have short half-lives, difficulty in crossing the BBB and poor pharmacokinetic profiles. Thus, research interest turned to the synthesis of small molecules that mimic neurotrophins action and selectively activate Trk receptors in order to be used as therapeutic agents in neurodegenerative disorders (Josephy-Hernandez et al., 2017). In this context, our group have synthesised and identified novel small steroidal derivatives of DHEA, an endogenous hormone precursor, that interact with the TrkA, TrkB and p75 neurotrophin receptors, exhibiting similarities to certain actions of NGF and/or BDNF, such as the protection of specific neuronal populations from degeneration (Calogeropoulou et al., 2009; Pediaditakis, Efstathopoulos, et al., 2016). These highly lipophilic molecules demonstrate significant potential as therapeutic agents against neurodegenerative diseases, as they can selectively mimic specific beneficial neurotrophic actions and pass the BBB while circumventing undesirable side effects.

Here, we provide a comprehensive overview of the role of neurotrophins and their prospective therapeutic uses in treating neurodegenerative diseases such as MS, AD, PD and ALS. We summarise the different approaches of NTFs administration to animal models or to patients suffering from neurodegenerative diseases, demonstrating the limitations holding NTFs back from successful clinical use. Building on these insights, we also review key studies that highlight the innovative potential of our small-molecule synthetic microneurotrophins. These compounds are uniquely capable of crossing the blood–brain barrier (BBB), selectively activating neurotrophin receptors, and mimicking the activity of endogenous neurotrophins—without eliciting the adverse effects typically associated with natural neurotrophins or endogenous steroids. These studies highlight the promising potential of synthetic microneurotrophins as groundbreaking therapeutic agents for various neurodegenerative disorders.

2 | NEUROTROPHINS AND THEIR RECEPTORS IN NEURODEGENERATIVE DISEASES: INVOLVEMENT IN NEURONAL DEATH, NEUROINFLAMMATION, DEMYELINATION AND NEUROGENESIS

2.1 | Alzheimer's disease (AD)

Alzheimer's Disease (AD) is a neurodegenerative disorder, the most common type of all dementias, marked by severe memory loss, cognitive decline and impaired ability to perform daily tasks (Prince et al., 2015). The main hallmarks of the disease include extracellular amyloid plaque deposition and intracellular hyperphosphorylated neurofibrillary tau tangles. Neurotrophins play a significant role in AD progression, with NGF emerging as a critical regulator of cholinergic neurons (Figure 1), whose degeneration characterises late-stage AD (J. Allen et al., 2011; Durany et al., 2000; Ginsberg et al., 2006; Hock et al., 2000; Michalski & Fahnestock, 2003; Peng et al., 2004). Reduced levels of BDNF in the AD brain imply impaired neurotrophic

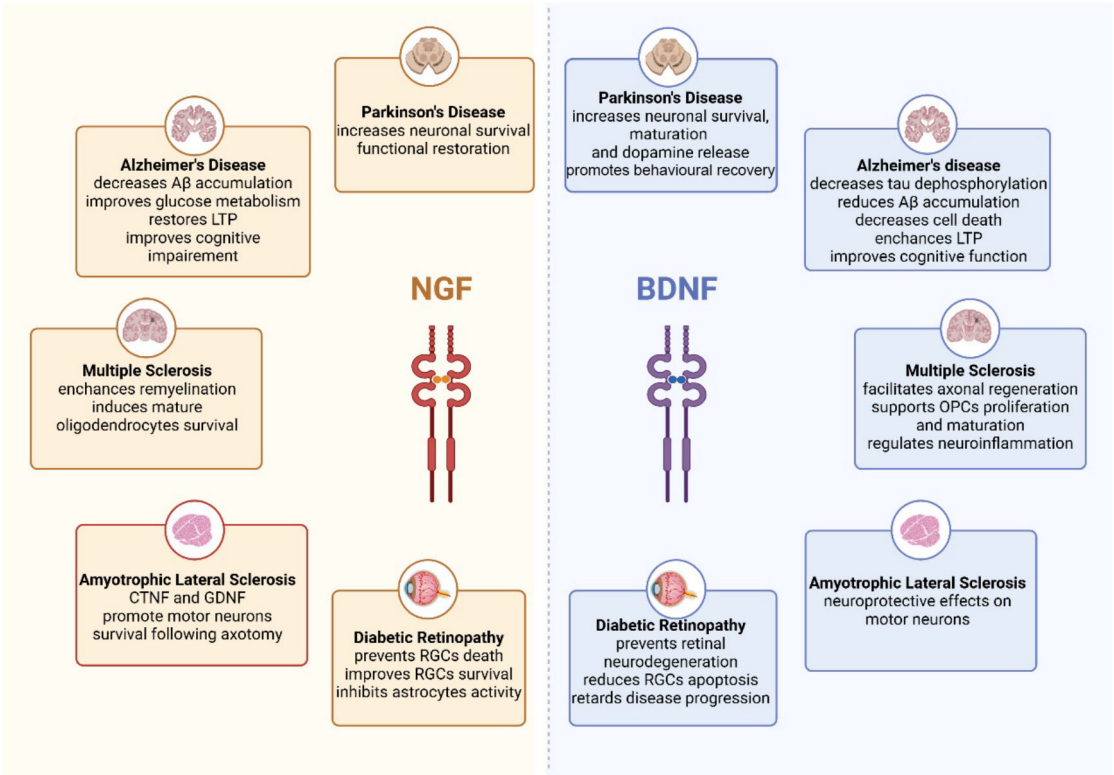

FIGURE 1 Schematic representation of the roles of neurotrophins NGF and BDNF in the treatment of neurodegenerative diseases. Created in BioRender.

support, possibly exacerbating neurodegeneration, while evidence indicates that enhancing BDNF signalling could improve cognition (Arancibia et al., 2008; Ibrahim et al., 2022; Jiao et al., 2016; Nagahara & Tuszynski, 2011). Elevated serum BDNF levels have also been linked to cognitive restoration (Weinstein et al., 2014). Moreover, signalling through p75NTR plays a key role in neurodegeneration associated with various diseases. Hence, the correlation between p75NTR and AD has been a subject of particular scrutiny in research.

Numerous studies highlight the therapeutic potential of NGF in AD (Aloe et al., 2015; Chan et al., 2004; Mitra et al., 2019; J. Wang et al., 2020). Reduced NGF levels in the nervous system and cerebrospinal fluid (CSF) of AD patients correlate with cholinergic degeneration, a hallmark of the disease (Budni et al., 2015; Francis et al., 1999). Mouse models lacking NGF or its high affinity TrkA receptor exhibit decreased choline O-acetyltransferase (**ChAT**) expression and cholinesterase activity in the basal forebrain and hippocampus (Crowley et al., 1994). Chronic NGF infusion restores long-term potentiation (LTP) in aged, cognitively impaired rats, further supporting its critical role in the CNS (Lübke et al., 2021; Villoslada et al., 2000). Additionally, reduced cortical TrkA levels are associated with lower cognitive performance in AD patients (Counts et al., 2004). This evidence suggests that declines in NGF and TrkA in the cortex and nucleus basalis of Meynert (nbM) could serve as early markers of AD onset (Mufson et al., 2012).

De-regulation of NGF is implicated in AD (Biernacki et al., 2005; Cattaneo & Calissano, 2012). In AD, deficits in NGF and degeneration of the basal forebrain cholinergic system are closely associated with cognitive decline and dementia (Iulita & Cuello, 2014). NGF facilitates the non-amyloidogenic cleavage pathway of amyloid precursor protein (APP), thereby reducing amyloid β-peptide (**Aβ**) generation in mouse brains (Yang et al., 2014). Interestingly, higher NGF levels have been detected in the CSF and dentate gyrus of AD patients compared to controls (Budni et al., 2015; Faria et al., 2014). Clinical trials reveal that NGF treatment resulted in lower Aβ1–42 levels in the CSF (Andreasen et al., 1999; Ferreira et al., 2015). NGF gene transfer therapy in early-stage AD patients showed axonal extensions towards the NGF source and activation of CREB and c-Fos markers (Tuszynski et al., 2015). Additionally, NGF administration improved brain activity, glucose metabolism, cognition and clinical status, while reducing brain atrophy and elevating CSF Aβ1-42 levels (Ferreira et al., 2015).

