Molecular approaches for spinal cord injury treatment

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Abstract

Injuries to the spinal cord result in permanent disabilities that limit daily life activities. The main reasons for these poor outcomes are the limited regenerative capacity of central neurons and the inhibitory milieu that is established upon traumatic injuries. Despite decades of research, there is still no efficient treatment for spinal cord injury. Many strategies are tested in preclinical studies that focus on ameliorating the functional outcomes after spinal cord injury. Among these, molecular compounds are currently being used for neurological recovery, with promising results. These molecules target the axon collapsed growth cone, the inhibitory microenvironment, the survival of neurons and glial cells, and the re-establishment of lost connections. In this review we focused on molecules that are being used either in preclinical or clinical studies, to treat spinal cord injuries, such as drugs, growth and neurotrophic factors, enzymes, and purines. The mechanisms of action of these molecules are discussed, considering traumatic spinal cord injury in rodents and humans.

Key Words: axonal regeneration; drugs; enzymes; growth factors; molecular therapy; neurotrophic factors; purines; spinal cord injury

Introduction

The central nervous system (CNS) responds differently to injuries when compared to the peripheral nervous system. In contrast to peripheral nerves, the central axons do not efficiently and adequately regenerate after lesion.

Spinal cord injury (SCI) occurs as a consequence of abrupt or sustained trauma to the spinal cord and represents a serious clinical condition. The extent of damage depends on the intensity of the trauma which directly interferes with the patient’s prognosis (Kuricova et al., 2014). SCI results in devastating social, physical, and financial burdens for patients and families. Recent studies have reported that the incidence of SCI worldwide has ranged between 10.4 and 83 cases per million per year (Singh et al., 2014; Hejrati and Fehlings, 2021). The primary mechanical trauma results in neuroglial cell death and axonal damage and, consequently, alteration in the network required for sensorimotor function. Following this initial insult, a secondary injury cascade is initiated, which is characterized by inflammatory cell infiltration, vascular effects such as hemorrhage, ischemia and edema, ionic imbalance, glutamate release, and excitotoxicity, free radical formation, and cytokine release, which generates further neuroglial cell death and aggravates neurological deficits and outcomes (Tator and Fehlings, 1991; Bareyre and Schwab, 2003; Rowland et al., 2008; Hejrati and Fehlings, 2021).

The difficulty in regeneration is mainly attributed to the microenvironment of the injured spinal cord (Kamada et al., 2005; Yiu and He, 2006). The proximal stumps of the injured nerve fibers are exposed to the inhibitory molecules of the reactive glial environment. The recruitment of inflammatory cells and astrocytes leads to the formation of a glial scar, usually accompanied by cavities filled with chondroitin sulfate proteoglycans (CSPGs). Other inhibitory molecules are Nogo, myelin-associated glycoprotein (MAG) and, oligodendrocyte myelin glycoprotein, components of the central myelin that also interfere in the regeneration of axons. Furthermore, after axonal injury, there is also a decrease in trophic factors supply, due to intrinsic neuronal changes such as atrophy and cell death (Kamada et al., 2005; Yiu and He, 2006).

In an attempt to optimize functional restoration of the lesioned CNS, numerous neuroprotective and neuroregenerative therapeutic approaches are emerging, such as cell therapy, which has shown favorable results with the use of different cell types such as pre-differentiated embryonic stem cells (Marques et al., 2010), dental pulp cells (de Almeida et al., 2011) and mesenchymal cells (Čížková et al., 2006; de Almeida et al., 2015; Ramalho et al., 2018). On the other hand, there is a wide range of molecular compounds that are currently being used for neurological recovery, with promising results.

The goal of molecular therapeutic intervention consists of promoting axonal regeneration and sprouting, protection of neurons from cell death, and enhancement of nerve fiber conduction (Thuret et al., 2006). It is important to note that sprouting of afferent fibers in the thoracolumbar spinal cord can contribute to some conditions such as autonomic dysreflexia (Rabchevsky, 2006).

Although most research aims at motor functional recovery as a major outcome, we acknowledge other comorbidities, such as neuropathic pain and neurogenic urinary tract dysfunction, as neglected SCI related conditions, gaining attention and being evaluated as treatment goals (Anderson, 2004; Hunt et al., 2021; Morse et al., 2021; Wang et al., 2021). There are a variety of molecules that can be used to either attenuate the damage caused by the secondary injury or to stimulate regeneration and restore lost connections and functions that occur in the spinal cord after injury. In this review, we will discuss some molecular compounds that have been used after SCI and provide a summary of these strategies.

