Chapter

Neuroprotective Properties of Peptides

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Abstract

The development of a treatment strategy for neurodegenerative disorders is a serious issue for the healthcare world and a crucial subject of discussion. In the past two decades, a lot of focus has been placed on identifying the pathophysiological processes involved in neuronal death linked to neurodegenerative disorders and developing a variety of treatment options for neuroprotection. Numerous research teams have studied the use of peptides as neuroprotective treatments for different types of neurodegenerative disorders for a long time. The review aims to provide details about the roles of erythropoietin (EPO), glucagon-like peptide-1 (GLP-1), granulocyte colony-stimulating factor (G-CSF), and oxytocin (OXT) in neurodegenerative disorders as well as what cellular and molecular mechanisms they trigger to elicit the neuroprotective action, with a focus on neurodegenerative disorders.

Keywords: erythropoietin, glucagon-like peptide-1, granulocyte colony-stimulating factor, oxytocin, peptides, neurodegenerative disorders, neuropeptides, neuroprotection

1. Introduction

It is becoming more well-accepted that secondary biochemical alterations that result in tissue loss, which are secondary to acute neurodegenerative disorders, play a significant role in the development of chronic neurological impairment. Neurodegenerative disorders such as motor neuron disease, Alzheimer's disease (AD), Parkinson's disease (PD), ataxia, spinal muscular atrophy, autism, amyotrophic lateral sclerosis, Huntington's disease, epilepsy, ischemic brain diseases, and central nervous system (CNS) diseases, such as stroke have also been linked to molecular pathways that contribute to cell damage and cell loss. Due to a lack of clinical efficacy or unpleasant side effects, several neuroprotective therapies intended to reduce neuronal death have been ineffective. This prompted researchers to investigate alternative therapeutic applications, such as peptides as neuroprotective agents [1–5]. Notably, several peptides have been applied in clinical settings, including erythropoietin (EPO), glucagon-like peptide-1 (GLP-1), granulocyte colony-stimulating factor (G-CSF), and oxytocin (OXT) [6–12]. **Figure 1** shows the synergistic neuroprotective effects of G-CSF, GLP-1, and EPO.