ProNGF, the precursor of NGF, plays a critical role in AD, with alterations in its levels linked to cognitive dysfunction in key brain regions, including the frontal cortex, posterior cingulate, superior temporal cortex and hippocampus (Mufson et al., 2012; Perez et al., 2014; Sperling et al., 2014). Accumulation of proNGF in the preclinical stages of AD correlates with cognitive decline (Peng et al., 2004) and contributes to neuronal degeneration through its preferential binding to cell death p75NTR receptor, bypassing the pro-survival effect of TrkA interaction (Al-Shawi et al., 2008; Ioannou & Fahnestock, 2017). Pan-neurotrophin p75NTR receptor is highly expressed in adult basal forebrain cholinergic neurons, which are among the earliest to degenerate in AD. The balance of pro-survival versus pro-apoptotic

signalling in these neurons may depend on TrkA and p75NTR stoichiometry, co-receptor availability and the physiological role of proNGF in different contexts (Bruno et al., 2004; F. Longo et al., 2008; F. M. Longo et al., 2007).

Studies highlight the critical role of p75NTR in AD pathogenesis, including its involvement in Aβ deposition (Y. J. Wang et al., 2011; Yao et al., 2015) and tau hyperphosphorylation (Shen et al., 2019), implicating the receptor in disease progression (Zeng et al., 2011). In vitro research demonstrates that Aβ-amyloid, a key component in AD brains, binds p75NTR, inducing pro-apoptotic effects (Knowles et al., 2009; Saadipour et al., 2013; Yaar et al., 1997). Notably, Yao et al. (2015) observed a significant reduction in p75ECD levels in the cerebrospinal fluid (CSF) and brains of AD patients and APP/PS1 transgenic mice. Another study reported elevated serum but reduced CSF p75ECD levels in AD patients compared to a control group, suggesting p75ECD as a potential AD biomarker. Notably, a small molecule that modulates p75NTR activity has successfully completed Phase 2a in patients with AD (Shanks et al., 2024).

BDNF is in the centre of research interest in AD because of the widespread expression of its receptor, TrkB, in the CNS and its critical role in neurogenesis, synaptic plasticity and repair (De la Rosa et al., 2019; Kramár et al., 2012; Miranda et al., 2019; Pencea et al., 2001). BDNF–TrkB signalling also regulates adult hippocampal neurogenesis, a process severely affected in AD (Colucci-D'Amato et al., 2020; Moreno-Jiménez et al., 2019; Salta et al., 2023; Vilar & Mira, 2016). Elevated serum BDNF levels in early-stage AD patients correlate with reduced cognitive decline (Buchman et al., 2016; Laske et al., 2011). Additionally, BDNF has demonstrated protective effects against amyloid-beta-induced neurodegeneration and demyelination in in vitro and in vivo models (Arancibia et al., 2008; Mitroshina et al., 2020; Nagahara et al., 2009; Zota et al., 2024). Its stimulation induces the de-phosphorylation of tau protein and shifts APP processing towards a non-amyloidogenic pathway (Jiao et al., 2016; Nigam et al., 2017). These findings highlight BDNF signalling as a potential therapeutic target for AD (Azman & Zakaria, 2022; Gao et al., 2022).

Reduced BDNF levels in the AD brain indicate insufficient neurotrophic support, potentially exacerbating neurodegeneration. Evidence suggests that enhancing BDNF signalling may improve cognition in AD (Arancibia et al., 2008; Jiao et al., 2016). In a mouse model with AD-like pathology, cognitive improvement from stem cell transplantation was lost when BDNF was depleted, but ectopic BDNF expression restored cognitive function (Blurton-Jones et al., 2009). Additionally, the Val66Met polymorphism in BDNF, common in Caucasian and higher in Asian populations, impairs BDNF sorting, transport and secretion, leading to hippocampal dysfunction (Kuczewski et al., 2010). Both sporadic and familial AD cases with this polymorphism exhibit faster cognitive decline, hippocampal atrophy and altered CSF tau levels, highlighting the potential of boosting BDNF signalling to enhance synaptic plasticity and cognition in AD (Boots et al., 2017; Lim et al., 2018).

Studies suggest that blocking glutamatergic neurons with scopolamine or stimulating the GABAergic system reduces BDNF mRNA levels in the hippocampus (Connor et al., 1997; Da Penha Berzaghi et al., 1993). The cholinergic system, known to regulate BDNF mRNA levels, also plays a role in this process (Phillips et al., 1991). Given that both the glutamatergic and cholinergic systems degenerate in AD, this highlights BDNF's potential contribution to cognitive impairment in AD (Connor et al., 1997; Coyle et al., 1983; Lübke et al., 2021). Reduced BDNF mRNA levels in the hippocampus of AD patients may contribute to basal forebrain cholinergic neuron atrophy (Lübke et al., 2021; Phillips et al., 1991). Moreover, BDNF administration has shown promising effects, such as decreased Aβ production, repair of Aβ-induced damage, reduced cell death, improved cognitive function, synaptic loss mitigation, and slowed cognitive decline (Rohe et al., 2009; Li et al., 2012). The enhancement of memory and LTP through increased TrkB signalling and BDNF expression further suggests the therapeutic potential of BDNF in AD (Ji et al., 2010; Monteggia et al., 2004; Wan et al., 2014).

Postmortem studies consistently show reduced levels of BDNF in the brains of AD patients (Meng et al., 2013; Michalski & Fahnestock, 2003). Elevating BDNF levels through gene transfer in the entorhinal cortex enhances memory and spatial learning in various models, including APP transgenic mice, aged rats and APP/PS1/tau transgenic mice following neuronal stem cell transplantation in the hippocampus (Blurton-Jones et al., 2009; Lattanzio et al., 2014; Nagahara et al., 2009). Studies in APP/PS1 mice show increased neurogenesis and BDNF mRNA levels in the hippocampus (Hsiao et al., 2014). In AD hippocampus, postmortem analysis reveals lower levels of BDNF mRNA. Aβ protein, a hallmark of AD pathology, inhibits pro-BDNF conversion to BDNF and affects BDNF levels through tau hyperphosphorylation via calcineurin activation (Ramser et al., 2013). Aβ also impairs retrograde transport of the BDNF–TrkB complex via the enzyme ubiquitin C-terminal hydrolase L1 (Poon et al., 2013). In vitro, oligomeric Aβ significantly reduces BDNF expression (Garzon and Fahnestock, 2007; DaRocha-Souto et al., 2012; Rosa & Fahnestock, 2015). Aβ interaction with **PKA** activation also decreases CREB phosphorylation and BDNF expression (Rosa & Fahnestock, 2015; Colucci-D'amato et al., 2020). BDNF may also influence APP processing via the non-amyloidogenic α-secretase pathway in neuronal cell lines (Holback et al., 2005). Although the exact effects of BDNF on Aβ production remain unclear, co-treatment with BDNF in the hippocampus or entorhinal cortex prevents Aβ1–42-induced impairment of LTP, highlighting its neuroprotective potential (Arancibia et al., 2008; Criscuolo et al., 2015; Kitiyanant et al., 2012; Lübke et al., 2021). However, delivery of BDNF through intracerebroventricular injections or other non-invasive methods has been unsuccessful because of side effects or low effectiveness (Givalois et al., 2004; Kopec et al., 2020).

Neurotrophin-3 (NT-3) levels remain stable in both AD brain and cerebrospinal fluid (Durany et al., 2000; Hock et al., 1998, 2000a, 2000b; Murase et al., 1994; Phillips et al., 1991). NT-3 increases APP promoter activity by 3.82-fold in PC12 cells, compared to NGF, which causes a 5.81-fold increase (Ge & Lahiri, 2002) and protects primary cortical neurons from amyloid-beta toxicity by inhibiting caspase cleavage and enhancing Akt phosphorylation through PI-3K signalling (Lesné et al., 2005). Additionally, NT-3 promotes the expression of

neuronal apoptosis inhibitory protein-1, preventing amyloid-beta-induced apoptosis. In lesion models mimicking AD, NT-3 prevents degeneration of noradrenergic neurons in the locus coeruleus (Arenas & Persson, 1994). Moreover, NT-3 overexpression facilitates the differentiation of bone marrow-derived mesenchymal stem cells (BMSCs) into neurons, improving cognitive function in AD model rats, whereas NT-3 silencing inhibits differentiation and exacerbates cognitive deficits (Yan et al., 2021). These findings suggest that NT-3 may have a therapeutic potential in neurogenesis and cognitive improvement in AD. However, its role appears less pivotal and versatile than NGF and BDNF in AD pathophysiology and treatment.