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A drug can be defined as any chemical substance, except for a nutrient or an essential dietary ingredient, which when administered to a living organism produces a biological effect. Thus, the pathophysiological processes elicited by SCI are theoretically possible to be targeted by pharmacological interventions. Despite decades of scientific studies, no drug tested so far has achieved clinical efficacy in phase III clinical trials making preclinical studies of pharmacological treatments to improve neurological function a priority in this research field. A selection of drugs that are currently employed for different pathophysiological aspects of SCI or that are being studied with promising results in both preclinical and clinical trials are listed below.

### Pharmacological Treatments for Spinal Cord Injury

**Dopamine, Atropine, Norepinephrine**

The neurogenic shock that follows SCI enhances the hypoxic damage caused by traumatic-induced vascular rupture. To minimize this condition, vasopressor and cardiac stimulant drugs such as dopamine, atropine, and norepinephrine, the muscarinic antagonist atropine, and the alpha1-adrenergic agonist midodrine are of utility in the acute clinical management of SCI patients (Markandaya et al., 2012). Additionally, prevention of further lesion of SCI may be accomplished by the use of the synthetic glucocorticoid agonist, methylprednisolone (MP). Being used since NACIS trials’ (Grossman et al., 2014). Also reducing glutamate-induced excitotoxicity, the glucocorticoid steroid with anti-inflammatory and antioxidant properties, but without its adverse events. Among these, emerged tirilazad, a non-steroidal anti-inflammatory compound that inhibits neuroinflammation and cell death, which is currently recruiting volunteers (NCT04295538). Finally, RGMa, myelin-associated glycoprotein, and Nogo-A, which also impair axonal remodeling and functional recovery (Lee et al., 2010). Thus, the blockade of the myelin inhibitors through intrathecal administration of the fragment crystallizable fraction of Nogo receptor 1 results in decreased actions through neogenin receptors, inhibiting axonal elongation (Mothe et al., 2017). Application of elezanumab, an anti-RGMa monoclonal antibody, promotes neuroprotection, neuroplasticity, and functional recovery following a thoracic hemisection of SC in non-human primates (Jacobson et al., 2011). Inspired by these promising preclinical results, a phase II clinical trial is currently recruiting volunteers (NCT04295538). Finally, RGMA, myelin proteins, and CSPG activate RhoA in growth cones, in such a way that RhoA acts as an intraneuronal hub to different inhibitory molecules of the extracellular milieu, signaling growth cone collapse (Wu and Xu, 2016). More recently, it was shown that both C3 transferase and Y27632 treatments inhibit RhoA, an early kinase, respectively, promoting axonal regeneration and recovery of hindlimb function after SCI in rodents (Dergham et al., 2002). This approach was translated to clinical trials, where VX-210, a cell-permeable derivative of C3 transferase, was employed. Although it gave promising results in phase I clinical trials, it did not reach the pre-defined efficacy endpoint in phase II (Fehlings et al., 2016).

**Leukocyte Common Antigen Related Phosphatase Related Peptides, NogoA Neutralizing Antibody, Elezanumab: Inhibitors of Growth Cone Collapse**

The SCI site remodeling is a challenge to axonal growth. The pro-inflammatory and neurotoxic epicenter is isolated from normal SC parenchyma by the gial scar, sparing the surrounding neural tissue. Conversely, scar-forming astrocytes secrete CSPG, which impairs axonal elongation (Yuan and He, 2013). Drugs that target these inhibitors have been tested for SCI repair. Leukocyte common antigen related phosphatase (LAR) was identified as a CSPG receptor that, once activated, induces growth cone collapse. Its systemic blockade with LAR-targeting peptides allowed serotoninergic regeneration and locomotor partial recovery in animal models (Fisher et al., 2011). Clinical trials employing LAR-targeting peptides were not conducted yet. Additionally, degenerating myelin sheath after SCI exposes MAG, oligodendrocyte myelin glycoprotein, and Nogo-A, which also impair axonal remodeling and functional recovery (Lee et al., 2010). Thus, the blockade of the myelin inhibitors through intrathecal administration of the fragment crystallizable fraction of Nogo receptor 1 results in decreased actions through neogenin receptors, inhibiting axonal elongation (Mothe et al., 2017). Application of elezanumab, an anti-RGMa monoclonal antibody, promotes neuroprotection, neuroplasticity, and functional recovery following a thoracic hemisection of SC in non-human primates (Jacobson et al., 2011). Inspired by these promising preclinical results, a phase II clinical trial is currently recruiting volunteers (NCT04295538). Finally, RGMA, myelin proteins, and CSPG activate RhoA in growth cones, in such a way that RhoA acts as an intraneuronal hub to different inhibitory molecules of the extracellular milieu, signaling growth cone collapse (Wu and Xu, 2016). More recently, it was shown that both C3 transferase and Y27632 treatments inhibit RhoA, an early kinase, respectively, promoting axonal regeneration and recovery of hindlimb function after SCI in rodents (Dergham et al., 2002). This approach was translated to clinical trials, where VX-210, a cell-permeable derivative of C3 transferase, was employed. Although it gave promising results in phase I clinical trials, it did not reach the pre-defined efficacy endpoint in phase II (Fehlings et al., 2016).