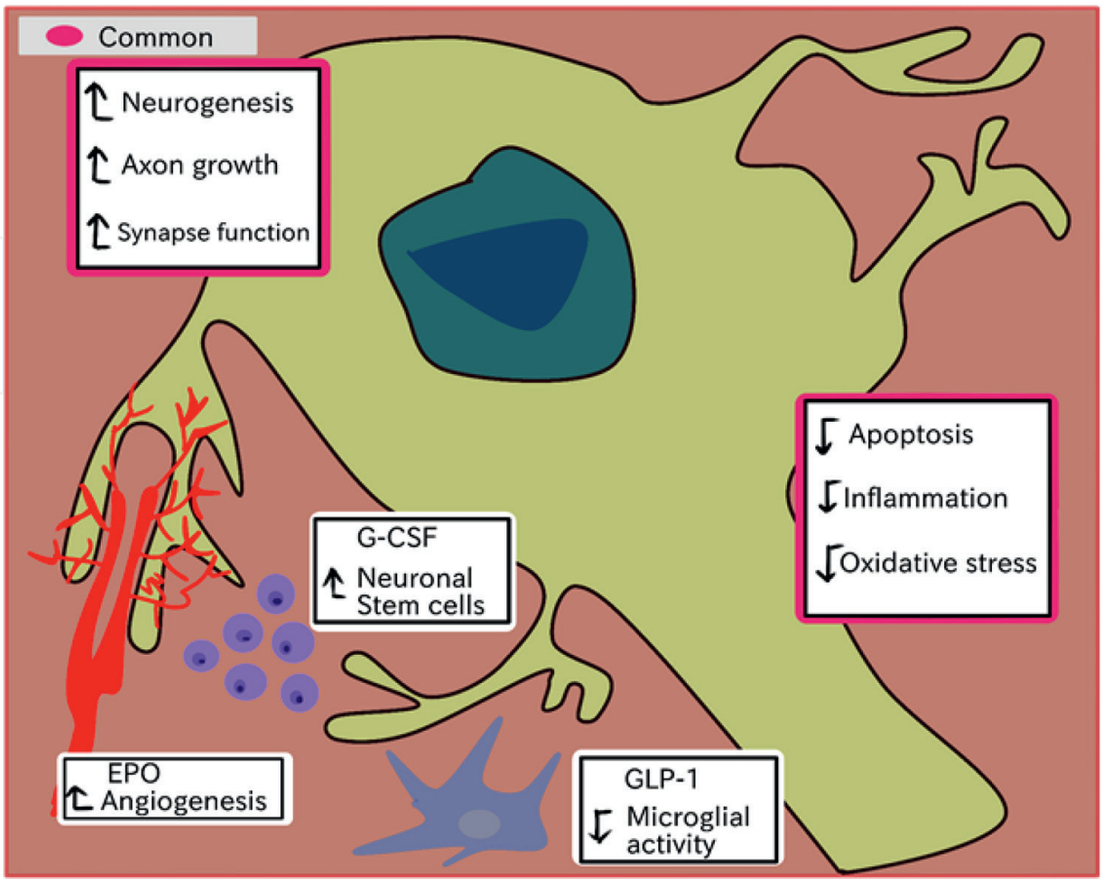

Figure 1.
The synergistic neuroprotective effects of G-CSF, GLP-1, and EPO promote neurogenesis, axon growth, and synaptic functioning while decreasing cell apoptosis, inflammation, and oxidative stress. Individually, G-CSF stimulates neural stem cells, EPO enhances angiogenesis, and GLP-1 decreases microglial activity.

2. Neuroprotective properties of erythropoietin

Human erythropoietin (EPO) is a 34 kilodalton (kDa) glycoprotein hormone formed up of four-helix loops. The gene for it is found on chromosome 7q11.22 and produces a 193-amino acid polypeptide chain [13]. The approaches of glycosylation and sialylation are also required for EPO to operate normally as they increase EPO's molecule's longevity and prolong its stay in circulation. The liver is the main site of EPO synthesis in individuals during fetal and neonatal life, but renal EPO messenger ribonucleic acid levels rise exponentially following 30 weeks of gestation, demonstrating the shift from the liver to the kidneys as the EPO production zone [14]. Also generated by cells from numerous organs, with the heart, spleen, lung, testis, ovaries, retina, and brain, where it exerts non-erythropoietic roles [15]. The discovery that the brain is one of these EPO-producing locations has captured the most interest. It is worth noting that prior line analyzing research has found that the pericytes in the brain and kidney both are transformed from the neural crest, which might also explain why they serve the same role in separate locations. The hippocampus, cortex, and midbrain were all reported to yield and express EPO inside the CNS. EPO has also been shown to have a crucial role in fostering and boosting neurogenesis, which is important for the growth of the brain and blood system [16], restricts cell damage, and prevents oxidation reactions. The peptide may have a favorable impact on the reduction of neuronal disorder due to its protective effects and ability to reduce reactive oxygen species (ROS) [6].

Erythropoietin receptor (EPOR) has a 225-amino acid subunit, a 23-amino-acid outer membrane segment, and a 235-amino-acid intracellular subunit. EPO activates secondary chemical signals like the signal transducer and activator of transcription 5 (STAT5), phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) through the hematopoietic system's attachment of EPO to its target, which proceeds in homodimerization [17]. EPO is a bioactive molecule that is formed in the brain and has an essential function in neural growth and synapse formation control. EPOR has been detected in vitro grown rat oligodendrocytes and astrocytes, and recombinant human EPO (rhEPO) treatment increases their development and reproduction, hinting that the EPO/EPOR linkage is vital in angiogenesis after trauma. The four specific EPOR versions that are present in various tissues are described [18].

1. The brain has the canonical isoform, which is primarily expressed in the hematopoietic system. EPO activates this subunit, which modulates EPO's activity in inflammation and hypoxia in neurons [19].

2. Neuronal cell safeguard is an expression of EPOR's second form. In this scenario, the EPOR monomer connects the beta common receptor (βcR; CD131), a characteristic target portion of interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The most prominent theory is that dimerization causes the development of a particular tissue-building receptor. The classical homodimer upregulating tends to be activated by the stimulation of this sensor in an identical method [20].

3. The substantia nigra's dopaminergic neurons have a tertiary version of the receptors, which is shorter than the full-length form and causes an alteration in the known to possess subdomain. The absence of STAT phosphorylation in the EPOR abridged isoform raises the possibility of another, as of before unidentified, mode of action [7].

4. Finally, it has been confirmed that the rat brain has a periplasmic soluble form of the receptor. Besides the subsequent mediators being activated, this isoform engages with EPO. Therefore, EPO's contact with other EPOR forms is limited due to its decreased accessibility. When there is ischemia, this isoform's translation is significantly suppressed, which starts a process that fights comprehensive EPOR [19].