2.2 | Parkinson's disease (PD)

PD is an age-related, highly heterogeneous neurodegenerative condition characterised by progressive loss of nigrostriatal dopaminergic (DA) neurons in the midbrain that leads to severe movement deficits and degeneration of peripheral DA neurons that mediates non-motor symptoms. The main pathological feature of PD is the presence of eosinophilic cytoplasmic inclusions in neurons, known as Lewy bodies, which primarily consist of aggregates of misfolded **alpha-synuclein** (a-syn) protein (Obeso et al., 2010; Wakabayashi et al., 2007). Currently, there are only symptomatic therapies without alleviation of disease progression.

Given the absence of a disease-modifying therapy for PD (AlDakheel et al., 2014), neurotrophins have elicited great interest as potential therapeutic agents (Figure 1). Several studies have reported reduced NGF and BDNF levels in rodent models and PD patients, correlating them with the disease progression (Fumagalli et al., 2006; Howells et al., 2000; Lorigados et al., 1992; Mogi et al., 1999). Interestingly, in the late stages of the disease, BDNF levels appear to increase, likely reflecting a compensatory mechanism to counteract neuronal damage (Teixeira et al., 2010). BDNF is essential for the maturation and survival of dopamine (DA) neurons, promoting DA release, presynaptic reuptake (Bosse et al., 2012) and protection against neurotoxic insults in both in vitro and in vivo models (Hyman et al., 1991; Tsukahara et al., 1995; Levivier et al., 1995; Yoshimoto et al., 1995). Additionally, BDNF enhances behavioural recovery in rats (Singh et al., 2006) and exhibits anti-apoptotic, anti-oxidative, autophagy-suppressing, and mitochondrial-restorative properties (S. Chen et al., 2017; Miller et al., 2021). Nevertheless, NGF showed initial promise in PD resulting in a longer graft survival after transplantation in putamen and increased functional restoration (Olson et al., 1991; Chaturvedi et al., 2006). However, poor adrenal graft survival and minimal behavioural improvements in clinical studies have stalled its therapeutic development (Hurtig et al., 1989; Peterson et al., 1989).

Glial cell-line derived neurotrophic factor (GDNF), widely recognised as the most potent neurotrophic factor for DA neurons, has shown conflicting results regarding its necessity for their survival in adulthood (Enterría-Morales et al., 2020; Kopra et al., 2015; Pascual et al., 2008). However, its receptor **RET** is essential for the maintenance of adult DA neurons (Kramer et al., 2007). GDNF demonstrates neurorestorative potential, promoting recovery of damaged DA neurons even when administered several weeks after neurotoxin treatment (Aoi et al., 2000). It surpasses BDNF in promoting the survival of SN pars compacta (SNpc) DA neurons in lesioned animal models (Lu & Hagg, 1997; Rosenblad et al., 2000; Sun et al., 2005). Furthermore, macrophage-mediated GDNF delivery protects against neurodegeneration and reverses motor and non-motor deficits in non-toxin PD models (C. Chen et al., 2019). Various delivery approaches, including infusion (Kirik et al., 2004), GDNF-producing cell transplantation (Shingo et al., 2002) and viral-mediated delivery (Björklund et al., 2000), provide neuroprotective effects in DA neurons in 6-OHDA and MPTP models in rodents and primates (Grondin et al., 2003; Palfi et al., 2002). However, clinical trials in PD patients have yielded unsatisfactory outcomes (Lang et al., 2006; Patel et al., 2013; Whone et al., 2019). Despite these limitations, neurotrophic factor-based therapies remain promising, although their clinical translation faces significant challenges (Chmielarz & Saarma, 2020).

2.3 | Multiple Sclerosis (MS)

MS is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS) (Dobson & Giovannoni, 2019). The aetiology of MS remains unknown, but it likely involves a combination of genetic predisposition and exogenous stimuli. MS pathology is characterised by an altered multidirectional interaction among different immune cell types in the periphery and resident CNS cells, associated with the formation of a glial scar and the focal destruction of the myelin sheath (Bennett & Stüve, 2009; Lucchinetti et al., 1996; McFarland & Martin, 2007). Despite extensive research, a compelling treatment is still elusive, especially for the progressive form of the disease (D'Amico et al., 2016; Ontaneda et al., 2015).

Several studies showed that neurotrophins NGF, BDNF and NT-3 exert an important role in the pathophysiology of MS (Gold et al., 2006) (Figure 1). Administration of BDNF and NT-3 is associated with an increase in the neuronal survival in Experimental Autoimmune Encephalomyelitis (EAE)-induced demyelination (Mo et al., 2010; Yan et al., 1992). EAE is characterised by severe loss of oligodendrocytes and consequent demyelination, probably caused by autoimmune components. Moreover, administration of NT-3 decreases demyelination volume and increases the number of mature oligodendrocytes (OL) in the lysophosphatidylcholine (LPC)-induced demyelination model (Jean et al., 2003), while NGF enhances remyelination in the same model (Althaus, 2004). NGF promotes the survival of mature oligodendrocytes (OL) (Cohen et al., 1996) and prevents the TNFa-induced oligodendrocytes (OL) cell death, limiting the loss of mitochondrial membrane potential (LMP) (Takano et al., 2000). Notably, deficient p75NTR expression alters the composition of cellular infiltrates and exacerbates symptoms in EAE (Copray et al., 2004; Küst et al., 2006) while enhanced expression of NGF and its receptors was shown in human MS lesions (Aloe, 1998; Aloe et al., 1994; Hurtig

et al., 1989; Laudiero et al., 1992; Peterson et al., 1989; Valdo et al., 2002).

BDNF is the most extensively studied neurotrophin in MS because of its neuroprotective and anti-inflammatory roles (Nociti, 2020). It enhances oligodendrocyte lineage cells, promotes myelin protein synthesis and facilitates axonal regeneration in rodent models (Fulmer et al., 2014; Gravel et al., 1997; McTigue et al., 1998). Exogenous BDNF administration via injection of BDNF-overexpressing T cells at lesion sites reduces EAE severity and provides direct axonal protection (Linker et al., 2010). In demyelinating conditions, BDNF supports oligodendrocyte progenitor proliferation and maturation (Tsiperson et al., 2015; Vondran et al., 2011; Wong et al., 2014) and regulates neuroinflammation via hedgehog and erythropoietin pathways, influencing astrocyte–microglia endogenous crosstalk (Lai et al., 2018). It also downregulates **COX2** and pro-inflammatory cytokines in microglia (Han et al., 2021). However, the therapeutic use of natural neurotrophins is limited by their inability to cross the BBB, poor pharmacokinetic stability and side effects such as dose-dependent hyperalgesia and obesity (Sandrini et al., 2018; Yi et al., 2014). Hence, the development of novel therapeutic candidates that mimic the biological properties of natural neurotrophins while overcoming the aforementioned limitations remains a critical research priority.

2.4 | Amyotrophic lateral sclerosis (ALS)

ALS is a progressive neurodegenerative disease caused by loss of motor neurons. Patients with ALS experience rapid deterioration in muscle function, with an average life expectancy of 3 to 5 years following diagnosis. Currently, there is no cure for ALS. The most effective therapy is a benzothiazole derivative that blocks glutamatergic neurotransmission, Riluzole, which prolongs survival by a few months, thus highlighting the need for new and more efficient drugs. Reduced levels of NTFs have been reported in ALS (Anand et al., 1995; Lee et al., 1996; Nishio et al., 1998; Ono et al., 1999), suggesting that loss of trophic support could be important in disease pathophysiology.