**Phosphatase and Tensin Homolog Antagonist Peptide 2 and 4, Bisperoxovanadium, TTK21: Promoters of Axonal Growth Intrinsically Important**

Combinational treatments stimulating the intrinsic growth capacity of CNS axons were the only approaches that have achieved both full-length regeneration and partial functional recovery within the lesioned CNS so far (De Lima et al., 2017). Phosphatase and tensin homolog (PTEN) is an enzyme that mediates the dephosphorylation of phosphoinositide-3 kinase (PI3K) targets, such as protein kinase B. Protein kinase B signaling pathway leads to mammalian target of rapamycin and S6 kinase activation, promoting protein...
synthesis and axonal elongation. PTEN systemic inhibition, with antagonist peptides PAP2 and PAP4, promotes serotonergic and corticospinal tract regeneration beyond lesion site, and locomotor function recovery in SCI animals (Ohtsue et al., 2014). Similarly, systemic treatment with the non-specific PTEI inhibitor, bisperoxovanadium, promoted tissue sparing and functional forelimb recovery after cervical spinal cord lesion in mice (Walker et al., 2012). Although bisperoxovanadium theoretically has a potential neuroprotective effect, it reduces neuroprotection and regeneration, its blockade of phosphatase activity impairs cell cycle progression required for cancer cell development (Scriven et al., 2003). Thus, PTEI inhibition seems a promising target for future clinical trials for SC repair. Besides, protein synthesis can promote axonal elongation requiring CSPGs to be transcribed and translated within the neuronal nuclei. Transcription machinery access to the genes requires chromatin remodeling, which is accomplished by post-translational modifications of histones or DNA itself. Delivery of TTK21, an activator of ChABC, can enhance protein binding proteins in CSPGs increased, thus loosening the binding of dorsal root ganglia neurons’ histones and promoted regeneration and sprouting of axons within the rodent’s SC, along with both sensory and motor improvements in behavioral assays (Hutson et al., 2019). The safety of histone acetylation promoters, such as valproic acid, is well known due to their use in the treatment of other pathologies in humans, such as epilepsy, encouraging clinical trials employing histone acetylation enhancers.

Therefore, besides the drugs available for SCI repair, several novel targets are being studied, aiming for the development of novel drugs that would eventually be able to modify other aspects of SCI pathophysiology. The combinatorial treatment with different drugs or with different regenerative therapies may have additive effects to overcome the inhibitory environment of the injured SC. Figure 1 exemplifies selected aforementioned drugs and their mechanisms of action.

**Enzymes**

**Chondroitinase**

After SCI, the physical barriers formed by the glial scars and the chemical substances secreted by them are great hurdles that inhibit the growth of central nervous system axons. The glial scar is composed of several components, of which CSPG is the most abundant (Zhang et al., 2013b). CSPG is the most prevalent extracellular matrix component secreted by astrocytes (Zhang et al., 2013a). Its inhibitory effects are accomplished by acting on oligodendrocytes and neurons, where they impair remyelination and axonal growth, respectively. CSPG signals through different receptors, such as LAR, protein tyrosine phosphatase α (PTPα) and Ngr 1, 2, and 3 (Sapieha et al., 2019). Stronger inhibition was found in a Scrt/mice (Griffiths et al., 2019). Early suppression of CSPG secretion from reactive astrocytes can reduce their inhibitory effect on nerve fiber regeneration (Zhang et al., 2013b). Therefore, focusing on early suppression of CSPG production by astrocytes may reduce their inhibitory effect on post-injury axonal regeneration (Profyris et al., 2004).

Chondroitinase ABC (ChABC) has been shown to promote regeneration of axons through the glial scar (Yick et al., 2003). ChABC is obtained from the bacteria Proteus vulgaris and acts by degrading the glycosaminoglycan side chains of CSPGs. Degradation of CSPG with the use of ChABC removes the inhibitory effect of CSPG secreted from the glial scar (Figure 2) (Raspa et al., 2011). It has been reported that ChABC treatment after SCI reinitiates post synaptic activity below the lesion site and promotes functional recovery of locomotor and proprioceptive behaviors in rats (Bradbury et al., 2002; Mahajan, 2018). Besides ChABC, infusion enhances recovery after experimental nigrostriatal lesions and in several animal models of SCI (Mountney et al., 2010). These promising results in animal models strongly drive the initiation of human tests (Mahajan, 2018).