EPO's main purpose is to manage the growth of hematopoietic cells, so it is essential to identify if targeting neural cells may have a strong effect. The modulatory effects of EPO on neuroplasticity may affect neural precursor cells of other sources as well. These actions may include rapid maturation and enhanced progenitor growth, which has been seen in hypoxic mesencephalic progenitor cells [21]. Additionally, brain stem cells generated from the spinal cord exhibited EPO-driven neurogenesis. Brain-derived neurotrophic factors can be induced by EPO to potentially stimulate neurogenesis. EPO promotes regeneration while also assisting in the suppression of apoptosis. Apoptosis is diminished by the engagement of the cascade EPOR molecules Janus kinase 2 and PI3K and the control of the regulatory protein Bad (the Bcl-2 associated agonist of cell death) [22].

EPO is synthesized in the kidneys and released into circulation in response to hypoxia. By focusing on EPO as a cascade protein controlled by hypoxia, the hypoxia-inducible factor-1 alpha (HIF-1α) was in effect discovered [19]. Conversely, it currently appears

that HIF-2α, also known as endothelial PAS domain protein 1, is much more essential than HIF-1 in driving the overexpression of EPO under deprivation [23]. The finding is that EPO and EPOR are generated in the brain's hippocampus and telencephalon, the two areas particularly vulnerable to hypoxia. Hence, it is theoretical to assume that EPO has a biological process in the brain that serves as a defense against hypoxia and perhaps ischemia [18]. In several additional neurodegenerative disorders, ROS also plays a role in causing cell damage and neuronal loss. In a rat model of vascular dementia reported by Erbas et al., EPO anti-oxidative capabilities particularly decrease beta-amyloid-induced apoptosis and boost tyrosine hydroxylase (TH) positive neural cells [24]. A crucial additional point in the stability of HIF and, thus, the synthesis of EPO is the creation of ROS generation in both hypoxia and hyperoxia. Although enhanced prolyl hydroxylation and thus reduced HIF function are heavily related to ROS blocking, it is unclear how extra or insufficient oxygen affects cell damage in the brain [25].

EPO has become a versatile tissue-protective mediator, in part because of its anti-inflammatory characteristics [26]. In fact, rhEPO penetrates the blood–brain barrier (BBB) whenever given to rats with localized ischemic injury, reducing the extent of the lesion by 50 to 75% [27]. In a laboratory autoimmune encephalitis form of multiple sclerosis, rhEPO inhibited the production and secretion of proinflammatory cytokines and growth factors, as well as the migration of cytokines through into the site of inflammation [23].

The second most prevalent neurodegenerative disorder is PD. Bradykinesia, stiffness, and tremor are only a few examples of motor and nonmotor features. Alpha-synuclein clusters, which are essential parts of Lewy bodies, and the growth of dopaminergic neurons in the atrophied substantia nigra pars compacta are two crucial pathogenic indicators [28]. According to a particular report of autophagy signals along with AMP-activated protein kinase and Unc-51-like autophagy activating kinase 1, EPO therapy stimulates the autophagy mechanism in rotenone-treated SH-SY5Y neurons (a neuroblastoma cell line called SK-N-SH that has triple-subcloned) [29]. EPO has various neuroprotective effects on astrocytes, microglia, and synapses and is implicated in the control of neuroinflammation. In fact, EPO prevents the death of vascular endothelium and the arousal of astrocytes, which maintains the BBB [30]. According to studies, EPO reduces levels of tumor necrosis factor-alpha (TNF-α) and increases levels of TH in rats that have had parkinsonism brought on by rotenone or 6-hydroxydopamine. This suggests that EPO may function through modulating neuro-inflammation in order to achieve its goals [24]. In a lipopolysaccharide-induced autistic rat model, EPO was also effective in enhancing cognition and neurochemistry [31].

The most prevalent kind of dementia, AD, is clinically defined by a memory deficit that worsens with time and a deterioration in cognitive abilities. Extracellular neuritic plaques induced by amyloid-beta (Aβ) formation and internal neuro-fibrillary bundles caused by hyperphosphorylation of the tau protein are the disease's defining features. The earliest signs that EPO could help with cognitive skills came from studies on non-neurological diseases when individuals receiving EPO during hemodialysis showed an increase in their mental abilities. Traditional pharmaceutical therapy for AD comprises acetylcholinesterase inhibitors, N-methyl-D-aspartate antagonists, and their potential combinations since no cure has been discovered [32]. EPO's health benefits have first been investigated at the molecular scale, employing both robust cell cultures and primary hippocampus neurons [16]. The chemical appears to be effective by blocking the apoptotic mechanism and protecting against Aβ toxicity [33].