Preclinical studies in ALS mouse models have demonstrated the potential efficacy of NTFs such as BDNF, **CNTF** and GDNF (Figure 1) (Acsadi et al., 2002; Bemelmans et al., 2006; Ikeda et al., 1995; Li et al., 2007; Mohajeri et al., 1999; Park et al., 2009; Sendtner et al., 1990, 1992; Suzuki et al., 2007; Yan et al., 1992). Investigations into the role of BDNF and its receptor TrkB in ALS have revealed variable expression patterns in Sod1 mutant mice and ALS patients. In mouse models, muscle BDNF levels have been reported to decrease (Harandi et al., 2016) or increase (Just-Borràs et al., 2019). In ALS patients, BDNF levels increased in muscles but remained unchanged in the spinal cord and CSF (Grundström et al., 2000; Kawamoto et al., 1998; Riolo et al., 2022). Serum BDNF levels showed variability, being reported as increased (Riolo et al., 2022) or unaltered (Cao et al., 2022; Tremolizzo et al., 2016). TrkB levels declined in SOD1-G93A mouse muscle (Harandi et al., 2016; Just-Borràs et al., 2019) but increased in ALS patient spinal cords, albeit with reduced activation (Mutoh et al., 2000). These inconsistent and even opposing changes in BDNF and TrkB expression suggest dysregulated signalling, which may represent either adaptive or maladaptive responses to ALS progression (Just-Borràs et al., 2019; Rei et al., 2022).

BDNF, known for its neuroprotective effects on motor neurons (Koliatsos et al., 1993), advanced into ALS clinical trials via subcutaneous and intrathecal administration (American Neurological Association, 1995; Ochs et al., 2000). However, neither systemic BDNF (25 or 100 μg kg^{-1}) nor its intrathecal delivery showed significant clinical benefits in phase III trials (BDNF Study Group, 1999; Kalra et al., 2003; Beck et al., 2005). Trials using BDNF-secreting cells also failed to improve motor function (Park et al., 2009; J. Wang et al., 2021). These failures may result from the limited ability of BDNF to cross the BBB (Pan et al., 1998; Pardridge, 2003; Poduslo & Curran, 1996) and its capability to activate the p75 receptor, associated with ALS pathophysiology and apoptosis (Lowry et al., 2001; Dupuis et al., 2008b). Notably, p75NTR antagonist slowed ALS progression in SOD-1 mice (Turner et al., 2004), suggesting that pro-apoptotic signalling may counteract BDNF's therapeutic effects. Further, post-trial studies using gene therapy in SOD-1 mice found no effect on disease progression or survival (Park et al., 2009), questioning BDNF's clinical utility.

Ciliary neurotrophic factor (CNTF) has long been known to play a neuroprotective role in several regions of the nervous system. CNTF promotes motor neurons survival in cell or organotypic cultures (Arakawa et al., 1990; Corse et al., 1999), and in vivo after axotomy-induced apoptosis in the rodent (Sendtner et al., 1991, 1994; Thau et al., 2012), while its deletion in mouse models leads to increased vulnerability of motor neurons and atrophy (Giess et al., 2002; Masu et al., 1993). These promising data paved the way for the first clinical trials of CNTF administration for ALS treatment. However, none of these trials had a significant effect on daily living activities outcomes and survival of ALS patients (ALS CNTF Treatment Study Group, 1996; Miller et al., 1996; Turner et al., 2001).

GDNF was investigated later than CNTF and BDNF, with preclinical studies demonstrating motor neuron rescue following axotomy and excitotoxic stress (Bilak et al., 2001; Buj-Bello et al., 1995; Giménez Y Ribotta et al., 1997; Kosuge et al., 2009). In the SOD-1 animal model of ALS, GDNF showed motor neuron protection but yielded variable outcomes on survival and neuromuscular junction integrity (Acsadi et al., 2002; Li et al., 2007; Mohajeri et al., 1999; Park et al., 2009; Suzuki et al., 2007). Although some studies reported improved disease progression and survival, others found no significant benefits (Acsadi et al., 2002; Park et al., 2009). Clinical trials using direct GDNF protein injections via subcutaneous or intrathecal routes showed no therapeutic effects because of its short half-life and limited tissue diffusion (Alisky & Davidson, 2000). A recent phase I/II trial addressed these limitations by injecting human neural progenitor cells (hNPC) engineered to secrete GDNF into the lumbar spinal cord, demonstrating safety and localised expression (Baloh et al., 2022). Based on evidence supporting cortical delivery, a new clinical trial is evaluating hNPCs–GDNF in the motor cortex.

2.5 | Diabetic retinopathy (DR)

DR is one of the most common long-term complications of diabetes that results in loss of visual acuity and blindness. Its multifactorial pathogenesis involves endothelial dysfunction, disruption of the blood-retinal barrier, oxidative stress, and inflammation driven by reactive oxygen species, advanced glycation end products, and a plethora of inflammatory mediators (Kowluru et al., 2015; Kowluru & Chan, 2007; Yu et al., 2015). Additionally, imbalance of retina's homeostatic equilibrium significantly contributes to DR development (Antonetti et al., 2012).

The imbalance between pro-survival neurotrophic factors and inflammatory components contributes to apoptosis and pro-inflammatory responses in DR (Antonetti et al., 2006). Alterations in NGF and BDNF levels have been observed in both patients and animal models of DR (Ali et al., 2011; Kaviarasan et al., 2015; Mysona et al., 2015; Ola et al., 2013). A proNGF/NGF imbalance marked by proNGF accumulation and reduced NGF levels has been implicated in retinal inflammation, neurodegeneration and BBB integrity (Al-Gayyar et al., 2011, 2013; Ali et al., 2011; Mysona et al., 2015). NGF administration prevents ganglion cell death in diabetic rats and restores TrkA levels in the retina, protecting retinal ganglion cells (RGCs) from degeneration in experimental model of diabetes (Colafrancesco et al., 2011; Hammes et al., 1995). Topical ophthalmic administration of NGF also protects RGCs in an animal model of glaucoma, in patients with glaucoma (Lambiase et al., 2009) and in the streptozotocin (STZ) model of DR (Mantelli et al., 2014). Furthermore, topical application of recombinant human-NGF significantly improves RGC survival and inhibits astrocyte activity in the optic nerve in a rat model of DR (Guo et al., 2020). These findings highlight the potential of NGF restoration as a therapeutic strategy to counteract early diabetic retinopathy.

Hyperglycaemia-mediated increased secretion of glucocorticoids and pro-inflammatory cytokines down-regulate the levels of BDNF (Kumamaru et al., 2008; Numakawa et al., 2010). Down-regulation of BDNF neuroprotective actions under hyperglycaemia renders retinal neurons vulnerable to damaging stimuli, leading to diabetic retinopathy (Ola et al., 2013). BDNF administration protects retinal neurons from hyperglycaemia in a dose-dependent manner in vitro (Liu et al., 2013). BDNF can also efficiently rescue DA amacrine cells from neurodegeneration and counteract the down-regulation of tyrosine hydroxylase (TH) levels seen under diabetic conditions in vivo (Seki et al., 2004). Intravitreal injections of pAAV-BDNF reduced RGC apoptosis and improved function in STZ-induced diabetic rats (Gong et al., 2012). Hence, restoring BDNF levels, either by counteracting hyperglycaemia-induced pathologic factors or administering exogenous BDNF, may prevent retinal neurodegeneration and retard disease progression. However, randomised, double-blind, placebo-controlled trials failed to demonstrate significant effects of subcutaneous NGF or BDNF injections for diabetic polyneuropathy (Apfel et al., 2000; Wellmer et al., 2001).

It is of interest that during retinal degeneration because of glaucoma or optic nerve transection, treatment with a mutant NGF that only activates TrkA, or with a biological response modifier that prevents endogenous NGF and pro-NGF from binding to the p75NTR receptor, affords significant neuroprotection. On the contrary, treatment of normal eyes with an NGF mutant-selective p75NTR agonist causes progressive RGC death, and in injured eyes accelerated RGC death (Bay et al., 2010). The intravitreal or subconjunctival depot of THX-B, a small molecule antagonist of the p75NTR receptor, was therapeutic and resolved the inflammatory, vascular and neurodegenerative phases of the retinal pathology of diabetic retinopathy (Galan et al., 2017; Platón-Corchado et al., 2017). Another approach used an engineered NT3-based mutant that broadly activates TrkA, TrkB and TrkC receptors while minimising $p75^{NTR}$ receptor binding provides enhanced neuroprotection in vivo by selectively promoting Trk-mediated pro-survival signalling and avoiding $p75^{NTR}$-induced toxicity in neurodegenerative disease models (Brahimi et al., 2021). Furthermore, targeting TrkC.T1 with isoform-selective small-molecule antagonists effectively reduces NT3-induced neurotoxicity, suppresses TNF-α elevation and preserves photoreceptors in a retinitis pigmentosa model, highlighting a novel therapeutic strategy centred on the modulation of receptor isoform-specific signalling to achieve neuroprotection (Brahimi et al., 2025).

