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Review Article

Non-invasive approaches to functional recovery after spinal cord injury: Therapeutic targets and multimodal device interventions

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ABSTRACT

This paper is an interdisciplinary narrative review of efficacious non-invasive therapies that are increasingly used to restore function in people with chronic spinal cord injuries (SCI). First presented are the secondary injury cascade set in motion by the primary lesion and highlights in therapeutic development for mitigating the acute pathophysiologic process. Then summarized are current pharmacological strategies for modulation of noradrenergic, serotonergic, and dopaminergic neurotransmission to enhance recovery in bench and clinical studies of subacute and chronic SCI. Last examined is how neuromechanical devices (i.e., electrical stimulation, robotic assistance, brain-computer interface, and augmented sensory feedback) could be comprehensively engineered to engage efferent and afferent motosensory pathways to induce neuroplasticity-based neural pattern generation. Emerging evidence shows that computational models of the human neuromusculoskeletal system (i.e., human digital twins) can serve as functionalized anchors to integrate different neuromechanical and pharmacological interventions into a single multimodal prothesis. The system, if appropriately built, may cybernetically optimize treatment outcomes via coordination of heterogeneous biosensory, system output, and control signals. Overall, these rehabilitation protocols involved neuromodulation to evoke beneficial adaptive changes within spared supraspinal, intracord, and peripheral neuromuscular circuits to elicit neurological improvement. Therefore, qualitatively advancing the theoretical understanding of spinal cord neurobiology and neuromechanics is pivotal to designing new ways to reinstate locomotion after SCI. Future research efforts should concentrate on personalizing combination therapies consisting of pharmacological adjuncts, targeted neurobiological and neuromuscular repairs, and brain-computer interfaces, which follow multimodal neuromechanical principles.

1. Background

The debilitating sequalae of spinal cord injuries (SCI) have, until very recently, been considered irreversible. Life expectancies of those with SCI were limited before improvements in acute clinical management emerged in the middle of the twentieth century (Middleton et al., 2012; Savic et al., 2017). Today, people with SCI are successfully reintegrating into society and, to some extent, individuals with incomplete injuries can live independently with nearly normal lifespans (Pershouse et al., 2012). Present reintegration, however, largely relies on compensatory tools and assistive devices rather than sustainable functional recovery (Côté et al., 2017). Therefore, restoration of volitional arm-hand function and/or locomotion remains a top priority (Holanda et al., 2017; Maciejasz et al., 2014). Lack of functional improvement can substantially increase rates of severe complications (e.g., respiratory failure, lower urinary tract disorder, and musculoskeletal defect; Hall et al.,

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2019).

The initial insult to a spinal cord, whether a contusion, compression, laceration, or penetration, instantly produces physical damage (i.e., the primary injury). Its pathological consequences are mainly determined by the lesion's scale and anatomical location (Ahuja et al., 2017; Freund et al., 2019). Immediately afterwards, cascades of biochemical and pathophysiological events set secondary injury processes in motion, which last for minutes, days, weeks, months, or even years, depending on the specific mechanisms involved, to exacerbate structural and functional losses (Ahuja et al., 2017). Typical secondary biochemical events include excessive release of norepinephrine (Vise et al., 1974) and glutamate or aspartate (i.e., excitotoxicity; Bell et al., 2017; Liu et al., 1991), reduced intraparenchymal oxygen (O_2), raised lactate level and lactate/pyruvate ratios (Bell et al., 2017; Farooque et al., 1996), ionic imbalance (e.g., extra- or/and intracellular Na^+, K^+, H^+, Ca^{2+}, Cl^-, OH^- disturbances; Agrawal and Fehlings, 1996; Teng and Wrathall, 1997), surges of reactive oxygen (ROS) and nitrogen species (RNS; Visavadiya et al., 2016; Yu et al., 2009), mitochondrial dysfunctions (e.g., respiration reduction, ↑ROS, and cytochrome *c* release), and caspase activation (Rabchevsky et al., 2020; Teng et al., 2004).

These perturbations produce acute (minutes to hours: e.g., < 48 h post injury [p.i.] in humans) and subacute (days to weeks: clinically, 48 h – 14 days p.i.) excitotoxicity (Liu et al., 1999; Wrathall et al., 1992), hemorrhagic necrosis and vascular/blood circulation disruptions (Matsushita et al., 2015; Mautes et al., 2000), ischemia (Brown et al., 2014), acidosis (Li et al., 2021; Teng and Wrathall, 1997), action potential conduction failure (James et al., 2011), and oxidative lesions (Christie et al., 2008; Liu et al., 2020; Visavadiya et al., 2016). Also occurring in these stages are neural cell necrosis, apoptosis, necroptosis, pyroptosis and parthanatos (Liu et al., 2020; Kuzhandaivel et al., 2010; Springer et al., 1999), axon and myelin destructions (James et al., 2011; Rosenberg et al., 1999a, 1999b), leukocyte infiltration (Fleming et al., 2006), neural and systemic inflammation (Bloom et al., 2020; de Rivero Vaccari et al., 2016), reactive astrogliosis (Anderson et al., 2016), and cystic microcavity formation (Losey et al., 2014; Miyao et al., 2020). Other pathophysiological events are endoplasmic reticulum stress (Saraswat Ohri et al., 2018b) and abnormal autophagy (Saraswat Ohri et al., 2018a).

The events jointly produce neural and vascular cell loss and disrupt ascending and descending neuropathways, neuromuscular communication, and the central pattern generation (CPG) network. These damages result in sensorimotor deficits below the level of injury and acute systemic disorders including respiratory dysfunctions, cardiovascular disorders, gastrointestinal abnormality, and gut dysbiosis (Aarabi et al., 2012; Furlan and Fehlings, 2008; Kabatas et al., 2008; O'Connor et al., 2018) (Fig. 1). The body, challenged by the primary and secondary assaults, rapidly activates its repair responses represented by transient neural stem cell (NSC) proliferation, beneficial inflammation, endocannabinoid production, and tissue healing. But the spontaneous responses are mostly futile attempts to restore neural function (Fig. 1a-c); however, they continually take place during all post-SCI stages, offering potential therapeutic targets (Arevalo-Martin et al., 2012; Sabelström et al., 2013; Teng, 2019a).

In the intermediate (weeks to months: 14 days – 6 months p.i. in humans) and chronic phases of SCI (months to years: clinically, > 6 months p.i.), accumulating secondary outcomes from a particular lesion level and severity combination gradually reach an equilibrium state. This is built via the interaction between the pathophysiological events and the body's endogenous healing mechanisms (see details above). Such an equilibrium defines a chronic clinical profile unique to each individual SCI case (Krishna et al., 2014). Without effective managements, any early chronic stage "equilibrium" will inevitably deteriorate. The downfall is caused by a slowly worsened interstitial environment, characterized by buildup of trace amines and their metabolites (Gozal et al., 2014; Li et al., 2017), pro-neuroinflammatory milieu, and a degenerating neuromusculoskeletal network (Fig. 1c) (Fleming et al., 2006; Clark and Findlay, 2017). For example, trace amines produced by pericytes were shown to activate receptors in the absence of monoamine neurotransmitters in the lesioned cord, which, depending on dose levels, could hinder motosensory function by inducing hypoxia and vasoconstriction (Gozal et al., 2014; Li et al., 2017).

The chronic pathology is characterized by axon demyelination (Guest et al., 2005), syrinx formation and enlargement (Krebs et al., 2016), astroglial scar aging (Yoon et al., 2018), and serotonin (5-hydroxytryptophan: 5HT) deprivation in the below-lesion cord (Ganzer et al., 2018). These are coupled with the maladaptive plasticity of the brain (Freund et al., 2011), spinal cord (Cadotte et al., 2012; Strain et al., 2019), peripheral nerves, and effector organs (Chariker et al., 2019; Kern et al., 2017; van De Meent et al., 2010). The impairments of muscles and bones jeopardize rehabilitation opportunities (Frontera et al., 2006; Clark and Findlay, 2017; Morse et al., 2008). Serious complications commonly arise in the respiratory (van Silfhout et al., 2016), lower urinary tract (Chan et al., 2018; Kanai et al., 2011), gastrointestinal (Holmes and Blanke, 2019; Jogia and Ruitenberg, 2020), cardiovascular (e.g., autonomic dysreflexia; Dorton et al., 2020; Eldahan et al., 2020), and reproductive systems (Stoffel et al., 2018) (Fig. 1c and d).