Additionally, it is probable to notice a decline in the inflammatory activity and an elevation in antioxidant responses. EPO seemed to minimize cell damage, inflammation, and tau hyperphosphorylation while enhancing neurogenesis [25]. On abnormalities in neuroplasticity, the chemical appears to have a repair impact [33]. This, in addition to the fact that EPOR is present in the hippocampus, raises the prospect that EPO may have clinical benefits in this situation [31].

Acute ischemic stroke is caused by a temporary or irreversible decrease in cerebral blood flow that is typically related to the blockage of a cerebral artery, an embolization, or localized thrombosis. A protective effect against ischemia injury is provided by the stimulation of HIFs, which stimulates downstream factors including EPO and vascular endothelial growth factor [23]. In hypoxic *in vitro* models, EPO expression levels in both rat astrocytes and neurons. EPO begins to act on frontal neuron progenitor cells, implying its role in neurogenesis. Bioactivity rises after EPO administration in primary hippocampal and cortical neurons exposed to cerebral ischemia, indicating its role in apoptosis and cell healing. By recovering hippocampal CA1 neurons from deadly ischemic damage, rhEPO treatment reduced ischemia-induced memory deficit. Other researchers reported that the indigenous EPO/EPOR system protects hypoxic astrocytes and oligodendrocyte progenitor cells, indicating that suppressing endogenous EPO in astrocytes results in diminished preservation of oligodendrocyte precursor cells and cell apoptosis [34].

High EPO dosages are beneficial in term neonates with hypoxic–ischemic encephalopathy (HIE) when the damage has not yet been established [35]. Animal studies have revealed that EPO can be given at high dosages around 6 hours after the beginning of brain damage to have a meaningful neuroprotective role. EPO potentially impacts the processes of cerebral flow restitution, angiogenesis, and neuroregeneration in this environment, reducing ischemia damage. Research data also show that EPO can be used as an adjuvant therapy with hypothermia or as a supplement for hypothermia in HIE [2].

3. Neuroprotective properties of glucagon-like peptide-1

The glucagon-like peptide-1 (GLP-1), a 30-amino acid peptide hormone, is synthesized in the intestinal endocrine L-cells by differential processing of the proglucagon gene. It is a member of the incretin subfamily. The "incretin effect" is when incretins cause the pancreas to release more insulin when blood sugar levels are high. Even before it leaves the gut, the hormone GLP-1 is quickly digested and rendered inactive by the enzyme dipeptidyl peptidase IV. This raises the probability that GLP-1 receptor (GLP-1R)-expressing sensory neurons in the liver and intestine communicate GLP-1 effects [36, 37]. There are the highest concentrations of GLP-1R in the pancreas, the gut, and the CNS, although they are also found in small amounts in the heart, the vasculature, the kidneys, and the lungs [38].

The GLP-1 is a complex hormone with a wide range of metabolic effects, including the glucose-dependent stimulation of insulin secretion, a reduction in stomach emptying and food intake, an increase in natriuresis and diuresis, and a modification of rodent B-cell proliferation. GLP-1 primarily acts as an incretin hormone by stimulating insulin secretion and inhibiting glucagon release, which together help to reduce postprandial glucose excursions. It has consequences for learning and memory, reward behavior, and palatability and has cardio-neuroprotective effects, reducing

inflammation and apoptosis. In addition to many GLP-1-based pharmacotherapies being tested in clinical settings for the treatment of obesity, GLP-1R agonists are successfully used in the clinic to treat type 2 diabetes mellitus (T2DM) and its related complications such as diabetic nephropathy [37, 39, 40].

Different from the intestinal system, GLP-1 is also produced in the brain, notably in the nucleus tractus solitarius (NTS) in the brainstem in particular. The paraventricular nucleus and arcuate nucleus are two regions of the hypothalamus that have GLP-1-expressing neurons. The management of appetite is aided by GLP-1 release, which also promotes a feeling of satiety [8, 41].

GLP-1 receptors are found in the substantia nigra, amygdala, hippocampus, hypothalamus, and NTS, as well as in cortical regions such as the lateral prefrontal cortex. These receptors may be stimulated to promote neurogenesis and synaptogenesis and to guard against oxidative stress, neuroinflammation, and apoptosis [41–44]. It is important to note that while blood-borne GLP-1 and GLP-1R agonists rapidly penetrate the BBB, incretins and their receptors are expressed in the CNS [3, 9].