3 | NEUROTROPHIN MIMETICS: A NOVEL APPROACH IN PHARMACOLOGY OF NEURODEGENERATION

3.1 | DHEA as an ancestral neurotrophin

In the early 1980s, Etienne Baulieu discovered the ability of neurons and glia to locally produce steroids by metabolising hormone precursors or synthesising steroids from cholesterol (Baulieu & Robel, 1990). Neurosteroids, produced by neurons, astrocytes and neuroglial cells, in the central and peripheral nervous systems, influence neuronal activity and differentiation, provide neuroprotection and promote neurogenesis (Compagnone & Mellon, 2000). The initiation of neurosteroid activities is thought to occur through the activation of receptors such as **$GABA_A$**, **NMDA** and **sigma-1** (Charalampopoulos, Margioris, & Gravanis, 2008; Charalampopoulos, Remboutsika, et al., 2008; Compagnone & Mellon, 2000).

Dehydroepiandrosterone (DHEA), the first characterised neurosteroid, serves as a precursor for androgens and oestrogens. Synthesised by the cytochrome 17 enzyme (CYP17) from cholesterol, its biosynthesis occurs in the gonads, adrenal glands and locally in the brain. Adrenal DHEA has a systemic function, while brain-generated DHEA acts locally in a paracrine manner, with age-dependent synthesis peaking in early adulthood and declining over time, especially in neurodegenerative diseases like Alzheimer's (Baulieu, 1998; Schumacher et al., 2003; Weill-Engerer et al., 2002).

Although no specific DHEA receptor was identified during the first decades of its characterisation, early studies revealed that DHEA is recognised with high affinity and a Kd at nanomolar level by membrane binding sites, mediating the activation of MEK/ERK and PI3K/Akt post-receptor signalling pathways, leading to the phosphorylation and mobilisation of transcription factors CREB and NFkappaB. The

latter control the transcription of anti-apoptotic **Bcl-2** proteins or the phosphorylation/deactivation of pro-apoptotic Bad proteins, protecting neuronal cells from apoptosis (Charalampopoulos et al., 2004, 2006; Charalampopoulos, Remboutsika, et al., 2008). PC12 cells, lacking $GABA_A$ or NMDA receptors and unable to metabolise DHEA into sex hormones, serve as a model for studying the membrane effects of DHEA in neuronal cell types (Greene & Tischler, 1976). DHEA, like NGF, prevents apoptosis through strikingly similar signal transduction pathways, suggesting a role for NGF receptors in the anti-apoptotic action of DHEA (Lazaridis et al., 2011; Riccio et al., 1999). Our group provided evidence that DHEA binds with high affinity (Kd at nanomolar level) and activates both membrane receptors of NGF, specifically TrkA and p75NTR, marking the first evidence of direct steroid binding to neurotrophin receptors (Lazaridis et al., 2011). Upon DHEA binding to TrkA, the receptor undergoes autophosphorylation at tyrosine residues, initiating a signalling pathway involving Shc-PI3K-Akt and Src-MEK–ERK kinases. Additionally, DHEA binding to the p75NTR receptor influences its interaction with effector proteins, such as TRAF6, **RIP2** and **RhoGDI**. The balance between TrkA and p75NTR receptors ultimately determines whether the cell will undergo apoptosis or survival (Lazaridis et al., 2011).

DHEA exhibits neuroprotective and pro-survival effects, promoting neurogenesis by increasing newly formed neurons in both rats and human neural stem cell (NSC) cultures. Its impact on NMDA and Sigma-1 receptors contributes to long-term NSC proliferation (Charalampopoulos, Remboutsika, et al., 2008). Pediaditakis et al. (2015) identified DHEA as an ancestral ligand for neurotrophin receptors, demonstrating its ability to interact with and activate vertebrate Trk receptors (TrkA and TrkC) and all invertebrate Trk receptors (Pediaditakis et al., 2015). Administration of DHEA to animal models of MS or PD had beneficial effects (Aggelakopoulou & Kourepini, 2016; Bélanger et al., 2006, 2006), which could be attributed to its neuroprotective (Charalampopoulos et al., 2004, 2006; Charalampopoulos, Margioris, & Gravanis, 2008; Charalampopoulos, Remboutsika, et al., 2008; Gravanis et al., 2012; Lazaridis et al., 2011; Maninger et al., 2009; Xie et al., 2019) as well as anti-inflammatory properties (Du et al., 2001; Maninger et al.,2009; Saijo et al., 2011; Straub et al., 1998; Hoyk et al., 2004; Hazeldine et al., 2010), including mitigation of microglia-mediated neuroinflammation (Alexaki et al., 2018; Saijo & Glass, 2011). However, the long-term administration of DHEA in these conditions has not proven beneficial, as it is metabolised in humans into oestrogens and androgens and their numerous metabolites, scrambling the endocrine system with potential side effects and increasing the risk for hormone-dependent neoplasias (Calogeropoulou et al., 2009; Compagnone & Mellon, 2000).

3.2 | DHEA derivatives as neurotrophin mimetics (microneurotrophins)

Based on the intriguing interactions of DHEA with the neurotrophin receptors system, our group designed, synthesised and screened a large chemical library of 17-spirocyclic steroidal analogues of DHEA for their ability to protect neurons against apoptosis and activate neurotrophin receptors (Figure 2). The rational design of the compound series left unchanged the 3β-OH group of DHEA because it is important for its neuroprotective properties (Calogeropoulou et al., 2009; Charalampopoulos et al., 2004), and the modifications were focussed on the C17 position important for steroidogenesis, thus avoiding steroid-like side effects. Synthetic 17-spiro derivatives of DHEA, devoid of endocrine effects (Calogeropoulou et al., 2009), form a novel group of non-toxic compounds capable of crossing the BBB and activating neurotrophin receptors, exerting in turn strong neuroprotective effects. Two BBB-permeable, 17-spiro-epoxy derivatives of DHEA, BNN27 and BNN20, were proven very effective as neuroprotective agents in various neuronal cell systems (Calogeropoulou et al., 2009). These analogues, termed 'microneurotrophins', act as activators of neurotrophin receptors.

BNN27 (17α,20R-epoxy-5-pregnene-3β,21-diol), the most studied microneurotrophin, derived from DHEA (Figure 2), activates the TrkA receptor by inducing its phosphorylation at tyrosine residues, initiating pro-survival signalling in cells (Pediaditakis, Efstathopoulos, et al., 2016). Binding studies confirm high affinity of BNN27 for both TrkA and p75NTR receptors, preventing apoptosis through the regulation of RhoGDI, TRAF6 and RIP2 protein interactions (Pediaditakis, Kourgiantaki, et al., 2016). BNN27 enhances the efficacy of low levels of NGF, promoting axonal outgrowth by facilitating the fast membrane re-entry of internalised TrkA receptor (Pediaditakis, Efstathopoulos, et al., 2016). Furthermore, BNN27 physically interacts with the p75NTR receptor in specific amino-residues of its extracellular domain, inducing survival of primary neuronal cells through the recruitment of p75NTR downstream effectors RIP2 and RhoGDI (Pediaditakis, Kourgiantaki, et al., 2016). Activation of p75NTR by BNN27 resulted also to anti-apoptotic effects, because of the decrease of phosphorylation of pro-apoptotic JNK kinase and to the cleavage of Caspase-3 in cerebellar granule neurons (Pediaditakis, Kourgiantaki, et al., 2016). Importantly, BNN27 does not show the hyperalgesic effects of NGF (Poulaki et al., 2021). BNN27 was also effective to enhance memory, to interact with the cholinergic system, to protect oligodendrocytes and myelin in demyelinating disorders, and provide therapeutic benefits for diabetic retinopathy by addressing neurodegeneration and inflammation (Bonetto et al., 2017; Ibán-Arias et al., 2018; Pitsikas & Gravanis, 2017).