In addition to acting individually, ChABC has been tested in combination with other pre-regenerative therapies as a potential treatment for SCI. Among them is the combination with enteric neural stem cells, bone marrow mesenchymal stem cells, barbary oxygen therapy, treadmill rehabilitation, GDNF, and other enzymes, like sialidase (Garcia-Altas et al., 2009; Zhang et al., 2013a; Shinozaki et al., 2016; Liu et al., 2018; Jeavons et al., 2021).

**Sialidases**

These enzymes are glycosidases responsible for the removal of sialic acid (SA) residues (desialylation) from glycan portions of either glycoproteins or glycolipids (Yuan et al., 2020). The Sias are a family of 9-Carbon containing acidic monosaccharides found on both N- and O-linked glycans of either glycoproteins or glycolipids. Sias is involved in many biological processes, as regulating cellular interactions in controlling activation, differentiation, transformation, and migration of cells (Moutney et al., 2013).

The hydrolytic removal of Sias (desialylation) from glycoproteins or glycolipids takes part in the regulation of various physiological and pathological pathways (Mountney et al., 2010). Desialylation of glycoconjugates influences cell signal transduction, adhesion, apoptosis, receptor trafficking, phagocytosis, cell migration, cell transformation, differentiation, migration, and neurotogenesis. Therefore, sialidases regulate many cellular processes in both physiological and pathological conditions by removing Sias from glycoconjugates (Yang et al., 2018).

The microenvironment of SCI is highly inhibitory for axonal regeneration. Endogenous inhibitors, including those on residual myelin, for example, MAG, contribute to regeneration failure. MAG binds to various neuronal receptors to inhibit axonal outgrowth, including Nogo receptors (Ngr1 and Ngr2), PirB, β1-integrin, and sialoglycans (Vyas et al., 2005; Mehta et al., 2007). Some neurons respond to MAG primarily via sialglycans, whereas others use Ngrs and other receptors. Gangliosides are the most abundant sialglycans on nerve cells. MAG inhibition of axonal outgrowth in some neurons is reversed by treatment with sialidase, an enzyme that hydrolyzes sialic acids and eliminates MAG-sialglycan binding (Figure 2) (Vyas et al., 2002). Sialidase treatment enhances recovery after spinal cord contusion in the rat (Mountney et al., 2010). Therefore, sialidase emerges as a potential biological drug for the treatment of axons, validating sialylglycans as therapeutic targets for the treatment of SCI.

Another important therapy, in addition to sialidase, is the use of polysaccharide (PSA). PSA is a natural, biodegradable, and negatively charged polysaccharide mainly used to attract multilayer cell adhesion (Chiba et al., 2018). Several studies report its importance concerning its therapeutic possibility. Among the advantages discussed above, it is known that PSA decreases tumor necrosis factor-α and IL-6 release, by carefully designed calcium-binding adapter molecule 1, microglia/macrophage activation, and reduces apoptosis-associated caspase-3 protein expression. In addition, PSA inhibits axonal demyelination and glial fibrillary acidic protein expression, increases neurofilament 200 expression, and improves the functional outcome (Mehanna et al., 2010; Zhang et al., 2018). Therefore, PSA also stimulates regeneration in the central nervous system after SCI (Saini et al., 2016).

In conclusion, among axonal regeneration inhibitor-targeted experimental therapies, two bacterial enzymes have emerged as potential drugs to treat SCI. ChABC cleaves inhibitory CSPGs and sialidase cleaves sialoglycans for MAG (Vicky et al., 2003; Mountney et al., 2013). Therefore, including the combination of such therapies can favor a better axonal regeneration, reflecting in potential functional recovery after SCI (Bradbury et al., 2002; Mountney et al., 2015).

**Growth and Neurotrophic Factors**

Growth factors and neurotrophic factors are secreted biomolecules that are present in the nervous system during development and throughout adult life; they promote neuronal cells development, differentiation and survival, neurite outgrowth, synaptogenesis, and neuroprotection in vitro and in vivo. Factors involved in the topography of axonal projections during development and regeneration. Growth factors can be produced by many different tissues; most neurotrophic factors belong to one of the three families: (A) neurotrophins (NGF, BDNF, NT3, NT4, and their receptors), (B) basic fibroblast growth factors (bFGF or FGF2) and (C) the insulin-like growth factor (IGF). In the cellular responses elicited by them often overlap.

