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Review

Maladaptive Proprioceptive Plasticity After Spinal Cord Injury: Mechanisms, Functional Consequences, and Therapeutic Targets

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Abstract

Spinal cord injury (SCI) produces immediate motor and sensory deficits and chronic secondary complications that diminish quality of life. Spasticity, characterized by altered sensorimotor control and manifesting as velocity-dependent hypertonia, clonus, and involuntary muscle spasms, affects 70–80% of individuals with SCI. Although classically attributed to lost supraspinal control, current evidence indicates that maladaptive plasticity within the proprioceptive sensory system is a major contributor to post-SCI spasticity and impaired motor recovery, acting through interacting structural, synaptic, ionic, and circuit-level mechanisms below the lesion. In this review we detail how group Ia and Ib afferents undergo pathological transformation after SCI: aberrant sprouting into denervated regions, synaptic hyperexcitability via calcium-permeable AMPA receptors (CP-AMPARs) and persistent inward currents (PICs), and impaired inhibition arising from reduced presynaptic inhibition and internalization of the potassium-chloride cotransporter 2 (KCC2). We examine how interneuronal dysfunction, including excitatory–inhibitory imbalance and neurotransmitter phenotype switching, amplifies aberrant sensory signals and how early post-injury disuse consolidates maladaptive synaptic pathways through a CP-AMPAR-mediated feedback loop. Recent evidence challenges the purely excitation-centric model of spasm generation, showing that failure of synaptic inhibition is an equally critical driver. Together, these processes convert normal proprioceptive signals into drivers of pathological excitation through their aberrant central processing, rather than through impairment of sensory transduction itself. Finally, we evaluate therapeutic strategies, including established pharmacological agents, KCC2-targeted therapies, combinatorial activity-dependent interventions, and neuromodulatory approaches such as transcutaneous spinal stimulation, that aim to counteract this maladaptive plasticity. Most structural and molecular elements of this framework derive from rodent models although their relative contribution and temporal ordering in human SCI remain to be established. These findings provide a rationale for early, targeted, multimodal intervention, while the optimal timing and combination of therapies in human SCI require further study.

Keywords: spinal cord injuries; muscle spasticity; proprioception; neuronal plasticity; stretch reflex; interneurons; motoneuron; neural inhibition; spinal cord stimulation; muscle hypertonia

1. Introduction

Spinal cord injury (SCI) is a severe neurological condition that produces not only immediate loss of motor and sensory function but also a cascade of chronic secondary complications that substantially impair quality of life [1]. Among these, spasticity is one of the most prevalent and functionally limiting sequelae. The classic definition by Lance [2] describes spasticity as a velocity-dependent increase in tonic stretch reflexes, accompanied by exaggerated tendon jerks and reflecting hyperexcitability of the stretch reflex. More recently, Pandyan et al. [3] proposed a broader operational definition encompassing disordered sensorimotor control resulting from upper motoneuron syndrome, manifesting as intermittent or sustained involuntary muscle activation. Both formulations acknowledge the complexity of the syndrome and the inadequacy of any single mechanistic explanation. Epidemiological studies indicate that spasticity affects 70–80% of individuals with SCI [1,4,5]. Spasticity can impede residual voluntary motor function and complicate rehabilitation. It also contributes to neuropathic pain and autonomic dysreflexia and imposes a significant burden on daily activities and psychosocial well-being [3,6,7].

For decades, the motor deficits of SCI were attributed primarily to the loss of descending supraspinal commands. An increasing body of evidence, derived predominantly from rodent models but corroborated by clinical electrophysiology, now suggests that active pathological changes also occur within the spinal cord below the injury site [6,8,9]. This review advances the view that maladaptive plasticity within the proprioceptive sensory system is a major, yet is an important and incompletely recognized contributor, driver of post-SCI pathophysiology. Large-diameter group Ia and Ib afferent fibers, which normally