3.2.1 | Microneurotrophins in animal models of neurodegenerative diseases

The aforementioned promising data of BNN27 action paved the way for extensive research on this microneurotrophin, as a potential lead molecule to develop a therapeutic strategy for a number of neurodegenerative diseases. Various microneurotrophins were thus tested in various animal models of human neurodegenerative diseases (mechanism of actions and effects are summarised in Figure 3). BNN27 inhibits apoptosis of NGF-deprived sympathetic neurons and reverses apoptosis of TrkA-sensory neurons in E13.5 NGF-deficient mouse embryos (Pediaditakis, Efstathopoulos, et al., 2016). Systemic

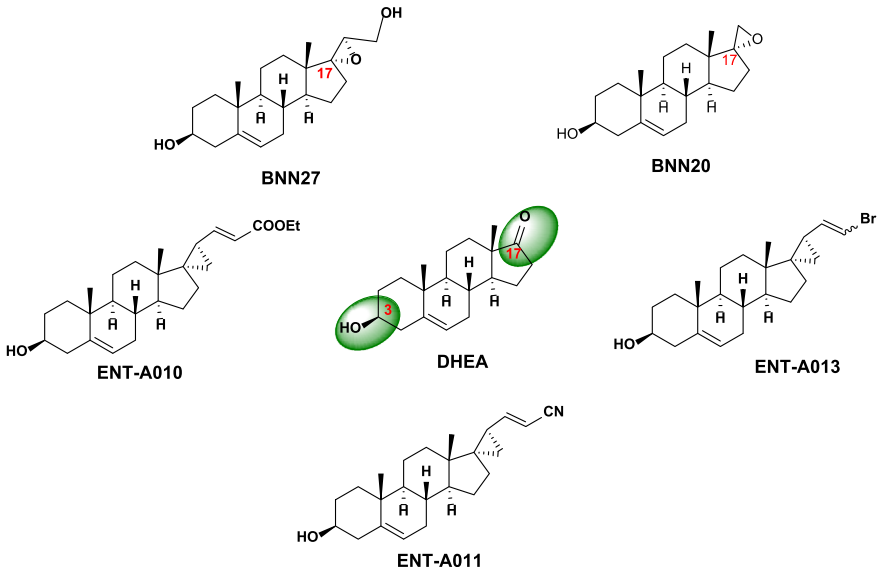

FIGURE 2 Chemical structure of potent synthetic microneurotrophins.

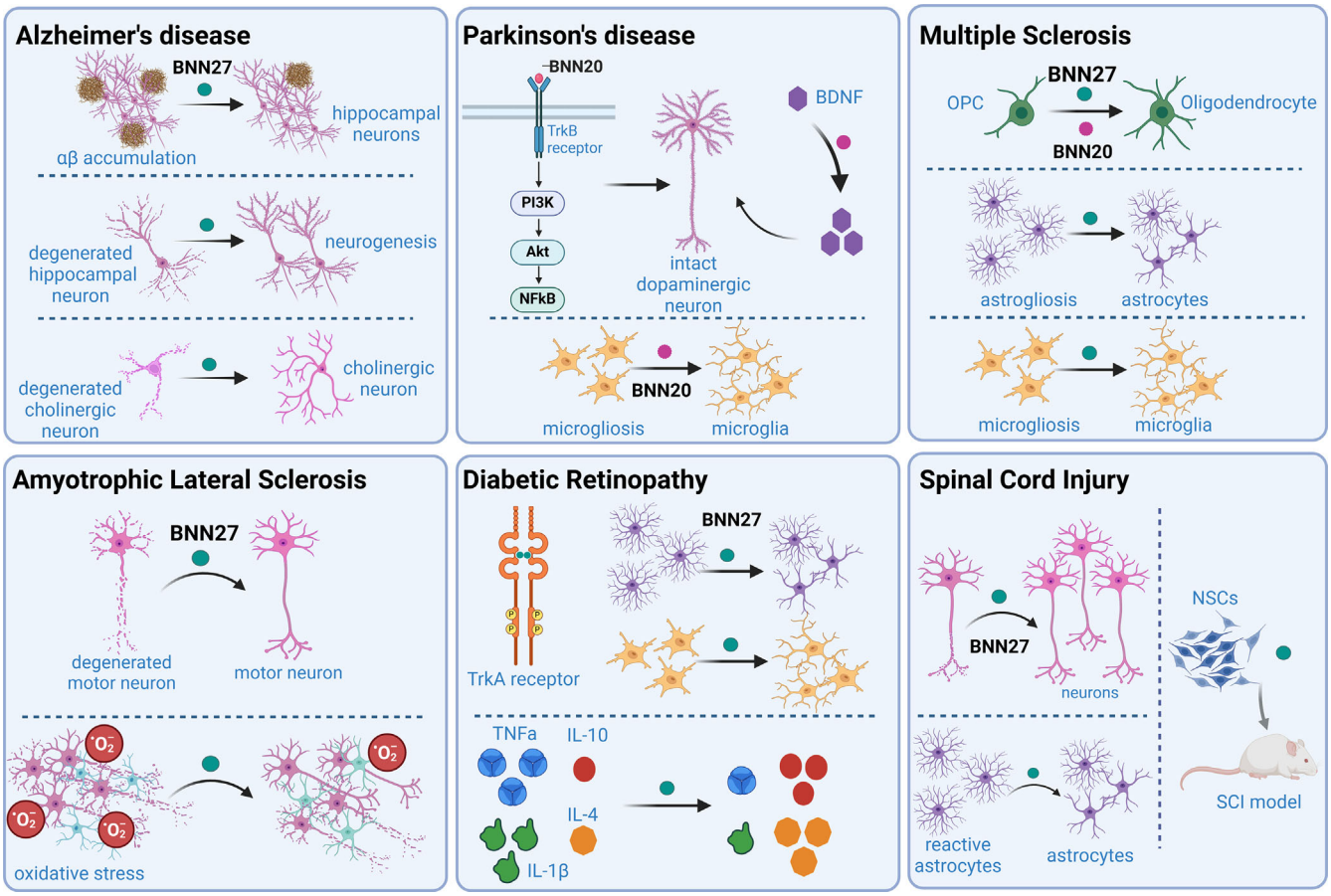

FIGURE 3 Schematic overview of the multifunctional roles of microneurotrophins BNN27 and BNN20 in neurodegenerative diseases. BNN27 exhibits diverse therapeutic potential across multiple neurodegenerative conditions. In Alzheimer's disease models, BNN27 reduces amyloid-β accumulation, promotes neurogenesis and provides neuroprotection. In models simulating multiple sclerosis, it facilitates oligodendrocyte precursor cells (OPC) maturation and attenuates inflammatory responses. In ALS models, BNN27 demonstrates neuroprotective and antioxidant properties. Additionally, in diabetic retinopathy, BNN27 reduces microgliosis, astrogliosis and pro-inflammatory cytokines while increasing anti-inflammatory cytokine levels. It enhances neuronal survival and mitigates astrogliosis in spinal cord injury (SCI) models, showing promise as a candidate for combinatorial therapies with neural stem cell (NSC) transplants. BNN20 exerts neuroprotection in Parkinson's disease models by activating the PI3K/Akt/NF-κB pathway and increasing BDNF levels. Moreover, BNN20 promotes OPC maturation highlighting its potential in the treatment of demyelinating diseases such as multiple sclerosis. Created in BioRender.

administration of BNN27 can also significantly reduce astrogliosis and increase neuronal density following dorsal column spinal cord injury (SCI) in mice at 12 weeks post injury. Furthermore, combined administration of BNN27 with NSC-seeded collagen-based scaffold grafts leads to increased density of survived implanted NSC-derived cells, making it an appealing candidate for combinatorial neuroregenerative therapeutic strategies (Georgelou et al., 2023).