In both humans and animals, GLP-1 modulates autonomic function and the stress response by activating the hypothalamic–pituitary–adrenal axis. It has antiapoptotic, neuroprotective, and neuromodulatory properties. GLP-1 agonism may have neuroprotective effects by lowering microglial activation, which in turn lowers the release of M1 macrophages (e.g. TNF-α and IL-1β). GLP-1 affects synaptic transmission and plasticity in the rat hippocampus, at least in part through glutamate absorption. Additionally, it has been shown that astrocytes express the GLP-1R, which is linked to the suppression of neural inflammation. In cell cultures, activation of the GLP-1R was associated with neurite outgrowth and neurotrophic impacts, such as hippocampus neurogenesis. Additionally, the receptor's upregulation in the hippocampus was connected to improvements in learning and memory [44]. On the other hand, GLP-1R expression in the hypothalamus was reported to be reduced in people with T2DM [45].

Preproglucan and consequently GLP-1 are mostly produced by proprotein convertase 1/3 expressing neurons in the caudal region of the dorsal vagal complex's (DVC) medial NTS and, to a lesser extent, the area postrema. Afferent vagal inputs, such as gastric distention, the activation of peripheral GLP-1Rs, or the release of the satiety-related hormones leptin and cholecystokinin, enhance the activity of preproglucagon-expressing neurons in the NTS. The NTS neurons create proglucagon and/or GLP-1-positive projections that are directed into the olfactory bulb, several hypothalamic nuclei, the bed nucleus of the stria terminalis, the lateral and medial septal nuclei, the amygdaloid complex, the septohippocampal area, the nucleus accumbens, and, less frequently, the medullary reticular formation, dorsal motor nucleus of the vagus, and the cortex. The GLP-1R is broadly distributed in the CNS, in contrast to the NTS, where GLP-1 production and distribution are limited [4].

In the treatment of stroke and neurodegenerative disorders such as AD, PD, amyotrophic lateral sclerosis, autism, schizophrenia, and other diseases such as diabetic retinopathy, ocular hypertension, and glaucoma, GLP-1 and GLP-1R have demonstrated remarkable neuroprotective effectiveness [3, 46–50].

GLP-1 analogs (including liraglutide, lixisenatide, semaglutide, exendin-4, and NLY01) exhibit strong anti-inflammatory effects. GLP-1R/gastric inhibitory polypeptide receptor (GIPR) dual agonists inhibited microgliosis, astrogliosis, and the expression of toll-like receptor-4 in a manner comparable to GLP-1 mimetics, however, they had a greater impact. Analogs of the GLP-1R (such as oxyntomodulin and exenatide) promote synaptogenesis, preserve synapses, increase hippocampus synaptic plasticity, and improve learning and memory [4, 49].

Alzheimer's disease and PD, both kinds of neurodegenerative disorders, have been linked to impaired insulin signaling [51]. The main clinical sign of AD is progressive ongoing dementia, which can be distinguished from other forms of dementia by intellectual symptoms such as memory loss and behavioral issues as well as cognitive symptoms such as reduced cognition. Similarities between AD and T2DM, which is thought to be a high-risk factor. Neurofibrillary tangles, which are shaped by hyperphosphorylated tau protein and can build up into oligomers and/or Aβ plaques, are one of the neuro-pathological characteristics of AD. Aβ buildup in AD has the potential to damage synapses and cause neuroinflammation by triggering astroglia and microglia cells [4, 52, 53].

Additionally, *in vivo* research using PD models has shown that unusually elevated levels of TNF-α and interferon-gamma (IFN-γ) secretion support the TNF-α/Janus kinase/signal transducer and activator of transcription and IFN-γ/MAPK/extracellular signal-regulated kinase-mediated activation of nuclear factor kappa-B in microglia and astroglia, respectively. Therefore, chronic neuroinflammation in AD and PD results in the permeabilization of the BBB by TNF-α and IL-1β; immune cell infiltration into the CNS; mitochondrial and axonal abnormalities; synaptic damage; and insulin resistance in the brain, as well as microglial, astrocyte, and neuronal malfunction and death [4].

GLP-1 directly promotes neurite development and synaptogenesis, in addition to shielding synapses from amyloid and oxidative damage. Additionally, GLP-1R activation has demonstrated synapto-protective qualities by promoting cytoskeletal actin/tubulin polymerization to induce neurite multiplication, branching, outgrowth in cell cultures (PC12, SH-SY5Y), and adult sensory neurons. It has been demonstrated in the rat model that lixisenatide, a GLP-1R agonist, also inhibits synaptic damage brought on by Aβ buildup, supporting spatial memory by influencing the PI3K pathway [4, 54].