In the USA, ~45.4% of patients were discharged with cervical SCI; the next most frequent injury levels were T12 (~6.1%) and L1 (~4.7%) (i.e., thoracolumbar SCI; 2019 data of The National Spinal Cord Injury Statistical Center: www.nscisc.uab.edu). Global data had similar distribution features (Lee et al., 2014). To consistently describe SCI, the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) was first published in 1982 by the American Spinal Injury Association (ASIA; Chicago, IL; 1982 [Google Scholar]). With periodic revisions, ISNCSCI (i.e., the ASIA Impairment Scale: AIS-A to E) has since become the most widely used SCI classification system (Kirshblum et al., 2020; Maynard Jr. et al., 1997). Based on the 2019 NSCISC data, at acute admission, 44.3% of individuals were diagnosed as AIS-A (complete), 12% as AIS-B (sensory only), 13.9% as AIS-C (non-functional motor), 19% as AIS-D (functional motor), and 10.9% as AIS-E (recovered).

Clinically, trauma to the spinal cord usually does not completely sever it. People with acute SCI who exhibit residual neurological signs below the lesion level were likely to have better prognoses for some natural or rehabilitation-induced recovery (Scivoletto et al., 2014). For example, there were 19.0% and 11.2% AIS-D participants at acute and rehabilitation admissions, respectively, which improved to 32.2% at system discharge (NSCISC: 2019 data). These facts have laid down the foundation for developing pharmacological, cell, bioengineering, gene, rehabilitation, and multimodal therapies to preserve, protect, regenerate, and reactivate the available neural matrix in the injured spinal cord to recover function.

2. Contemporary management of acute SCI

The management of acute SCI has successfully evolved from basic life support and wound care to comprehensive approaches. Prior to the end of the second world war, SCI was the most lethal encounter of all traumas and invariably resulted in a dismal prognosis. Marked progress has since been made to qualitatively improve outcomes (Shank et al., 2019). Present common protocols involve surgical decompression and stabilization, with or without neuroprotective or anticoagulative pharmacological interventions, treatment or prevention of infection and complication, and optimization of patients' options for rehabilitation (Côté et al., 2017; Furlan et al., 2011).

Decompression and stabilization, albeit with lack of consensus about timing of intervention, can minimize acute impairments to the cord that would otherwise aggravate pre-existing conditions and jeopardize clinical prognosis (Fehlings et al., 2012; Kim et al., 2018). Importantly, decompression via laminectomy and myelotomy was first investigated by Dr. Alfred Reginald Allen in 1911, in which the intervention

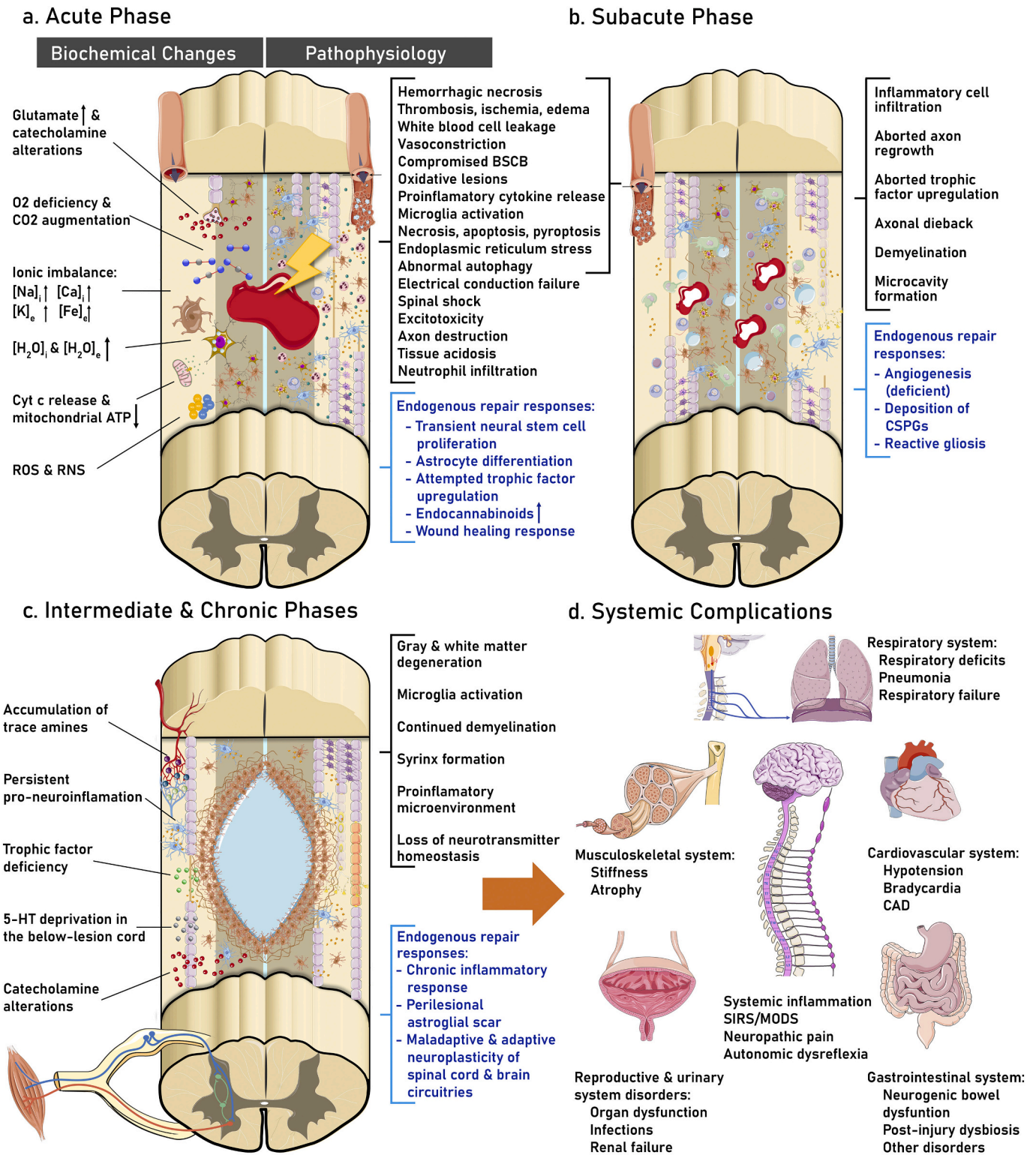

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Fig. 1. An overview of pathophysiology and clinical outcome of traumatic spinal cord injury. Clinical spinal cord injury (SCI) produces acute (0-48 h), subacute (2-14 days), intermediate (2 weeks-6 months) and chronic (> 6 months) phases of pathophysiological consequences. (a) In acute SCI, primary mechanical insult to neurons, glial cells, axons, and blood vessels sets a series of biochemical and pathophysiological events in motion, forming secondary injury processes. (b) Continued ischemia and inflammation cause delayed neural cell death, axon demyelination, neuron degeneration, glial malfunction, reactive gliosis, and suppression of endogenous repair responses in the subacute phase of SCI. The events jointly promote development of cystic microcavities (see details in c). The spinal cord, in response, strengthens its healing process consisting of astrocyte and pericyte proliferation, astrogliosis, inflammatory responses, etc., to close the wound despite major concession to neurological recovery. (c) Around the injury epicenter, post-traumatic syrinx formation is developing in more severely lesioned spinal cords in the intermediate phase and lasts into the chronic stage. Incessant in both phases are Wallerian degeneration, microglia activation, and production of pro-inflammatory cytokines. Inhibitory and excitatory neurotransmitters are imbalanced, paralyzing neural circuitry. Moreover, excessive accumulation of endogenous trace amines triggers capillary constriction and hypoxia. Serotoninergic innervation is deprived below the lesion and catecholamine/glutamine/peptide neurotransmission altered. The spinal cord, brain, and peripheral effectors (see specifics in d) endure maladaptive plasticity and chronic degeneration. (d) SCI results in systemic complications affecting multiple organs, especially after high-level lesions. Commonly compromised are the motosensory, musculoskeletal, respiratory, cardiovascular, lower urinary tract, gastrointestinal (including gut microbiota), reproductive, autonomic, and immune systems, further aggravating disability. If not effectively treated, the complications may instigate SIRS and MODS.
Abbreviations: (1) 5-HT: 5-hydroxytryptamine (also called serotonin); (2) CSPGs: chondroitin sulfate proteoglycans; (3) Cyt *c*: cytochrome *c*; (4) MODS: multiple organ dysfunction syndrome; (5) RNS: reactive nitrogen species; (6) ROS: reactive oxygen species; and (7) SIRS: systemic inflammatory response syndrome.

improved neural outcomes in an experimental model of spinal cord contusion (Allen, 1911). Whether myelotomy has tangible clinical efficacy for acute SCI remains to be further verified (Koyanagi et al., 1989; Telemacque et al., 2020). Thus, for standardizing surgical treatment protocols, using an evidence-based decision-making approach is crucial. To achieve better clinical outcomes, combinational use of pharmacological treatment is imperative (Fehlings et al., 2017).