3.2.2 | Microneurotrophins in the rat streptozotocin model of diabetic retinopathy

BNN27 was shown to partially but statistically significantly reverse diabetes-induced retinal damage in the experimental rat streptozotocin (STZ) model of diabetic retinopathy by activating the TrkA receptor, decreasing pro-death p75NTR receptor levels, inducing cleavage of pro-apoptotic **caspase-3** and reducing glial activation. BNN27 systemic intraperitoneal administration also reduced the pro-inflammatory **TNFa** and **IL-1b** and increased the anti-inflammatory **IL-10** and **IL-4** cytokine levels (Ibán-Arias et al., 2018). Targeting both the neurodegenerative and inflammatory components of the disease, microneurotrophin BNN27 seems to have the pharmacological profile for the design of promising novel therapeutic agent for DR. To follow up on these findings, the efficacy of BNN27 when administered topically as eye drops in diabetic rats was also investigated. Indeed, BNN27 reversed diabetes-induced damage in RGC axons and amacrine neurons expressing NFL and bNOS/TH, respectively, in a dose-dependent manner. The involvement of TrkA receptor activation and subsequent phosphorylation of the downstream ERK1/2 kinase signalling pathway in mediating the pro-survival effects of BNN27 was confirmed in this system, consistent with previous findings of systemic BNN27 administration (Ibán-Arias et al., 2019). Hence, topical administration of BNN27 may offer an effective and less invasive treatment for DR by restoring the balance between pro-survival neurotrophic and inflammatory factors while minimising systemic effects (Iban-Arias et al., 2019).

On the contrary, systemic BNN27 administration in an experimental retinal detachment-induced mouse model resulted in increased gliosis and was insufficient to protect photoreceptors from cell death (Tsoka et al., 2018). It is possible that a different dose of BNN27 accessing the retina may be responsible for the lack of protection when added systemically. Moreover, differences in response to BNN27 may be because of the different pathophysiology pathways and cell types involved in DR and retinal detachment. Indeed retinal detachment has characteristics of an acute ischaemic trauma to the retina, while DR is a chronic metabolic diabetic condition.

3.2.3 | Microneurotrophins in the rat model of pharmacologically-induced schizophrenia

Given the antioxidant and anti-inflammatory properties of BNN27, along with its modulatory action on neurotrophins levels (Glajch et al., 2016; Ibán-Arias et al., 2018; Pediaditakis, Efstathopoulos, et al., 2016; Pediaditakis, Kourgiantaki, et al., 2016) and on factors which have been associated with schizophrenia (Bitanihirwe & Woo, 2011; Khandaker et al., 2015; Rodrigues-Amorim et al., 2018), the ability of BNN27 to counteract schizophrenia-like behavioural deficits produced by ketamine (an NMDA receptor antagonist) in rats has also been investigated. Interestingly, BNN27 was capable of attenuating ketamine-induced ataxia and hypermobility and counteracting ketamine-induced non-spatial and spatial recognition memory deficits. Simultaneously, it reduced social isolation produced by glutamate hypofunction (Zoupa et al., 2019). A functional interaction between BNN27 and the DA system has also been illustrated by the effectiveness of BNN27 in repairing DA dysfunction caused by apomorphine, attenuating cognitive impairments induced by this D1/D2 receptor agonist in rats (Pitsikas et al., 2021). These findings support a potential role of BNN27 in the alleviation of some behavioural alterations related to schizophrenia. Notably, BNN27 appears to lack anxiolytic or antidepressant properties (Kokras et al., 2020), aligning with findings from a clinical trial involving DHEA in patients with schizophrenia, where DHEA improved negative symptoms but not depressive symptoms or anxiety (Cai et al., 2018). However, DHEA affects locomotion, progesterone and testosterone levels, as well as the glutamatergic and GABAergic systems of the hippocampus and prefrontal cortex in a sex-dependent manner (Kokras et al., 2020).

3.2.4 | Microneurotrophins in the cuprizone mouse model of demyelination

Research on the role of BNN27 on mouse glial population has revealed that it exerts trophic effects on mature oligodendrocytes, protecting them from cuprizone-induced apoptosis, in a TrkA-dependent manner. In vitro, BNN27 promotes oligodendrocyte maturation and reduces microglial activation. In the in vivo cuprizone-induced mouse demyelination model, BNN27 preserves mature oligodendrocytes and mitigates microgliosis and astrogliosis, while it has no impact on the remyelination process (Bonetto et al., 2017). Furthermore, microneurotrophin BNN20, a C17-spiroepoxy DHEA analogue (Figure 2), was shown to promote oligodendrocyte maturation possibly through TrkB receptors, while it diminished astrocytic accumulation, leading to a faster remyelination process in the LPC-induced demyelination mouse model (Kalafatakis et al., 2021). Our findings suggest that microneurotrophins BNN27 and BNN20 may serve as lead molecules to develop non-toxic, BBB-permeable synthetic activators of neurotrophin receptors that could prove effective in demyelinating and neurodegenerative diseases, such as MS.

3.2.5 | Microneurotrophins in the SOD1 mouse model of amyotrophic lateral sclerosis (ALS)

The promising neuroprotective effects of BNN27 in various neuronal cell types drove us to test its effects in an animal model of devastating ALS. In the SOD1-G93A mouse model of ALS, BNN27 administration,

via subcutaneously pellet implants containing either placebo or BNN27, mitigated motor impairments in the Paw grip endurance (PaGE) and rotarod tasks in female mice, while no effects were observed in males. However, BNN27 treatment did not affect other behavioural or neuropathological markers in either sex (Glajch et al., 2016).

However, BNN27 attenuated the loss of motor neurons and promoted their survival in co-cultures with astrocytes derived from ALS patients with SOD1 mutations, via the reduction of oxidative stress (Glajch et al., 2016). The differences in the effects of BNN27 in rat and human models of ALS might be because of species differences in BNN27 bioavailability and metabolism, with much faster degradation in mouse hepatocytes than in humans.

3.2.6 | Microneurotrophins in the 5xFAD mouse model of Alzheimer's disease

The neurogenic and neuroprotective properties of the microneurotrophin BNN27 have been explored in the 5xFAD mouse model of AD. The compound significantly reduced toxic amyloid-β deposition in whole brain of the animals and decreased inflammation. BNN27 treatment restored the size of cholinergic neurons and decreased the population of $p75NTR^{+}/ChAT^{+}$ neurons, exerting a neuroprotective effect. BNN27 also enhanced adult hippocampal neurogenesis and synaptogenesis, finally restoring working memory and leading to cognitive improvement. Moreover, BNN27 administration in both isolated hippocampal NSC and hippocampal neuronal cultures exhibited a strong anti-apoptotic effect against amyloid-β-induced toxicity (Kokkali et al., 2024). Overall, BNN27 offers a multifactorial, BBB-permeable, non-endocrine, non-toxic lead molecule to design NGF analogues with beneficial effects in the neuronal loss and memory deficits associated to AD (Kokkali et al., 2024; Bennett et al., 2016; Pediaditakis, Efstathopoulos, et al., 2016; Pediaditakis, Kourgiantaki, et al., 2016). Additionally, the successful intranasal delivery of BNN27 via mucoadhesive liposomes or nanoemulsions enables a rapid and enhanced nose-to-brain compound transport, presenting a noninvasive, patient-friendly strategy for an efficient therapeutic administration (Kannavou et al., 2023).

It is of note that BNN27 plays a crucial role in recognition memory, and its interaction with the cholinergic system seems to be relevant to cognition. Indeed, the compound effectively counteracted delay dependent and scopolamine-induced (a muscarinic cholinergic receptor antagonist) non-spatial and spatial recognition memory deficits in rats (Pitsikas & Gravanis, 2017).

Recent studies introduced novel NGF mimetics possessing a substituted 17-spirocyclopropyl functionality, namely ENT-A013 and ENT-A010 (Figure 2), which surpass BNN27 in metabolic stability and potency (Rogdakis et al., 2022; Yilmaz et al., 2022). These recent microneurotrophins prevent synaptic loss and amyloid-induced apoptosis in hippocampal neurons and promote survival of primary dorsal root ganglion (DRG) neurons after NGF removal (Rogdakis et al., 2022; Yilmaz et al., 2022). ENT-A013 selectively activates the TrkA receptor, exhibiting neuroprotective and anti-amyloid effects by activating TrkA and downstream kinases Akt and Erk1/2 (Rogdakis et al., 2022). Nevertheless, systemically administered ENT-A010 affects the morphology, transcriptional profile and homeostasis of hippocampal microglia in LPS-treated mice in a TrkA-dependent manner. It also increases amyloid-beta uptake and NGF expression in primary microglia in vitro (Yilmaz et al., 2022). These findings highlight these small molecules as promising candidates for targeting TrkA-mediated pro-survival signalling in neurodegenerative diseases including AD.