**Fibroblast growth factor**

When discovered, FGF was an unknown protein extracted from the cow’s pituitary gland and was named NIH-LH-B8 (Armelin, 1973). It seemed to have a highly specific activity, turning resting-state 3T3 fibroblast lineage into a highly active fibroblast-like phenotype (Dumontet and Issad, 1974). Nowadays, FGF is known to be a protein family composed of 23 trophic factors which exert a wide variety of effects such as proliferation, differentiation, migration, chemotaxis, neurogenesis, and axonal growth. Among these proteins, the basic fibroblast growth factor (bFGF or FGF2) emerges as a potential treatment in the medical regenerative field (Itoh and Ornit, 2008). FGF2 promotes mitogenic activity, stem cell-state steadiness, and cell survival (Ding et al., 2010; Mossaheli-Mohammadi et al., 2020). These are useful properties for foreseeing a novel treatment for SCI. Using a thoracic spinal cord transection model in C57BL/6J mice, Huang and colleagues observed, 12 weeks after injury, increased density of axons and better-spared tissue after intravenous injection of human umbilical cord-derived stem cells expressing bFGF (bFGF-MSCs) as compared to vehicle administered control mice and to umbilical cord-derived stem cells without bFGF expression and control mice (Zhu et al., 2020a). Dawley rats of a construitive model of SCI, similar results were noticed with allograft transplantation of AAA-VAV-transfected neural stem cells carrying the bFGF gene inside the lesion’s epicenter. It was also observed more spared neurons, axonal growth, and discrete astrogliosis in the bFGF treated group compared to the control group (Zhu et al., 2020b). The above evidence demonstrates that bFGF has multiple unique functions, bFGF binds to its transmembrane receptor degrading P3K/AKT/mTOR, RAS/MAPK, and PLCγ (Figure 3) pathways (Zhou et al., 2018; Cai et al., 2021).

bFGF similar drugs were synthesized and membranes with drug-delivering scaffolds are being developed as possible treatments to spinal cord injuries (Zhou et al., 2018; Edamura et al., 2020; Imagama et al., 2020). Despite these promising results, bFGF research is still in the pre-clinical stage.

**Platelet-derived growth factor**

PDGF was initially identified as having a growth-promoting activity in platelets, being later verified its production by many varieties of cell types, such as glial...
most of them exert their trophic effects through tyrosine kinase receptors classical activation. The FGFR (BFGF), PDGFR (PDGF), TRKA (NGF), TRKB (BDNF), and EGF (EGR) dimerization triggers many intracellular signaling pathways, including the Ras-MAPK, the PI3K, AKT/mTOR, and PLCγ-dependent pathway. However, GFRα1 and CNTF-Rα1, which bind to GDNF and CNTF respectively, need to form a complex multisub unit receptors system to signal. GDNF can be signaled by GDNF-GFRα1-RET signaling complex (canonical way), or by GDNF-GFRα1-NCAM complex (alternative pathway) and activate AKT/mTOR and MAPK pathway. CNTF can signal by a heterodimer (gp130-LIFRβ) activating JAK/STATs pathway and other signaling ways. TRKs activation by these factors can promote neuronal survival, synaptic plasticity, neurite outgrowth, axon growth, protein synthesis, and cell proliferation. AKT: Ak strain transforming; BDNF: brain-derived neurotrophic factor; CNTF: ciliary neurotrophic factor; CNTF-Rα1: ciliary neurotrophic factor receptor α1; EGF: epidermal growth factor; EGR: epidermal growth factor receptor; FGF: fibroblast growth factor receptor; GDNF: glial cell line-derived neurotrophic factor; GFRα1: GDNF receptor alpha-1; gp130: glycoprotein 130; JAK: janus kinase; LIFRβ: leukemia inhibitory factor receptor β; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; NCAM: neural cell adhesion molecule; NGF: nerve growth factor; PDGFR: platelet-derived growth factor receptor; PI3K: phosphatidylinositol 3-kinase; PLCγ: phospholipase C gamma; Rac: ras sarcoma virus; RET: rearranged during transfection; STAT: signal transducer and activator of transcription; TRK/A/B: tyrosine kinase receptor A/B; BFGF: fibroblast growth factor beta.