2.1. Developing a standardized drug treatment for acute SCI

Bench-side pharmacological research in the early 1980s uncovered the effects of methylprednisolone (MP; a glucocorticoid) on inhibition of lipid peroxidation in cell membranes, reduction of intraparenchymal ischemia, and enhancement of aerobic energy metabolism in animal models (Hall and Braughler, 1981; Hall et al., 1984; Young and Flamm, 1982). The findings, together with the clinical anti-inflammatory and antiedemic effects of MP, facilitated the launch of the Second National Acute Spinal Cord Injury Study (NASCIS II; Bracken et al., 1990). In an earlier trial, which was termed NASCIS I post hoc, a smaller dose regimen of MP given over 10 days post SCI produced no significant therapeutic results (Bracken et al., 1984; Bracken et al., 1985). In distinction, evaluating MP, naloxone, and placebo, the NASCIS II trial revealed significant benefits of high-dose MP (30 mg/kg, i.v. bolus, plus a 23-h infusion at 5 mg/kg/h) when the first dose was given within 8 h p.i. (Bracken et al., 1990). Sustained therapeutic effects were observed in neurologically complete or incomplete recipients. However, adverse effects typically associated with steroid therapy were recorded, including gastrointestinal bleeding, wound infections, and delayed wound healing, although the reported incident frequency was not statistically higher than that of placebo-treated patients (Bracken et al., 1990).

In the early 1990s, the aforementioned results enabled the Upjohn Company, the MP supplier, to register the drug for treating acute SCI in Canada, several Western European countries, and most Far Eastern countries. In contrast, the Food and Drug Administration (FDA) of the USA, in approving any application of a drug for the intended population, required tangible evidence of efficacy from two adequately controlled clinical trials (Darrow et al., 2020). This criterion made filing a new drug application for the MP treatment of acute SCI infeasible based solely on data from NASCIS II. NASCIS III, although validating MP's benefits, had no placebo control group due to ethical concerns about the exclusion of treating SCI patients with an MP formula holding reported advantages. Also, the evidence for claimed replications of NASCIS II's outcomes from other countries was deemed insufficient (Otani et al., 1994; Petitjean et al., 1998).

The regimen, nevertheless, was subsequently adopted as the standard of care for acute SCI, because, worldwide, MP had been in clinical use for many other indications (Bracken et al., 1997). Notably, in more recent clinical studies, the efficacy of high-dose MP appeared questionable (Suberviola et al., 2008). The treatment was also linked with significantly higher rates of severe complications (e.g., pneumonia, decubitus ulcer, and thrombosis; Chikuda et al., 2014). As such, many institutions decided to stop treating SCI with systemic high-dose MP (Chikuda et al., 2014; Felleiter et al., 2012). Since then, the field has not come up with another internationally accepted drug treatment for acute SCI.

2.2. Other drugs investigated for secondary injury amelioration

2.2.1. Adrenergic compounds

Intraparenchymal hemorrhagic necrosis has been a classic drug target due to its aggravating effect on other secondary events (e.g., sizes of lesion volume and gliosis) and therapeutic opportunities (e.g., cell or biomaterial transplantation; Hong et al., 2017). Early studies aimed at impeding the formation of hypoxic hemorrhagic necrosis and lesion size tested norepinephrine synthesis blocker alpha methyl tyrosine (or alpha receptor antagonists phenoxybenzamine and mellaril; Osterholm, 1974; Osterholm and Mathews, 1972). The treatment yielded some positive pilot results that were, however, not replicable (Gurden and Feringa, 1974). Conversely, administration of clenbuterol, a β_2-adrenoceptor agonist, significantly ameliorated ischemia/reperfusion injury-induced spinal motor neuron loss and locomotion deficit in rabbits (Chen et al., 2013). Epinephrine (agonist of both alpha and beta adrenoceptors) and isoprenaline (nonselective agonist of beta adrenoceptors) treatment significantly suppressed cytotoxic edema of astrocytes in vitro and in acutely injured rat spinal cords by activating beta adrenoceptors in vivo (Vardjan et al., 2016). Taken together, future investigations to validate and translate these findings should determine the role of each adrenoceptor subtype in triggering specific pathophysiological events (e.g., vasogenic edema after ischemia/reperfusion versus cytotoxic edema post contusion) in a time-dependent manner.

2.2.2. Therapeutic agents to diminish gliosis

The proliferation of reactive astrocytes and microglia generates a glial scar that has long been postulated to be a physical barrier to axonal regeneration. Aiming to overcome this obstacle, trypsin, hyaluronidase, and elastase were systematically investigated for the purpose of dissolving the glial scar to promote axon regeneration. It was eventually concluded that enzymatic digestion of the glial scar tissue cannot induce axon regrowth and locomotion recovery (Guth et al., 1980).

The post-SCI glial scar (i.e., the glial cell border surrounding the lesion core) is formed by multiple types of cells (e.g., astrocyte, microglia, and NG2 glia). The extracellular matrix (ECM) in the core region contains a variety of proteoglycans or proteoglycan-like molecules such as chondroitin sulphate proteoglycans (CSPGs) and cytotactin/tenascin that were found to be inhibitors of axonal growth (Carlstedt et al., 1989; McKeon et al., 1991). The focus was thereby shifted towards developing chondroitinase ABC (ChABC), which removes glycosaminoglycan chains

on the CSPGs, into a therapeutic agent (Bradbury et al., 2002). Numerous studies showed the effect of ChABC on shrinking the scale of glial scars or axon dieback and promoting corticospinal tract regeneration in different SCI models (Busch et al., 2009; Houle et al., 2006).

Importantly, the regrowth of serotonergic axons may not be affected by the presence of the astroglial scar (Hawthorne et al., 2011). Recent papers also described that SCI animals receiving genetic ablation of astrocytic scar had higher degrees of axon dieback and no regrowth of corticospinal and sensory tracts across the lesion site when compared to control treatment (Anderson et al., 2016). In post-T9-10 transection rats that recovered locomotion under epidural electrical stimulation (EES), quipazine (a 5HT receptor agonist) treatment, and training, the total amount of CSPG expression significantly increased with time after injury (Al'joboori et al., 2020). Hence, deeper understanding of the divergent impacts produced by different cell types and ECM components in the glial scar will facilitate identification of effective therapeutic targets for spinal cord repair (Fawcett, 2020).

2.2.3. Axon repair and regeneration agents

Promoting axonal function and regeneration has been another primary focus in therapeutic developments for SCI. Reviewed here were three different approaches. First, a voltage dependent potassium channel antagonist, 4-aminopyridine (4-AP), was tested for enhancing action potential propagation in demyelinated axons of injured spinal cords to improve locomotion (Gruner and Yee, 1999; Segal and Brunnemann, 1998). Although gait and locomotor function were improved in many studies, benefits were variable and certain side effects (e.g., vasospasm) occurred, preventing it from being formally licensed to treat clinical SCI (DeForge et al., 2004; Grijalva et al., 2003; Segal et al., 1999). Encouragingly, 4-AP (Dalfampridine/Ampyra®) received FDA approval in 2010 to strengthen ambulation in patients with multiple sclerosis (MS) after multiple phase II and III trials had demonstrated its enhancement of both walking speed and function in about one third of MS patients (Dunn and Blight, 2011).