Both TrkA and p75NTR receptors for NGF play significant roles in AD pathology, with altered expression in the hippocampus, particularly in cholinergic neurons (Bruno et al., 2023, Ginsberg et al, 2019; Hefti & Will, 1987). TrkA ablation in the basal forebrain disrupts cholinergic function (Sanchez-Ortiz et al., 2014), while p75NTR deletion can rescue synaptic loss, amyloid-β accumulation and cognitive decline in AD models (Demuth et al., 2023; Qian et al., 2019). Notably, p75NTR mediates neurotoxic and pro-inflammatory effects of Aβ, exacerbating AD progression (Knowles et al., 2009; Perini et al., 2002). ENT-A044, the novel neurotrophin analogue, exhibits context-dependent effects on p75NTR, inducing apoptosis in human NSCs but promoting survival of mouse neurons, offering a potential new class of pharmacological agents in AD therapeutics (Papadopoulou et al., 2023).

It is well established that BDNF holds a pivotal role in neurogenesis, synaptic plasticity and repair (De la Rosa et al., 2019; Kramár et al., 2012; Miranda et al., 2019). Hence, research efforts have increasingly focussed on the development of neuroprotective small molecules that selectively target TrkB receptor (Antonijevic et al., 2024; Narducci et al., 2023). Our synthetic compound ENT-A011, a novel BDNF mimetic, demonstrated the ability to protect mouse and human neurons and their precursors against amyloid-β (Aβ)-induced toxicity while it propagates the proliferation of mouse hippocampal and human-induced pluripotent stem cell-derived neurons, mitigating cell death in human neural progenitor cells (hNPCs) exposed to Aβ toxicity, primarily by modulating a core gene network overlapping with that of BDNF, as identified through RNA sequencing (Charou et al., 2024).

3.2.7 | Microneurotrophins in the Weaver mouse model of PD

Microneurotrophin BNN20 (Figure 2) has demonstrated neuroprotective effects both in vitro and in vivo in Weaver mice, an animal model of PD. BNN20 was shown to activate both TrkA and TrkB receptors mimicking the effects of NGF and BDNF, respectively, and efficiently inducing the association of the p75NTR receptor with its effector protein RIP2 (Botsakis et al., 2017; Calogeropoulou et al., 2009; Lazaridis et al., 2011). It was effective in protecting DA neurons and their terminals in vivo, in 'Weaver' mice by activating neurotrophin receptor TrkB, inducing its pro-survival, post-receptor PI3K-Akt-NFkB signalling pathway. BNN-20 exerted its beneficial effect by strongly

TABLE 1 Neuroprotective, anti-neuroinflammatory and neurogenic effects of microneurotrophins.

In vivo animal model	Human disease	Microneurotrophins
Cuprizone mice Bonetto et al. Glia 2017 Kalafatakis et al. J Neurosci Res 2021 Poulai et al. Biomedicines 2021	Multiple sclerosis demyelination	BNN27 BNN20
Weaver transgenic mice Botsakis et al. Neuropharmacology 2017 Panagiotakopoulou et al. Neuropharmacology 2020	Parkinson's disease	BNN20
Streptozotocin rats Iban-Arias et al. Diabetes 2017 Iban-Arias et al. Arch Cli Exp Opthal 2021 Tsika et al. Pharmacol Res Perc 2021	Diabetic retinopathy	BNN27
SOD1 transgenic mice Glajch et al. PLoS One 2016	Amyotrophic lateral sclerosis	BNN27
5xFAD transgenic mice Kokkali et al. Mol Psychiatry 2024 Pitsikas & Gravanis Neurobiol Learn Mem 2017 Zoupa et al. Neuropharmacology 2019 Pitsikas et al. Psychopharmacology 2021 Pitsikas et al. Behav Brain Res 2022 Rogdakis et al. Biomedicines 2022 Yilmaz et al. Biomolecules 2022 Papadopoulou et al. Int J Mol Sci 2023 Charou et al. Stem Cell Res and Ther 2024	Alzheimer's disease, cognitive impairment	BNN27 ENT-A010 ENT-A011 ENT-A013 ENT-A044

elevating the anti-apoptotic Bcl-2/Bax ratio, inducing an anti-inflammatory and antioxidant activity and restoring BDNF levels (Botsakis et al., 2017). Notably, the strong anti-neuroinflammatory effect of BNN20 in Weaver mice seems to be also mediated through microglia, because it effectively counteracted the activation of microglia, inducing its shift towards an M2 neuroprotective stage (Panagiotakopoulou et al., 2020).

4 | CONCLUSION

The mechanisms underlying the onset of most neurodegenerative diseases remain unclear, limiting the development of systematic therapies effective enough to control or even reverse these disorders. The important, although complex, involvement of neurotrophins in promoting neuronal protection and neuronal and myelin regeneration, in addition to their anti-neuroinflammatory effects controlling the activation of glia, offers a promising avenue for a symptomatic therapeutic approach of neurodegenerative and de-myelinating disorders. However, limitations such as neurotrophin short half-lives, their difficulty crossing the BBB and their low pharmacokinetic stability hinder their clinical applications, particularly for long-term administration, necessary for these chronic diseases. Synthetic mimetics of endogenous neurotrophins and activators of their receptors, such as microneurotrophins hold potential as a multimodal symptomatic strategy to enhance in parallel neuronal survival, neuronal and myelin regeneration, inhibition of gliosis and neuro-inflammation, targeting the main neurobiological endpoints of these diseases. Microneurotrophins have been pre-clinically tested in various animal models of various neurodegenerative diseases (relevant publications summarised in Table 1) and may offer new therapeutic agents to reverse or compensate deficits and impairments associated with neurodegenerative diseases and demyelinating disorders in a more effective and less invasive way than the exogenous transplantation of neural and oligodendrocyte precursors or administration of natural neurotrophins, with better pharmacokinetic and pharmacodynamic profiles. Multifaceted neurotrophin mimetics and their combinations provide the pharmacological basis for proposing a brand-new symptomatic therapeutic approach to neurodegenerative diseases to simultaneously control neuronal death, demyelination and neuroinflammation while boosting neuronal repair through neurogenesis. Experimental evidence suggests a role for neurotrophic factors, including NGF and BDNF, in the progression of pancreatic cancer and the mechanisms by which the sympathetic and parasympathetic nervous systems regulate tumour cell growth, migration and invasion (Xu et al., 2024). It is thus important to test the effects of microneurotrophins, activators of TrkA and TrkB receptors for NGF and BDNF, in pathophysiology models of this devastating cancer.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Christopoulos, Davenport, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Beuve, et al., 2023; Alexander, Kelly, Mathie, Peters, Veale, Armstrong, Buneman, Faccenda, Harding,

Spedding, Cidlowski, et al., 2023; Alexander, Mathie, Peters, Veale, Striessnig, Kelly, Armstrong, Faccenda, Harding, Davies, Aldrich, et al., 2023).

AUTHOR CONTRIBUTIONS

Ioanna Zota: Investigation, Methodology and Writing – original draft. **Theodora Calogeropoulou**: Conceptualisation, Funding acquisition, Validation, Review and Editing. **Konstantina Chanoumidou**: Investigation, Methodology and Review. **Ioannis Charalampopoulos**: Conceptualisation, Funding acquisition, Validation, Review and Editing. **Achille Gravanis**: Conceptualisation, Funding acquisition, Supervision, Validation, Writing and Editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest, except Achille Gravanis as the cofounder of BioNature E.A. LTD and proprietor of compounds BNN27 and BNN20 (patented with the WO 2008/1555 34 A2 number at the World Intellectual Property Organization).

DATA AVAILABILITY STATEMENT

N/A Review.

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