Exenatide (exendin-4, a synthetic peptide containing 39 amino acids) was shown in studies to protect against ischemia-induced neuronal death by upregulating GLP-1R expression, primarily in gamma-aminobutyric acid–releasing (GABAergic) interneurons or astrocytes in the gerbils' hippocampal CA1 region. After a stroke in mice, it reduced neurological impairments. When administered 4 weeks before and 2–4 weeks after generating stroke in diabetic rats, a clinical dose of exendin-4 also decreased cell damage, stopped microglial infiltration, and enhanced stroke-induced neuroblast production and proliferation of neural stem cells [3]. GLP-1 and GLP-1R agonists provide protection for many systems as well as CNS, by promoting neurogenesis and synaptogenesis and preventing oxidative stress, neuroinflammation, and apoptosis.

4. Neuroprotective properties of granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor (G-CSF), now referred to as colony-stimulating factor 3 (CSF-3), is a 25-kDa glycoprotein that is encoded by the Csf3 gene on the human chromosome 17 [55]. It is a growth factor that promotes the proliferation, differentiation, and survival of hematopoietic progenitor cells. G-CSF is essential for the migration of hematopoietic stem cells as well as the proliferation and differentiation of granulocyte progenitors. It promotes the differentiation of hematopoietic progenitor cells into neutrophils and modulates neutrophil migration, as well as having trophic effects on several cell types, including neurons [56–58].

G-CSF typically influences myeloid cell development from progenitor cells to mature neutrophil granulocytes during hematopoiesis [59–61]. It functions via a homodimeric granulocyte colony-stimulating factor receptor (GCSF-R) and is expressed on myeloid cells ranging from myeloblasts to mature neutrophils. GCSF-R is found at a low density on the cell surface (700–1500 per cell) and has a strong affinity for G-CSF. Low occupancy at the receptors is adequate to achieve the maximum biological response. G-CSFR is composed of a single extracellular domain, a transmembrane domain, and an intracellular domain [62, 63]. The extracellular domain contains immunoglobulin (Ig)-like domains, a cytokine receptor homologous (CRH) domain, and three fibronectin (FN)-III-like repeats. The Ig-like domains and the CRH domain are important in G-CSF binding, whereas the FN-III-like repeats are involved in receptor dimer stability [64]. Numerous cells, including bone marrow, fibroblasts, macrophages, endothelial cells, glial cells, and neurons of various brain regions, all contain G-CSFRs [65–67]. G-CSF regulates hematopoietic cell proliferation, differentiation, and survival primarily via activating the Janus kinase/STAT, Ras/MAPK, and AKT/PI3K pathways [58].

G-CSF has been demonstrated to increase neutrophil chemotaxis and phagocytosis, as well as increase bactericidal and fungicidal activities, antibody-induced cell toxicity, and complement receptor expression (CD11b, CG18b, CD35) [67]. G-CSF administration stimulated monocytes to produce IL-10 and mobilizes T helper type 2 cells, promoting dendritic cells, which may contribute to the reduction of T cell reactivity [68]; G-CSF also increases the survival of neutrophils and their progenitors, including stem cells. Clinical studies have shown that the duration of severe neutropenia following chemotherapy is shortened and neutrophil counts recover more quickly when G-CSF is administered to cancer patients who have had both allogeneic and autologous bone marrow transplantation [69].

Recent research has demonstrated the neuroprotective impact of G-CSF treatment, which is due to its high antioxidant, anti-inflammatory, and antiapoptotic properties [10, 11]. In a number of ischemic rodent models, G-CSF has been demonstrated to provide long-term neuroprotection by encouraging somatic growth and improving sensorimotor and neurocognitive skills [70, 71]. The neuro-regenerative and neuroprotective properties of G-CSF have also been demonstrated in preclinical studies in a number of neurodevelopmental disorders, including autism, spinal cord injury, cerebral ischemia, PD, and AD [5, 10, 72–74]. To investigate the possibility of using G-CSF for AD treatment, two different Aβ protein aggregate-induced AD mice models were used. Interestingly, they found that G-CSF-induced bone marrow stem cell release enhanced neurogenesis around Aβ plaques in mouse brains and greatly restored the neurological function of AD mice [75]. Recombinant human G-CSF (filgrastim) was authorized for use by the Food and Drug Administration in 1991 to treat cancer patients receiving myelotoxic chemotherapy [76]. According to a wealth of research, the G-CSF molecule and its recombinant form, filgrastim, have the potential to treat cerebral ischemia, stroke, and neurodegenerative disorders such as Huntington's disease, amyotrophic lateral sclerosis, AD, and PD [58, 77]. The therapeutic efficacy and safety of G-CSF are supported by all available clinical and preclinical research data, establishing its value as a treatment for neurodegenerative disorders.