Second, blocking Nogo, an inhibitor of axonal outgrowth, is another experimental strategy to treat SCI. For this purpose, both Nogo Receptor-66 antagonists or antibodies against Nogo-A have been intensively investigated. In vivo animal studies showed that these agents stimulated axonal sprouting of corticospinal, rubrospinal, and serotonergic axons into and across the lesion area, and promoted gait and motor recovery (Freund et al., 2007; GrandPré et al., 2002; Merkler et al., 2001). Despite some replicative studies failing to find significant benefit of a Nogo-66 antagonist, peptide NEP1-40 (Steward et al., 2008), the anti-Nogo-A antibody ATI355 showed tolerability by participants when evaluated in the first phase I study, permitting the trial to advance into phase II (Kucher et al., 2018).

Third, developing agents to disrupt the RhoA/Rho kinase pathway, which reportedly had many negative effects after SCI, including neurite growth inhibition, cell death, demyelination, inflammation, and neuropathic pain (Monnier et al., 2003). Two types of drugs to block this pathway have been extensively studied: RhoA inactivators and Nogo inhibitors (Monnier et al., 2003). BA-210 (Cethrin®), a RhoA inhibitor, was evaluated in a small number of participants and found to have variable outcomes. In a cohort of 48 patients with complete SCI (cervical: $n = 16$, thoracic: $n = 32$), BA-210 treatment was found to be more beneficial for individuals with cervical injuries than thoracic injuries, but there was high inter-patient variability (Fehlings et al., 2011).

In general, drug development is a complex, lengthy, and costly process. In the case of BA-210/Cethrin®, the drug took a circuitous route to enter a phase IIb/III trial under the name of VX-210 (Fehlings et al., 2018), following even earlier studies in 2000 and the clinical evaluation run by Alseres Pharmaceuticals in 2007 (Baptiste et al., 2009). Because interim analyses failed to show efficacy, Vertex Pharmaceuticals Inc., the trial sponsor, decided to halt development of VX-210 in 2019. Clinical trials like these underscored some of the major difficulties in developing therapeutics for SCI, regarding how to select new drug candidates, interpret results, determine appropriate sample size and control setting, use adequate statistical analyses, and assess proper cause and effect relationships (Friede et al., 2018).

2.2.4. Stem cell-based approaches

Propelled by advances in stem cell biology and material science research, new opportunities to invent neural repair strategies comprising stem cells, with or without biomaterial scaffolding or encapsulation, have been actively pursued (Teng et al., 2002; Vismara et al., 2017). Nationally, the Japanese government in 2019 approved a therapy of systemically administering human mesenchymal stromal stem cells (hMSCs) for patients with acute SCI. This instantly triggered concerns from the international community, mainly about the clinical trial's design that was the basis for the approval (e.g., small sample size, lack of a double-blinded approach, no inclusion of a sham operation group, etc.; Cyranoski, 2019a, 2019b). Japan's ministry of health formally responded to the criticisms, reiterating impracticality to run a double-blinded study on an autologous cell therapy and the ethical dilemma of sham surgeries for neurotrauma patients (Miyamoto, 2019). Clearly, more laboratory and clinical investigations are needed before drawing conclusions according to internationally agreeable criteria.

Nevertheless, in the Japanese protocol, the impact of hMSCs (i.v.) was largely derived from their ability to secrete trophic factors and other cytokines to suppress inflammation (and other secondary injury events) and stimulate beneficial plasticity. These mechanisms are different from conventional neural repair roles of stem cells (e.g., neural cell replacement and promotion of long-distance axon regeneration). Characterized more recently was the innate "functional multipotency" of stem cells (e.g., MSCs, NSCs, etc.), enabling them to exert neurotrophic, anti-inflammatory, immunoregulatory, and homeostatic influence (Osaka et al., 2010; Teng, 2019b). The classic definition of totipotency, pluripotency and multipotency of stem cells principally touches on their capacity to differentiate into different cell lineages and types. In distinction, functional multipotency reveals a more enriched repertoire of signaling, epigenetic, genetic, and cellular events that allow stem cells to build homeostasis during development and adulthood to maintain function of an organ system (Teng, 2019a).

Implementing this stem cell theory has played an important role in correctly investigating stem cells to advance basic biology and therapeutic translation. Our studies helped to define *recovery neurobiology* (Ropper et al., 2017; Teng, 2019a), which describes the ability of the injured adult spinal cord, under proper treatment, to deploy polysynaptic neural circuits different from normal neurophysiological pathways to enable postinjury restoration of function. Activation of the essential components of recovery neurobiology (i.e., propriospinal projection network, serotonergic neuromodulation, neuromuscular junction, and CPG) has effectively reinstated function for both experimental and clinical SCI (Gill et al., 2018; Ropper et al., 2017).

3. Efficacious treatments for chronic SCI

Primary challenges of chronic SCI are worsening disability, lack of spontaneous improvement below injury level, complications, and neuromuscular/musculoskeletal deterioration (Fig. 1c and d) (Adams and Hicks, 2005; Huie et al., 2017). Yet, compared to limited progress made in therapeutic management of acute SCI, there have been remarkable achievements in developing clinical rehabilitation therapies for chronic SCI (Gagnon et al., 2018; Rupp et al., 2015). This is attributable to newly gained understanding of neuroplastic mechanisms and their potentiators in both experimental and clinical settings, which led to breakthroughs in designing functional recovery strategies targeting the reactivation of the CPG circuitry (Behrman et al., 2006; Donati et al., 2016; Gill et al., 2018; Harkema et al., 2011; Hubscher et al., 2018).

Appropriate electrical stimuli that trigger CPG activation have been shown to induce functional recovery in animal models and individuals with even severe SCI (Gerasimenko et al., 2008; Harkema et al., 2011;

Megía García et al., 2020). As described above, clinically classified complete injuries rarely destroy the entire CPG network that is mainly in the lumbar cord (Harnie et al., 2019; O'Shea et al., 2017). Unlike the corticospinal tract, the segmental spinal neural circuits do not directly mediate volitional movement. They, however, can elicit rhythmic motor and locomotor patterns, serving as a target for developing pharmacological neuromodulation, computer interfacing, functional stimulation, and comprehensively integrated rehabilitation systems (e.g., the human digital twin; see below; Krucoff et al., 2016; McPherson et al., 2015; Pizzolato et al., 2019; Sasada et al., 2014).

3.1. Pharmacological neuromodulation for chronic SCI

Based on the pathophysiological characteristics of chronic SCI (Fig. 1c and d), the late phase functional deficit severity of each patient is determined by "the equilibrium" interactively reached between the primary lesion plus secondary injury events and the endogenous repair process. To approach a higher functional state in the dynamic system over time p.i., it is preferable to therapeutically optimize the recovery activities (Teng, 2019a). It has been demonstrated that pharmacological neuromodulations, when used as part of a multifaceted strategy, are efficacious in refining neuroplasticity, pain management, neurologic function, and complication reduction. These treatments are believed to work mainly by enhancing communications of the CPG network, spinal cord learning circuitry, and sensorimotor, neuromuscular-musculoskeletal, and inter-neurotransmission systems (Grau et al., 2020; Knikou et al., 2017; Rodgers et al., 2019).

Modulation of monoamine neurotransmitters in the descending noradrenergic, serotonergic, and dopaminergic pathways have surfaced as the leading pharmacological foci. For instance, based on the distinct spectrum of kinematic, kinetic, and clonus electromyogram (EMG) characteristics that each monoaminergic receptor modulated, optimal combinations of pharmacological treatments and electrical spinal cord stimulation were designed. The multimodal monoaminergic therapy restored coordinated hindlimb locomotion with nearly normal weight bearing without supraspinal innervation in paralyzed rats after spinal cord transection (Musienko et al., 2011). In general, studies have examined the mechanisms of drug action on direct activation of the (1) noradrenergic/adrenergic, (2) serotonergic, or/and (3) dopaminergic neurotransmission in the spinal cord regarding plastic changes in the CNS, to enhance proprioceptive feedback, locomotion, respiration, and muscular and/or cardiovascular fitness (see details in Table 1).