Figure 2 | Role of enzymes after spinal cord injury. After spinal cord injury, a glial scar is formed at the injury site and CSPG is secreted by reactive astrocyte. The CHABC degrades the side chains of GAGs and, therefore, CSPG degradation occurs. The blocking of the CSPGs enable axonal regeneration. Regarding sialidase, its activity is to remove sialic acid, promoting the elimination of MAG-sialic acid binding. The blocking MAG allows axonal regeneration. These are strategies to allow functional recovery after spinal cord injury. CSPG: Chondroitin sulphate proteoglycan; GAGs: glycosaminoglycans; MAG: myelin associated glycoprotein.

cells and neural progenitors. There are four different PDGF genes (PDGFA-D) that encode PDGF-α, β, γ, and δ. PDGF-α, β, and δ can dimerize with different affinities to one of the three tyrosine kinase receptors (PDGFR-α, PDGFR-β, and PDGFR-δ) and signal by various intracellular pathways associated with cell division and growth, including the PI3K/AKT/ mTOR pathway, RAS/MAPK, and STAT families, besides PLCγ activation as seen in Figure 3 (Andrè et al., 2008).

In an experimental study, PDGF protects against blood-s spinal cord barrier disruption after SCI by remodeling the neurovascular units, upregulating tight and adherens junctions, and promoting autophagic flux activation (Ye et al., 2021). The blood-spinal cord barrier plays a vital role in SCI recovery, thus its preservation can reduce other degenerative events such as loss of microvasculature, infiltration of blood-derived macrophages, neuroinflammation, oxidative stress, glial scar formation, and cell death.

Inflammatory response and M1 or M2 subtype polarization of macrophages/monocytes in microglia/macrophages, reducing calcium-activated proteases and calcium-dependent Caspase-3 activation and neuronal apoptosis. Besides, it reduces microglial/macrophage p38 MAPK activation and factor-related molecule. (2) Baclofen activates GABAB receptors, hyperpolarizing the neuron that switches its axonal phenotype to a growth competent state. (3) PTEN inhibitors release the blockade of the growth factor stimulation of PI3K/AKT/mTOR-S6 induction of protein synthesis and axon growth. (4) TTK21 activates the Histone Acetylase cAMP response element-blocking protein (CBP)/PI300, facilitating the transcription machinery access to regenerative-related genes. (5) LAR antagonists impair growth cone collapse, via decreased RhoA activation. (6) MP activates glucocorticoid receptors in microglia/macrophage, polarizing the inflammatory response to the M2 profile. (7) Tirilazad promotes ROS scavenging, preserving spinal cord tissue. (8) NGR1 antagonists impair growth cone collapse, via decreased RhoA activation. (9) VX-210 inhibits RhoA activation directly, impairing growth cone collapse. cAMP: cyclic adenosine monophosphate; CBP: CREB binding protein; P300: GABAB; gamma-aminobutyric acid B receptor; LAR: leukocyte common antigen related phosphatase; M1: macrophage 1; M2: macrophage 2; MAPK: mitogen-activated protein kinase; MP: mTOR: mammalian target of rapamycin; NGR1: Nogo receptor 1; PDGFR: platelet-derived growth factor receptor; PI3K: phosphatidylinositol 3-kinase; PTE: phosphatase and tension homolog; Rac: Ras homolog family member A; ROS: reactive oxygen species; S6: ribosomal S6 kinase; TTK21: N-(4-chloro-3-(trifluoromethyl)phenyl)-2-propoxy-benzamide; VX-210: Rho inhibitor VX-210.
GDNF contributes to astrogliosis modification by glial fibrillary acidic protein and CSPGs down-regulation, resulting in secondary damage reduction and robust axonal regeneration in adult rats (Deng et al., 2011; Anderson et al., 2018). Also, it stimulates the myelination (Zhang et al., 2009) and extends axonal growth on axonal regrowth (Anderson et al., 2018), being involved in neuronal survival and formation of the neuromuscular synapse during development and disease (Deng et al., 2011; Anderson et al., 2018).

Since GDNF does not cross the blood-spinal cord barrier, it demands local administration or conjugating GDNF with other molecules, such as viral proteins, antibodies, or genetically modified cells that secrete GDNF, overcoming this limitation. Combining GDNF administration and SC transplantation has been proposed as a possible strategy to promote axonal regeneration and myelin formation after SCI (Deng et al., 2011), and the combination of GDNF with other neurotrophic factors enhances its therapeutic capability (Anderson et al., 2018).