5. Neuroprotective properties of oxytocin

The CNS's glial, microglial, and neuronal interactions are incredibly dynamic and responsive to various stimuli. As chemical messengers that communicate both within

the brain and between the brain and the body, hormones are essential for the body's homeostasis. OXT is a nonapeptide generated in the hypothalamic paraventricular (PVN), supraoptic (SON), and accessory nuclei (AN) [78, 79]. Via G-protein-coupled receptors, OXT affects the central and peripheral nervous systems. Various peripheral tissues, including the pancreas, blood vessels, ovary, thymus, skin, placenta, testis, heart, adipocytes, and kidney, also generate it [80]. OXT is crucial for aggression, sexual and maternal behavior, neuromodulation, social memory, and bonding. It helps in the evacuation of milk from the mammary gland during breastfeeding and is a powerful stimulator of uterine contractions [81]. The structure of vasopressin, a similar nonapeptide with only two amino acid differences from OXT, is extremely similar to that of OXT. Oxytocin receptor (OXTR), which together with the related V1a, V1b, and V2 vasopressin receptor subtypes form a subfamily of the large G protein-coupled receptor superfamily, is the sole receptor for OXT that is currently known [82].

Studies have shown that lower levels of central endogenous OXTergic activity are related to social behavior profiles that are compromised [83, 84]. Several psychiatric disorders such as social anxiety, major depressive disorder, autism spectrum disorder, addiction, depression, and schizophrenia have been connected to disturbed brain OXTergic signaling [78, 85]. Numerous animal experiments published in the literature demonstrate OXT's neuroprotective properties. The immune system regulation, social neuroprotection, antiapoptotic, anti-inflammatory, and antioxidative actions of the OXT hormone are among its neuroprotective properties. It also controls the immunological and autonomic nervous systems in addition to the brain and reproductive system [86]. There are several medicines that have side effects including autotoxicity, neurotoxicity, and nephrotoxicity. Since oxidative stress and inflammation are important in the pathogenesis of neurological disorders, and the antioxidant/anti-inflammatory properties of OXT are widely recognized, there has been numerous research on OXT's positive effects in neurotoxicity prevention [85, 87]. Microglia, the brain, and the spinal cord's resident macrophages are the innate immune system's main line of defense. Microglia and astrocyte intercommunication controls the inflammatory response in the brain. TNF-α, IL-1, IL-6, and IL-12 are a few proinflammatory cytokines that are produced and secreted in relation to M1 microglia polarization, which in general react to defend tissue and increase the elimination of infections. Overactivation or dysregulation of the M1 microglia phenotype, on the other hand, may increase neuronal damage caused by pathogenic stimuli and toxins, resulting in more extensive damage to neighboring neurons. Recent studies showed that OTX is important in the regulation of microglial reactivity in the growing brain [88, 89]. The relationship between neuroinflammation, microglial activation, and neuronal death has also been explored in several neurodegenerative disorders, including autism, frontotemporal dementia (FTD), ALS, PD, AD, and Huntington's disease. Recent research has revealed that autistic brains have activated microglia. OXT treatment has been shown to diminish activated microglia in the hippocampus and amygdala and enhance the behaviors of autistic mice, lowering anxiety, depression, and repetitive behavior, as well as improving social contact [90]. According to a study, depending on the type of memory test and the psychobiological importance of the stimuli, the effects of intranasally administered OXT in humans revealed that the hormone selectively affected memory performance [91]. In their research, Erbaş et al. investigated the neuroprotective effects of OXT on rotenone-induced PD in rats. According to their research, oxytocin may protect dopaminergic neurons from rotenone-induced injury while also restoring them [92]. Postmortem brain tissue from patients with Huntington's disease with varying