3.1.1. Adrenoceptor (α_2 and β_2) agonists

Clonidine, acting as an α_2-adrenoceptor agonist, potentiated locomotor recovery in chronic spinalized models by augmenting crossed extensor responses via stimulating CPG neurons (Barbeau and Rossignol, 1991; Frigon et al., 2012; Naftchi, 1982). Clinically, with incorporation of progressive weight support and treadmill training, two participants with stabilized spastic paraplegia of SCI after receiving a coadministration of clonidine and cyproheptadine exhibited less clonus and more phasic EMG activity in their lower limbs during overground locomotion with the aid of Canadian crutches. Cyproheptadine is a first-generation antihistamine with anticholinergic, antiserotonergic, and local anesthetic properties (Fung et al., 1990). However, when used alone, clonidine improved locomotion in spastic paretic condition but not in paraplegic SCI (Stewart et al., 1991). The data suggested that neuromodulation for sensorimotor improvement after SCI involved multiple neurotransmitter and neuromuscular systems. Noticeably, all published human studies were in case report format and mostly performed in the late 20th century. More investigations on this topic are needed, especially those designed to determine the mechanism of clonidine's impact on spasm and locomotion, to prevent serious side effects (e.g., bradycardia; Rosenblum, 1993), and to achieve additive or synergistic outcomes when applied with other classes of drugs and gait training (Domingo et al., 2012; Frigon et al., 2012).

Table 1
Summary of pharmacological neuromodulatory agents for subacute and chronic spinal cord injury

Drug	Mechanism of Action	Effect in Spinal Cord Injury	References
Clonidine	α_2-adrenoceptor agonist	In animals: potentiated locomotor training and enhanced recovery of locomotion. In humans: variable effect on locomotion (e.g., reduced clonus, improved phasic EMG activity).	Barbeau and Rossignol, 1991; Frigon et al., 2012; Naftchi, 1982; Stewart et al., 1991
Clenbuterol	β_2-adrenoceptor agonist	In animals: reduced muscle atrophy and bone demineralization; enhanced functional recovery and tissue sparing at the site of injury; and stimulation of NGF expression.	Hayes et al., 1995; Zeman et al., 1987, 1997, 1999
Salbutamol	β_2-adrenoceptor agonist	In humans: increased voluntary muscle force.	Martineau et al., 1992
Metaproterenol	β_2-adrenoceptor agonist	In humans: increased voluntary muscle force and protein turnover rates in skeletal muscles.	Hostrup et al., 2018; Signorile et al., 1995
Formoterol	β_2-adrenoceptor agonist	In humans: induced anabolic response in skeletal muscles.	Mayne et al., 2015
Buspirone	Full agonist on presynaptic 5-HT_{1A} autoreceptors and partial agonist on postsynaptic 5-HT_{1A} receptors	In animals: reversed respiratory abnormalities and facilitated locomotor function by re-establishing symmetrical gait with long lasting effects. In humans: improved locomotion, muscle coordination, and upper limb strength when combined with appropriate rehabilitation; enhanced respiration, cardiovascular function, and thermoregulation; facilitated neurotransmission in dormant descending pathways; and reduced susceptibility to chronic SCI-induced hypocapnic central sleep apnea.	Choi et al., 2005; Courtine et al., 2009; Freyvert et al., 2018; Gad et al., 2017; Gerasimenko et al., 2015; Jeffrey-Gauthier et al., 2018; Loane and Politis, 2012; Maresh et al., 2020; Teng et al., 2003; Vivodtzev et al., 2020
DOPA	Increased dopamine and noradrenaline production and release of neurotransmitters from the descending	In spinal animals: generated rhythmic motor output in the absence of phasic peripheral feedback when co-	Andén et al., 1966; Grillner and Zangger, 1979; Radhakrishna et al., 2017)

(continued on next page)

Table 1 (*continued*)

Drug	Mechanism of Action	Effect in Spinal Cord Injury	References
	noradrenergic pathway	administered with the monoamine oxidase inhibitor nialamide. In humans: induced locomotor-like EMG patterns in AIS-A/B participants when co-administered with buspirone and carbidopa.	

Abbreviations: 5-HT: 5-hydroxytryptamine; DOPA: l-3,4-dihydroxyphenylalanine or levodopa; EMG: electromyogram; NGF: nerve growth factor.

Clenbuterol, at low doses, is a long acting β_2-adrenoceptor agonist ($T_{1/2}$: 25-39 h). In earlier experimental reports, clenbuterol markedly reduced muscle atrophy and neuromuscular scoliosis by retarding denervation-induced loss of muscle contractility and bone mineralization in models of peripheral nerve lesion and SCI, respectively (Zeman et al., 1987; Zeman et al., 1997). It also spared white matter and enhanced hindlimb function in SCI rats, likely by increasing the expression of nerve growth factor (NGF) and basic fibroblast growth factor (bFGF/FGF2; Hayes et al., 1995; Zeman et al., 1999). However, since 2006, clenbuterol has not been included as an ingredient in any therapeutic drug approved by the FDA because of its adverse effects and abuse potential (www.drugbank.ca/drugs/DB01407).

In contrast, salbutamol, an FDA-approved β_2-adrenoceptor agonist for bronchodilation, used in short term (i.e., 14 or 21 days) administration increased voluntary muscle strength, including the maximum static inspiratory mouth pressure in men. However, there were variations in the magnitude and duration of this effect between muscle groups (Martineau et al., 1992). Prolonged use of metaproterenol, another β_2-agonist, strengthened skeletal muscles in participants with chronic SCI (Signorile et al., 1995). In a recent randomized, placebo-controlled, cross-over study (n = 12 trained men), salbutamol (6 × 4 mg, p.o.) augmented protein turnover rates in skeletal muscle 0.5-5 h after resistance exercise, through concomitant cAMP/PKA and Akt2 signaling (Hostrup et al., 2018). It is worth noting that although newer generation β_2-agonists (e.g., formoterol) experimentally induced anabolic responses in skeletal muscle following denervation at doses linked with fewer side-effects on the heart, compared to clenbuterol and fenoterol (Mayne et al., 2015), their potential to harm the cardiovascular system has not been completely abolished (Hostrup et al., 2020).

3.1.2. Serotonergic (5HT: 5-hydroxytryptamine) agonists

The potency of $5HT_{1A}$ activation for functional restoration after SCI was first demonstrated by the reversal of respiratory abnormalities resulting from either T8 contusion or C5 hemicontusion in rats following treatment with buspirone and 8-OH-DPAT (Choi et al., 2005; Teng et al., 2003). The effect was mediated through 5-HT_{1A} receptors because both buspirone (BuSpar®: a $5HT_{1A}$ partial agonist) and 8-OH-DPAT (a $5HT_{1A/7}$ full agonist, depending on species) improved post-SCI respiration. Furthermore, pretreatment of animals with p-MPPI, a 5-HT_{1A} selective antagonist, abolished the beneficial impact of either drug (Choi et al., 2005; Teng et al., 2003). The data suggested that activation of $5HT_{1A}$ receptors could be an effective strategy for recovering respiratory function and other types of patterned motor activities p.i. (Teng et al., 2003).

In vitro, *N*-methyl-D-aspartate (NMDA) induced fictive locomotion in the neonatal rat spinal cord. Adding 5-HT to the preparation improved left/right and flexor/extensor alterations that were recorded from the 3rd and 5th lumbar ventral roots, respectively. Although the effect could only be partly reproduced by stimulating 5-$HT_{2A/2c}$ receptors, daily administration of p-chloro-phenylalanine (PCPA) to suppress 5-HT synthesis (starting on the day of birth) or application of either a 5-HT_2 or 5-HT_7 receptor antagonist disorganized the NMDA-triggered locomotor rhythm in the preparation. After adding 5-HT to the bath, locomotion-like activity was restored in spinal cords collected from animals pretreated with PCPA. Thus, 5-HT appeared to be pivotal in enhancing the locomotor-related alternations (i.e., CPG activity) in neonatal rat spinal cords in vitro (Pearlstein et al., 2005). Contrarily, stimulation of 5-HT_{1A} and 5-HT_7 receptors by 8OH-DPAT was able to produce CPG activity in mice with T9-10 spinal cord transection in vivo (Landry et al., 2006). When combined with EES and locomotor training, buspirone treatment activated and recruited the lumbar CPG circuitry via affecting sensory input and functionally remodeling the pace-making pathways in rats with T7 spinal cord transection (Courtine et al., 2009). Administration of buspirone strengthened locomotion (e.g., improving the number of steps taken, between hindlimbs coupling strength, angular excursion of the hip joint, and paw positioning) in mice with either T8 transection or a dual lesion paradigm of T7 hemisection and T8 transection that was done at the end of a 3-week training period after T7 hemisection. Also, buspirone treatment achieved long-term improvement of symmetry, paw positioning at contact, and paw drag when combined with locomotor training in mice with dual T7 and T8 lesions (Jeffrey-Gauthier et al., 2018).