**Nerve growth factor**

After its identification in 1953 by Rita Levi Montalcini, Viktor Hamburger, and Stanley Cohen, NGF revealed its protagonist role among trophic factors in regeneration after SCI ( Sharma, 2007). The presence or absence of NGF in the CNS microenvironment, or even its precursor form, proNGF, is responsible for intricate molecular mechanisms, which will lead to neuronal survival or apoptosis via TrkA or low-affinity NGF receptor (LNGFR/p75NTR). Specifically, NGF will either induce transcription factor activity such as NF-kB, CREB, ELK1, and regulator factor bcl2, which are involved in cell survival or will induce c-Jun/C-Fos AP-1 apoptotic activity. To induce cell survival or cell death, NGF has to interact with TrkA or proNGF promoting an amplification downstream RAS/MAPK or PI3K/Akt/mTOR pathways (Figure 3) which have also been implicated in other trophic factor mechanisms and axonal regeneration (Lee et al., 2001; Freeman et al., 2004).

Experimental studies indicate that NGF released from neural progenitor cells transplanted inside the cerebral cortex of an organotypic model promoted axonal growth through a corticospinal tract (Kamei et al., 2009). Neuron survival, axonal growth, decreased apoptosis, spared parenchyma, reduced formation of cavities, reduced astrogliosis, and better motor function recovery were seen in murine models after SCI when treated with different NGF delivery methods (Song et al., 2021; Xia et al., 2021). Preclinical studies have shown encouraging results. Therefore, NGF is one of a few trophic factors being already studied in a clinical trial. In one study, 46 patients with motor and sensory functions were hampered by lumbar intervertebral disk herniation. Between the groups (Chesta et al., 2021). In this research, the group treated with intramuscular methylcobalamin-NGF injection presented, weeks after the decompression surgery, better neurological outcomes compared with the group that underwent decompression surgery followed by just methylcobalamin intramuscular injection.

**Brain-derived neurotrophic factor**

BDNF is another extensively studied neurotrophin. Like NGF, BDNF has neuronal survival and axonal elongation properties, also participating in neuronal plasticity, formation, and cognition (Kamei et al., 2009). Neuron survival, axonal growth, decreased apoptosis, spared parenchyma, reduced formation of cavities, reduced astrogliosis, and better motor function recovery were seen in murine models after SCI when treated with different NGF delivery methods (Song et al., 2021; Xia et al., 2021). Preclinical studies have shown encouraging results. Therefore, NGF is one of a few trophic factors being already studied in a clinical trial. In one study, 46 patients with motor and sensory functions were hampered by lumbar intervertebral disk herniation. Between the groups (Chesta et al., 2021). In this research, the group treated with intramuscular methylcobalamin-NGF injection presented, weeks after the decompression surgery, better neurological outcomes compared with the group that underwent decompression surgery followed by just methylcobalamin intramuscular injection.

**Ciliary neurotrophic factor**

CNTF release is enhanced after SCI by invading Schwann cells, local astrocytes, and muscle fibers and maintains survival and differentiation of various neuronal and nonneuronal cell types. CNTF is a glycoprotein that belongs to the IL-6 family, and its heterotrimetric receptor is composed of the CHI4L1 receptor alpha (CNTFRα), glycoprotein-130 (gp130), and the leukemia inhibitory factor receptor (LIFRβ, also known as CD118). The CNTF/CNTFRα complex subsequently binds to gp130 and LIFRβ, and this heterodimerization activates the JAK/STATs pathway, RAS/MAPK, and PLCγ (Figure 3), which promote diverse gene transcription regulation (Chen et al., 2009; Pasquin et al., 2015). Alternative activation of IL6Ra/gp130/LIFRβ tripartite receptor by high CNTF concentration might contribute to the extreme weight loss observed in humans and animals upon CNTF systemic administration (Sleeman et al., 2000). On the other hand, local administration of CNTF does not show side effects and can promote motor neuron survival, protect neurons in the red nucleus, promote axonal regeneration, increase sensory and motor neuron survival, enhance tissue sparing, modulate astrocytic and microglial activity in the vicinity of the injury, increase the survival and differentiation of adult oligodendrocyte precursor cells, enhance remyelination, and improve functional outcomes (Ye et al., 2004; Cao et al., 2010). Besides, CNTF influences neuroinflammation by macrophage chemotaxis or reactive astrocytes. CNTF can regulate the reactive astrocyte polarization from A1 (neurotoxic) to the A2 (neuroprotective) phenotype and promote A2-type reactive astrogliosis by activating the STAT3 signaling pathway. Also, STAT3 might be essential for glial scar formation and astrocytic neuroprotective profile after SCI (Zhang et al., 2021).

**Purines**

In the field of CNS injuries treatments, molecular therapies have shown promising results in regeneration, neuroprotection, and other effects. Nowadays, it is widely known that purines nucleosides, such as adenosine, adenosine’s metabolic subproducts inosine and guanosine, exert more biologically neutral effects related to the nucleic acid constitution and cell energy metabolism (Ribeiro et al., 2016). Here we review the contribution of purines on SCI treatment (Figure 4).