Peptides	Role in neuroprotection	Function
EPO	Neurogenesis↑ Neurotrophic effects↑	Promotes and enhances neurogenesis by activating brain-derived neurotrophic factors and acting on neural progenitor cells
	Oxidative stress↓ Mitochondrial dysfunction↓	Restricts cell damage and reduces neurological dysfunction via its protective effects and ability to minimize reactive oxygen species
	Neural growth↑ Synaptic plasticity↑	Activates secondary chemical signals (STAT5, PI3K, and MAPK) and functions in neural growth and synapse formation control
	Functional recovery↑	Promotes rapid maturation and enhanced progenitor growth in hypoxic mesencephalic progenitor cells
	Regeneration↑	Promotes regeneration assisting in the suppression of apoptosis
	Maintains the blood–brain barrier↑	Prevents the death of vascular endothelium and the arousal of astrocytes
	Neuroinflammation↓	Reduces levels of tumor necrosis factor-alpha, declines the inflammatory activity, and elevates antioxidant responses
	Inhibition of apoptosis↑	Blocks the apoptotic mechanism and protects against amyloid beta toxicity, minimizes cell damage, and tau hyperphosphorylation in Alzheimer's disease
	Cognition↑	Reduces ischemia-induced memory deficit, protects hypoxic astrocytes and oligodendrocyte progenitor cells in acute ischemic stroke
	Neurodegeneration↓	Impacts the processes of cerebral flow restitution, angiogenesis, and neuroregeneration reducing the effects of ischemia in hypoxic–ischemic encephalopathy
GLP-1	Apoptosis↓	Promotes neuroprotective, neuromodulatory, and antiapoptotic activities.
	Inflammation↓	Lowers microglial activation and the release of M1 macrophages
	Cognition↑	Promotes synaptogenesis, preserves synapses, increases hippocampal synaptic plasticity, and improves learning and memory
	Synaptogenesis↑	Promotes neurite development and synaptogenesis shielding synapses from amyloid and oxidative damage.
	Neuroprotection↑	Reduces neurological impairments
G-CSF	Cell survival↑ Apoptosis↓	Regulates hematopoietic cell proliferation, differentiation, and survival via activating the Janus kinase/STAT, Ras/MAPK, and AKT/PI3K pathways
	Neuroinflammation↓ Regeneration↑	Increases neutrophil chemotaxis and phagocytosis
	Neurotrophic effects↑	Stimulates monocytes to produce IL-10, mobilizes T helper type 2 cells, and promotes dendritic cells
	Neurogenesis↑	Releases enhanced neurogenesis around Aβ plaques and restores the neurological function of Alzheimer's disease

Peptides	Role in neuroprotection	Function
OXT	Neuroprotection↑	Mediates social neuroprotection, antiapoptotic, and antioxidative actions
	Neural growth↑ Neurogenesis↑	Controls the immunological and autonomic nervous systems
	Brain development↑	Regulates the microglial reactivity in the growing brain to diminish activated microglia in the hippocampus and amygdala
	Cognition↑	Lowers anxiety, depression, and repetitive behavior and improves social contact
	Neurodegeneration↓ Neuroinflammation↓	Protects dopaminergic neurons from rotenone-induced injury and restores

EPO: erythropoietin, GLP-1: glucagon-like peptide-1, G-CSF: granulocyte colony-stimulating factor, OXT: oxytocin.
↑: enhance.
↓: decrease.

Table 1.
An overview of the roles and effects of peptides in neuroprotection.

Vonsattel grades (grades 2–4) that had been immunohistochemically processed showed a selective 45% loss of OXT neurons and smaller cell sizes in the remaining OXT neurons [93]. Individuals with the mutant HTT gene had a significant 38% reduction in OXT cerebrospinal fluid levels, according to a recent study [94]. Patients with motor manifest and premanifest Huntington's disease have been found to have a positive correlation between OXT plasma levels and depression in a clinical study [95]. Additionally, a selective OXT loss in HD, ALS, and FTD has been linked to hypothalamic pathology [96]. OXT's anti-inflammatory and neuroprotective effects suggest that it may represent a possible therapeutic approach for the treatment of neurodegenerative and neurodevelopmental disorders.

Table 1 summarizes the functions and neuroprotective properties of peptides (EPO, GLP-1, G-CSF, and OXT).

6. Conclusion

Although neurodegenerative disorders are pathological conditions linked to aging, neurodegeneration frequently goes undetected for a long time and neuronal death happens gradually over the course of a lifetime before the first clinical signs can be observed. Increasing preclinical and clinical evidence demonstrating the efficacy of EPO, GLP-1, G-CSF, and OXT in treating various brain diseases shows that these molecules are versatile and have strong immunomodulatory, anti-inflammatory, anti-apoptotic, and neuroprotective properties. Given their beneficial effects on the brain, immunological system, reproductive system, and autonomic nervous system, these peptides hold promise as potential future treatments for neurodegenerative disorders.

Acknowledgements

A bibliometric research was performed on research and review articles published in the Scopus and PubMed databases using the keywords "erythropoietin," "glucagon-like peptide-1," "granulocyte colony-stimulating factor," and "oxytocin" and their neuroprotective effects on neurodegenerative disorders such as "Alzheimer's disease," "Parkinson's disease," "ataxia," "spinal muscular atrophy," "autism," "amyotrophic lateral sclerosis," "Huntington's disease," "epilepsy," "ischemic brain diseases," and "stroke". Current research and literature have been reviewed.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Neuroprotective Properties of Peptides
DOI: http://dx.doi.org/10.5772/intechopen.109967

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