In clinical rehabilitation, buspirone treatment augmented muscular coordination and the effort level that a participant with AIS-B generated in the exoskeleton while stepping, producing a refined continuous, smooth stepping motion in the exoskeleton in addition to autonomic improvements (cardiovascular function and thermoregulation; Gad et al., 2017). Buspirone co-administered with transcutaneous electrical stimulation (TES) in chronic AIS-B participants (C5 or above; motor complete) significantly increased mean hand strength (Freyvert et al., 2018). Newly published results demonstrated that buspirone (7.5–15 mg, b.i.d., p.o.), not trazodone (100 mg/day; a 5HT uptake inhibitor) or placebo, significantly reduced chronic SCI-caused susceptibility to induced hypocapnic central sleep apnea by reducing chemosensitivity and increasing CO_2 reserve (Maresh et al., 2020).

The effects of use and non-use of buspirone were examined in participants (n = 21; <2 years of SCI from C4 to T3) who underwent 6 months of equal exercise training facilitated by functional electrical stimulation (FES), i.e., direct skeletal muscle stimulation to generate muscle contraction and movement. The participants on buspirone (n = 10; 29 ± 17 mg/day), compared to well-matched individuals without buspirone (n = 11), had significantly greater increases in peak oxygen consumption (VO_2peak) and peak ventilation (VEpeak). While changes in VO2peak and VEpeak were correlated across all patients ($r = 0.63$, $p < 0.01$), participants on buspirone showed the strongest correlation ($r = 0.85$, $p < 0.01$). Only in the buspirone group were changes in respiratory function significantly correlated with increased peak tidal volume ($r > 0.66$, $p < 0.05$). The data demonstrated that buspirone improved cardiorespiratory adaptations to FES-exercise training in individuals with chronic high-level SCI. These close associations between augmented ventilatory and aerobic capacities indicated that improved respiratory function was the primary mechanism (Vivodtzev et al., 2020).

The majority of serotonin in the spinal cord originates from the raphe nuclei, which makes this neuromodulation innervation (i.e., there is no intrinsic 5HT synthesis in the adult mammalian spinal cord) vulnerable to neurotrauma (Perrier and Cotel, 2015). In mammalian spinal cords, 5-HT_{1A} receptors, which are coupled to different messenger pathways via association with Gα isoforms or βγ signaling in different cell types (Rojas and Fiedler, 2016), are primarily located on the soma and proximal dendrites of serotonergic-innervated locomotor-activated neurons in Rexed laminae I-IV, VII, VIII and X of thoraco-lumbar segments of cats (Giroux et al., 1999; Noga et al., 2009). In human lumbar spinal cords, 5-HT_{1A} receptors were mostly distributed in Rexed lamina II of the dorsal horn and in the ventral horn, participating in afferent, sensorimotor, and CPG regulation (Perrin et al., 2011). Presently, buspirone is one of the

most widely investigated and clinically used neuromodulation drugs. It agonizes inhibitory presynaptic and postsynaptic $5HT_{1A}$ receptors (e.g., somatodendritic autoreceptors, postsynaptic heteroreceptors, etc.), while also having possible other weaker interactions (Loane and Politis, 2012). While discussion of other receptor subtypes of 5HT is beyond the scope of this review, it should be mentioned that intrathecal antagonism of spinal 5-HT_7 receptors disrupted spontaneous locomotion in intact animals, but not fictive locomotion induced by stimulation of the mesencephalic locomotor region. Since locomotor coordination in adult mammals requires the sensory input, the results suggested a 5-HT_7 receptor-mediated role in modulating afferent pathways to operate CPG (Cabaj et al., 2017). Thus, targeting $5HT_{1A}$, 5-$HT_{2A/2c}$, and $5HT_7$ receptors for neuromodulation may constitute a fruitful strategy to restoring locomotion after SCI.

3.1.3. Dopaminergic modulation

Descending dopaminergic pathways from the brain, specifically that originating from the A11 area of the diencephalon, may be the major source of dopamine within the mammalian spinal cord. These tracts play crucial roles in sensorimotor integration, locomotion regulation, and pain modification (Barraud et al., 2010; Sharples et al., 2014). In early laboratory studies, adding DOPA to chronic spinal preparations liberated catecholamines (i.e., dopamine and noradrenaline). The data suggested that DOPA augmented the synthesis and terminal release of neurotransmitters from the descending noradrenergic pathway (Andén et al., 1966). Administration of DOPA together with the monoamine oxidase inhibitor nialamide (i.v.) generated rhythmic motor output in the absence of phasic peripheral feedback in models of spinalization at different levels (i.e., T12, and L5-S1; Grillner and Zangger, 1979).

To modulate multiple neurotransmission systems governing the CPG network, a tri-therapy of buspirone, carbidopa, and levodopa was administered to mice with T9-10 spinal cord transection. The treatment enabled the mice to manifest episodes of steady weight-bearing stepping (Guertin et al., 2010). In a subsequent study, spinalized mice given the tri-therapy with or without clenbuterol, plus regular treadmill training for 8 weeks, exhibited locomotor movement and gradually increased muscle mass (Ung et al., 2012). Furthermore, delivery of a combined recipe of NMDA, 5-HT, and dopamine produced fictive locomotion in rodent spinal cords. This was disrupted via activation of the bradykinin receptor B2 by the inflammatory nonapeptide bradykinin, a secondary injury molecule of SCI (Mandadi et al., 2016).

The laboratory data suggested that dopaminergic stimulation co-enhanced with other neurotransmission systems could be an effective formula for locomotor recovery. Supporting this notion, a double-blind, placebo-controlled, randomized phase I/IIa study on safety and efficacy of treatment with buspirone/levodopa/carbidopa (Spinalon™) revealed that locomotor-like EMG patterns were displayed only in participants (AIS-A/B) who received Spinalon™ treatment (Radhakrishna et al., 2017). Notably, buspirone, clenbuterol, and levodopa can stimulate production of neurotrophic factors and antioxidants by neural cells (Hayes et al., 1995; Zhang et al., 2006). This type of trophic and protective support is missing in lesioned adult spinal cords and essential for neural repair and plasticity-based functional recovery (Teng, 2019a). Therefore, if multiple neurotransmitters in the spinal cord CPG circuits are pharmacologically modulated, locomotion is likely inducible in clinical chronic SCI. The efficacy can be further increased if the drug treatment is combined with rehabilitation training, especially those integrated by multimodal neuromechanical protheses (see details below).

3.2. Neuromechanical prostheses to restore function for chronic SCI:

Neuromechanical prostheses encompass assistive and rehabilitative devices that interface with the individual's sensorimotor system (Pizzolato et al., 2019). Biological signals acquired via neuromechanical prosthesis include a range of electrical biopotentials (e.g., electroencephalograms [EEG], EMG, electrocardiogram [ECG]), biomechanical variables (e.g., limb movement and forces, hand gestures), and respiratory parameters (e.g., tidal volume, rate, and minute ventilation). These signals, if appropriately interpreted, can be used to understand a person's motor intention and, accordingly, control electrical (e.g., electrical stimulation) and mechanical (e.g., exoskeletons) actuators to generate movement. Neuromechanical prostheses can compensate for the SCI-caused loss of afferent feedback by redirecting and augmenting sensory input from disrupted pathways to residual ascending tracts representing the affected peripheral target, in order to reengage the somatotopic area remapped by SCI (Leemhuis et al., 2019) (Fig. 2). Successful neuromechanical prostheses should provide electrical and mechanical support that is commensurate with the person's own neuromuscular capabilities, and consistent with the excitations of still intact neural pathways.

3.2.1. Electrical stimulation

Generation of movement via FES and/or mechanical means, which also appropriately triggers peripheral mechanoreceptors, may reinstate lower limb motor synergies. FES gained heightened attention after a seminal study by McDonald et al. (2002), showing that long-term training using FES for cycling in one individual with cervical SCI improved the scale from AIS-A to AIS-C within 3 years. FES cycling also improved motor function in people with complete or incomplete SCI after a 10-week intervention. However, in another study, no improved AIS reclassification was achieved for individuals with complete SCI. The lack of efficacy in using FES alone over a shorter time course may relate to its inability to engage supraspinal and intraspinal neurocircuitry, despite its benefits of increasing aerobic capacity and preventing muscle atrophy (Griffin et al., 2009; Ragnarsson, 2008).