Purines are derived from the degradation of DNA and RNA and play a fundamental role in the maintenance of the nervous system. They are involved in various processes, including neurotransmission, synaptic plasticity, and neurovascular coupling. In the context of SCI, purines have been extensively studied for their potential therapeutic effects. Adenosine and its metabolites, inosine and guanosine, are key players in the modulation of neural plasticity and neuroprotection. In this review, we will focus on the actions of purines in the context of SCI, highlighting their role in promoting neuroprotection and regeneration.
in osinone that can act as an agonist, binding directly to A1, A2A, and A3, and can trigger the well-known effects of these receptors (Haskó et al., 2004; Weihlinda et al., 2016; Vincenzi et al., 2020). Like adenosine, osinone concentration, both intra and extracellularly, is regulated by nucleotide transporters (Dodd et al., 2016). Unlike adenosine, osinone is more stable and has a half-life of approximately 15 hours (Weihlinda et al., 2016). Besides the binding to ARs, osinone can diffuse into neurons and activate the mammalian target of rapamycin (mTOR) via a protein kinase A (PKA)-dependent pathway that regulates axonal growth (Kim et al., 2013).

After spinal cord lesion, injured and uninjured axons can form compensatory circuits, extending collateral branches (Kim et al., 2013). In a model of spinal dorsal column transaction, the use of osinone stimulated the sprouting of axons from the corticospinal tract to the contralateral side. Furthermore, this treatment can establish propriospinal ipsilateral projections, partially reestablishing corticospinal control at the lumbar level, improving motor function recovery (Kim et al., 2013). After a compressive SCI, the oral administration of osinone showed a major sparing of the white matter and improved the survival of ventral horn motorneurons, and recovery of motor function (Kuricova et al., 2014). A model using complete transection or compressive SCI induced neurogenic detrusor overactivity. Two ways of osinone administration were performed: (1) in compression (in both compression and transection groups); (2) 8 weeks (only in compression group) after injury. In osinone administered both 6 weeks (immediate administration) and 14 weeks (delayed administration) after injury showed significant attenuation of detrusor overactivity. Transection SCI induces a local inflammatory reaction and persistent demyelination in the white matter around the lesion site (Jiang et al., 2003). Using a compressive SCI model and intraperitoneal (i.p.) administration, guanosine demonstrated effects over myelination, stimulating oligodendrocyte progenitors to differentiate into mature cells. This was confirmed using a specific marker of mature oligodendrocyte, the monoclonal antibody Rip, and observing a great number of Rip-positive cells. They also immunostained sections for MBP and showed the presence of MBP-positive and Rip-positive cells, corroborating observed improvement in myelination which resulted in better locomotor function (Jiang et al., 2003). Guanosine also has a neuroprotective effect after SCI. Using a compressive SCI model and i.p. administration, guanosine preserved the function of long tracts, enhanced the recovery of bladder function within 7 days, exerted an immunomodulatory effect, attenuating the activation of microglia/macrophage, and significantly suppressed apoptosis (Jiang et al., 2007). The i.p. administration can rapidly increase the levels of guanosine and its metabolites (guanine, xanthine, and uric acid) in the brain and SC, despite purine metabolism in peripheral tissue. Immediately after the i.p. injection, the proportion of guanosine-guanine is 2:1. Thirty minutes after the i.p. injection, guanosine (13) (Jiang et al., 2003). This improvement is mediated by the activation of P3K/Akt, a pathway responsible for myelination, enhances axonal regeneration, and exerts neuroprotection, improving functional recovery, after SCI. Up to now, no clinical trials have been reported employing guanosine after SCI.

Conclusion

Central axons fail to regenerate appropriately after a traumatic lesion. Therefore, the damaged connections are not reestablished after SCI, leaving permanent dysfunctions. Among several therapeutic interventions, molecular therapy has been showing promising results in terms of functional recovery. Pharmacological, growth and neurotrophic factors, enzymes, and purines are being tested as a treatment after SCI. The mechanism of action of these molecules targets the axon collapsed growth cone, the inhibitory microenvironment, and the survival of neurons and glial cells, particularly the oligodendrocytes that form the central myelin sheath. Despite several decades of experimental studies, most of these molecules are still at the preclinical stage; therefore, there is a growing need for more robust and well-designed experiments. Furthermore, there are still some studies focusing on the combination of molecules or association of molecular therapy with different strategies, such as cell therapy, exercise, among others. Experimental studies focusing on combinations of molecules and/or pro-regenerative strategies are needed and, hopefully, will provide better outcomes in terms of functional recovery after SCI.

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