Continuous EES employs an electrical signal of constant amplitude and frequency, selected through experimentation (Harkema et al., 2011), to induce muscle contraction and facilitate generation of rhythmic movement. It can additionally engage the proprioceptive circuits via stimulation of the lumbosacral segment. By reactivating the CPG, EES enabled AIS-A people to stand, walk, or cycle with minimal assistance (Angeli et al., 2018; Harkema et al., 2011). EES has been combined with physical training of standing (Wenger et al., 2016), multimodal exercises (e.g., seated trunk balance, standing balance and stepping, range of motion; Wenger et al., 2016), and stepping or gait retraining with body weight support (Angeli et al., 2018; Wagner et al., 2018). However, continuous EES has been shown to disrupt afferent signals generated by mechanoreceptors of intact muscles, tendons, and joints (Formento et al., 2018), a type of input that is believed essential to activate and modulate the CPG (Lavrov et al., 2008). To solve this conflict, a computational model representing the salient anatomical and physiological features of lower limb muscles and CPG was developed to modulate EES and minimize antidromic collisions along proprioceptive afferent pathways (Formento et al., 2018; Wagner et al., 2018). This spatiotemporal-modulated EES was applied to three participants (AIS-C/D) who subsequently regained voluntary control over paralyzed muscles and maintained it even in absence of stimulation (Wagner et al., 2018). Thus, refining appropriate timing, amplitude, frequency in stimulation delivery to facilitate segmental proprioceptive, and, perhaps, other deep sensory inputs appears necessary for recovering sustainable patterned motor neuron functions.

TES is a non-invasive alternative to EES, wherein electrodes are positioned on the surface of the skin, commonly between spinal processes (cathode) and on iliac crest (anode). TES modulates the excitability of the spinal cord, evoking the reconnection between supraspinal and intraspinal networks (Kakulas, 1999). In a prototype study, five participants with cervical or thoracic motor complete SCI (AIS-B) underwent an 18-week intervention. TES elicited a stepping-like motion when participants were concurrently asked to produce a voluntary effort. When participants were administered buspirone (7.5 mg, b.i.d., p.o.), the combined neuromodulation generated voluntary muscle contraction and additive motor effect (Gerasimenko et al., 2015). As

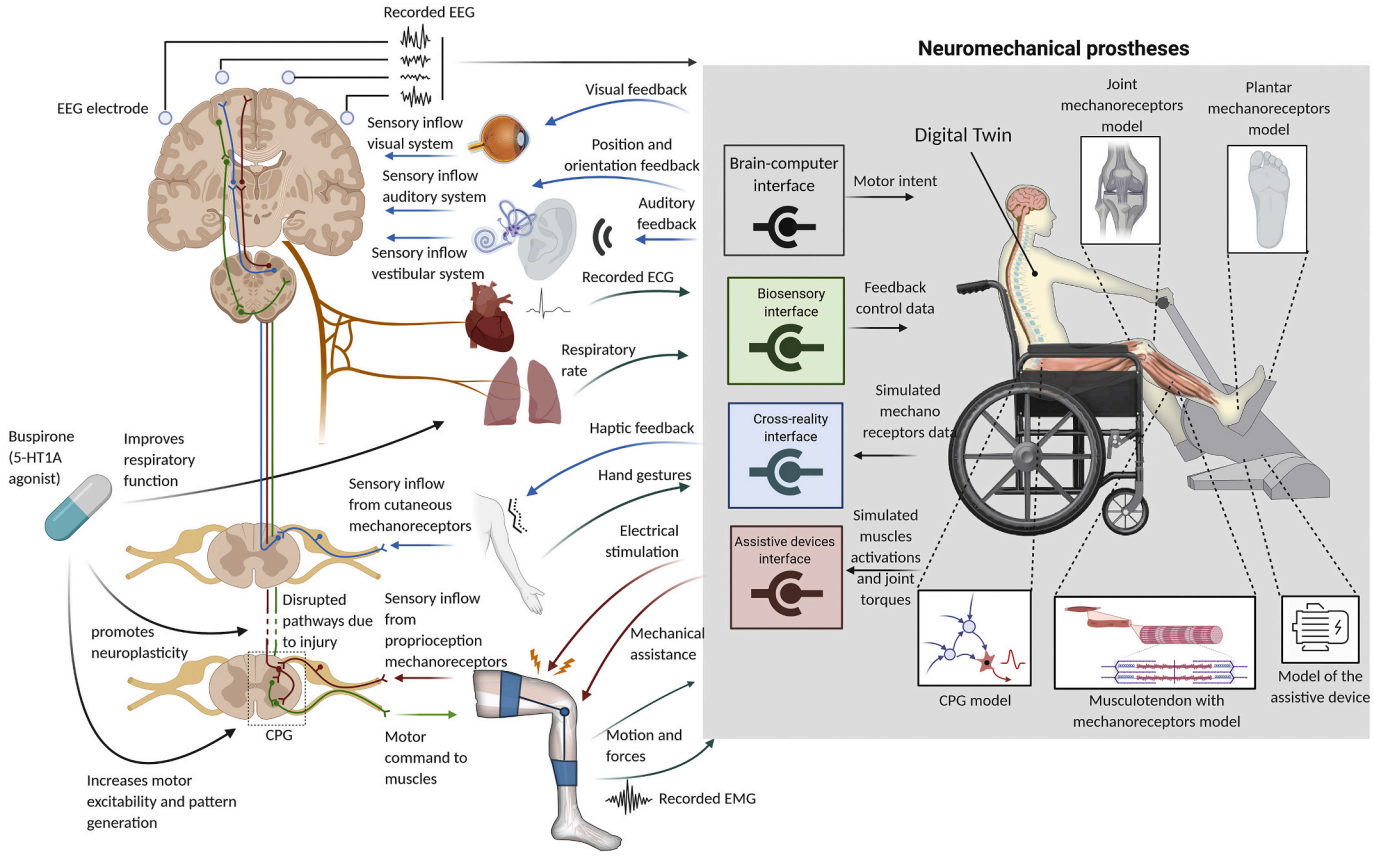

Fig. 2. Schematic representation of the interaction between the central and peripheral nervous systems with neuromechanical prostheses and pharmacological adjuncts. Disrupted descending neural tracts prevent motor commands to reach spinal circuits distal to the injury to activate muscles for movement generation. The interrupted motor pathway can be re-functionalized via a neuromechanical prosthesis, wherein electroencephalograms (EEG) associated to the motor intent of the individual are interpreted by a brain-computer interface and converted into a target motion and muscle activation patterns through a personalized digital twin of the individual. Muscle activation patterns and joint torques simulated by the digital twin are provided to assistive devices (e.g., functional electrical stimulation and rehabilitation robotics) that generate limb motion. As ascending afferent pathways are also damaged, sensory inflow from cutaneous mechanoreceptors, as well as that of the visual, auditory, and vestibular systems can be used to augment or substitute the afferent signal from proprioception mechanoreceptors in the lower limbs. In this regard, the digital twin can simulate proprioception mechanoreceptor data from muscles, tendons, plantar foot, and joints to redirect it to corresponding somatosensory areas via cross-reality interface (e.g., virtual reality, haptic feedback, and auditory feedback). Biosensory signals, derived from EMG, heart and respiratory rate, as well as patterned motion from the upper limbs (e.g., hand gestures), are interpreted by the digital twin to adapt and control the rehabilitation therapy. Finally, drugs such as buspirone can be co-administered to improve respiratory function in order to enhance tolerance to the intensity of aerobic exercise, promote neuroplasticity and neurorepair, and increase motor excitability (note: plotting of Fig. 2 was assisted by BioRender.com).

described above, similar combinatorial TES and buspirone treatments also restored discernible degrees of hand function or locomotion in individuals with AIS-A/B injuries at different spinal cord levels (Freyvert et al., 2018; Gad et al., 2017).

Electrical stimulation of spinal cord or muscles is often paired with some form of mechanical assistance, delivered by a practitioner (e.g., limb mobilization during physical therapy) or via motorized devices. Mechanical assistance can help with limb movement when insufficient force is produced via volitional or electrically induced muscle contraction, but can also extend training session durations. However, to our best knowledge, no published study has shown that mechanical assistance alone, regardless of the delivery modality, resulted in reclassification of SCI from AIS A/B to AIS-C/D. Clearly, electrical stimulation, pharmacological neuromodulation, and mechanical assistance in combination can have additive or synergistic effects of improving motosensory function for chronic SCI.

3.2.2. *Brain-computer interfaces (BCIs)*

Concurrent engagement of efferent and afferent pathways during rehabilitation has been considered essential in the recovery of motosensory function. To this end, BCIs have been garnering interest as a vehicle to engage cerebral cortical networks during rehabilitation (Donati et al., 2016). BCIs translate acquired EEG signals into real world commands representing the intent of the user. The act of thinking about performing a movement (i.e., motor imagery) is transformed into a command for the neuromechanical prosthesis and, consequently, into a real action. Importantly, BCI-enhanced neuromechanical prostheses have been engineered to bypass SCI lesions, enabling certain degrees of voluntary control of the affected limbs via electrical stimulation (Ethier et al., 2012). Current BCI paradigms, although only classifying a finite number of motor intentions (limited by the number of surface EEG channels and the signal quality), can detect gross motor initiatives (e.g., walking). This was made possible by advanced artificial intelligence and machine learning algorithms, which have been continuously improved by increasing the amount of EEG data decoded into coordinated motor instructions to directly operate the muscles (Lotte et al., 2018) or exoskeletons (Benabid et al., 2019).

Implanted electrode arrays to access cortical signals (Oxley et al., 2016; Musk and Neuralink, 2019) are leading to a generational leap in amount and quality of available EEG data. These innovations enabled an increased number of user-intentions that can be correctly classified by artificial intelligence algorithms but are unlikely to lead to physiological control of paralyzed limbs. This is because neural information from the motor cortex cannot be directly mapped to movement, which has to

work in consortium with the musculoskeletal system under the environmental context before a naturally synchronized limb movement can be generated. Similar challenges were met when trying to adapt artificial intelligence methods to map EMG signals closely associated to muscle force production, to directly produce movement (Zhang et al., 2020; Kapelner et al., 2020). To overcome these hurdles, new systems that integrate computational models of the spinal cord, somatosensory apparatus, and musculoskeletal input (e.g., human digital twins; see below), can be designed in the future to generate better mapping between EEG and movement, to deliver truly embodied neuromechanical prostheses.

3.2.3. The human digital twin

The digital twin is a high-fidelity multiscale computation model composed of numerous subsystems that are described and interconnected via mathematical relationships. This modern paradigm, initially devised and deployed in the aerospace industry, enables monitoring of physical quantities that cannot be observed via direct measurement (Glaessgen and Stargel, 2012). Following SCI, below-lesion sensory input cannot be conveyed to the brain, causing a loss of body position, CPG function and movement awareness, and ensuing reorganization of the somatosensory cortex (Nardone et al., 2013). Neuromechanical prostheses can relay the disrupted proprioceptive information to the body sites with intact sensory inflow. This augmented sensory feedback, or artificially generated biofeedback, has been utilized to enhance or substitute proprioception (Giggins et al., 2013; Shokur et al., 2016). Therefore, combinations of visual (e.g., virtual reality), haptic, or auditory monitors, and positional/orientation feedback (i.e., vestibular input) can be provided to people with SCI via the human digital twin that is designed to interpret heterogeneous biosensory data (e.g., EMG, ECG, EEG, forces and movement, respiration, hand gestures, etc.) to improve rehabilitation training outcomes (Fig. 2). However, there is presently no consensus regarding the optimal delivery modality and amount of biofeedback, which type of afferent signals to augment, and how to best convert mechanoreceptor signals into interpretable feedback data. We and others postulated that providing biofeedback that is consistent and time-synchronized with native and intact proprioceptive signals might more effectively promote functional recovery in chronic stage of SCI (Jackson and Zimmermann, 2012; Pizzolato et al., 2019).

The importance of employing both efferent and afferent neuropathways during rehabilitation was indicated in a phase I study that combined BCI, biofeedback, and graded gait training (i.e., combination of exoskeleton and body weight supported walking; Donati et al., 2016). After a 12-month intervention, four participants (50%) improved from AIS-A/B to AIS-C. While AIS classification was unchanged in the other four (AIS-A/B), all participants showed some improvement in their measured EMG signals, with five showing improved ambulation ability compared to baseline. In a subsequent phase II study, all participants continued their training under the same protocol for an additional 14 months, resulting in AIS-C reclassification for all of participants (Shokur et al., 2018). Two of these, who were reclassified from AIS-A to AIS-C, also underwent additional gait retraining using a combination of BCI, haptic feedback, and FES, showing further increased lower extremity motor score after 22 training sessions (Selfslagh et al., 2019). The encouraging results from these studies, albeit with small sample sizes, suggested that reestablishment of neural function after severe SCI is possible with non-invasive multimodal therapeutic approaches.

Enabling coordination between assistive devices and the individual with SCI requires correct understanding of the complex and causal interplay between the different elements of the neuromusculoskeletal system, according to their roles in generating and sensing movement. In this context, a digital twin can be designed to interpret heterogeneous biosensory input and cybernetically coordinate the participant's conscious intention, appropriately augmented feedback, and proper control of the electromechanical multimodal assistive devices (e.g., exoskeletons, electrical stimulation) (Fig. 2). Moreover, digital twins implementing large-scale neuromusculoskeletal models, must entail mathematical descriptions of muscles, tendons, joints, and bones that closely match the individual's physiological, anatomical, and functional capacities (Pizzolato et al., 2017), thereby allowing researchers to unveil the mechanistic causal relationships between neural motor command and final movement for different neuromuscular conditions (Sartori et al., 2017). Recent advancements in computational biomechanics have also produced real-time human digital twins, which are able to instantaneously predict the internal state of musculoskeletal tissues (e.g., stress/strain) and associated motor command (Pizzolato et al., 2020), and to interface with electromechanical assistive devices (Sartori et al., 2018). This will help pave the way for the application of the human digital twin in complex rehabilitation therapies, where the treatment is automatically optimized to match the neuromuscular capabilities of the individual.

4. Conclusions

Major progress made in the past 30 years has demonstrated that patterned motor activities can be rekindled below the spinal cord lesion without direct supraspinal innervation. The neurobiological mechanisms underlying such recoveries have been targeted for developing noninvasive therapies to improve function after SCI. Pharmacological approaches employing individual or combined drug treatments, which manipulated receptors of neuromodulators (e.g., $5HT_{1A}$ receptors) or monoamine neurotransmission, exhibited efficacious clinical outcomes. The necessity for the intervention to simultaneously affect multiple components of the sensorimotor neural network was corroborated by data generated from cell therapy investigations for repairing the injured spinal cord (e.g., donor cell-exerted neurotrophic, anti-inflammatory, and homeostatic effects). Lastly, neuromechanical prostheses-based rehabilitation protocols were more effective for chronic SCI when they were performed in combination with drug administration (e.g., 5-HT_{1A} receptor agonists). Furthermore, the potency of the treatments could be additively or synergistically enhanced by their combination with functional training therapies.

For qualitative therapy improvement, the human digital twin represents a powerful multimodal strategy to integrate innate volitional pathways with different forms of neuromechanical assistance to cybernetically tailor a particular rehabilitation therapy to meet an individual's clinical needs. If designed to also incorporate the effects of pharmacological agents and TES/EES/FES, the system may constitute a novel drug-device therapy. Overall, the findings from the literature review suggested that to move the field forward, it is important for future research and development operations to focus on (*i*) formulating pharmacological and cellular treatment regimens that can concurrently modulate key neurotransmission and homeostatic processes to mitigate secondary injury and optimize repair, (*ii*) developing BCI-integrated neuromechanical prostheses (e.g., human digital twins) that can coordinate the participant's conscious drive with biosensory inputs and outputs of FES/EES/TES, activity training, and drug administration devices, (*iii*) advancing the understanding of the neurobiological mechanisms of the CPG reactivation in the adult mammalian spinal cord after injury, and (*iv*) organizing phase II and III trials with adequate statistical power, proper control setting, and multicenter participation to standardize new SCI treatment.

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