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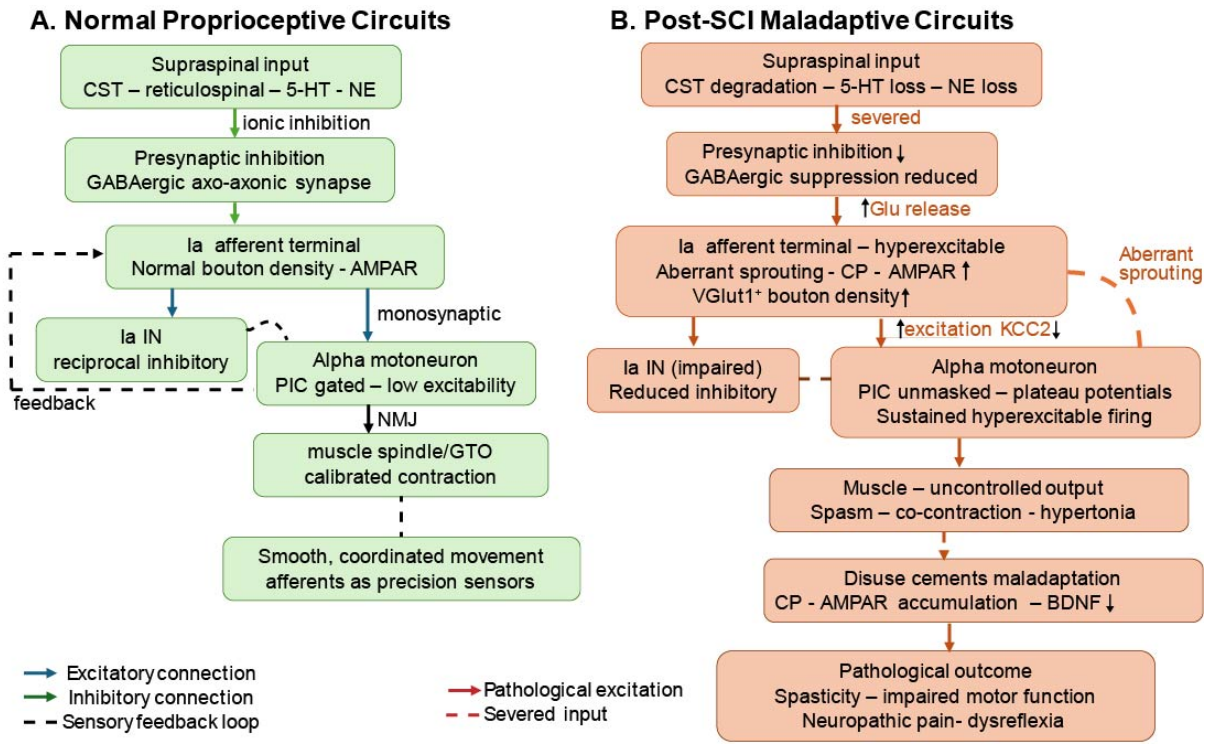


Fig. 1. Schematic overview of normal versus maladaptive proprioceptive circuit after SCI. (A) The intact proprioceptive circuit showing Ia afferent input → α-motoneuron monosynaptic excitation, modulated by Ia inhibitory interneurons (reciprocal inhibition), presynaptic inhibition (PSI) from GABA interneurons, and descending corticospinal/brainstem tone. Green arrows = excitatory; green dashed = modulatory inhibitory; blue = descending pathways. (B) Maladaptive circuits following SCI. Key maladaptive changes are highlighted in red: sprouted VGlut1^{+} Ia terminals (larger synaptic contacts on α-motoneurons), loss of PSI (dashed red line across afferent terminal), KCC2 internalization (orange symbol at GABA synapse indicating chloride shift), excitatory interneuron hyperexcitability, and deep dorsal horn bursting interneurons, and severed descending CST. Green dashed arrows = inhibitory connections; red arrows = pathological excitation; red dashed lines = severed or weakened pathways. CST, corticospinal tract; PSI, presynaptic inhibition; Ia IN, Ia inhibitory interneuron; PIC, persistent inward current; CP-AMPAR, calcium-permeable AMPA receptor; KCC2, potassium-chloride cotransporter 2; GTO, Golgi tendon organ; 5-HT, serotonin; NE, norepinephrine.

encode muscle length, tension, and joint position to facilitate coordinated movement, undergo dramatic changes after SCI. Through abnormal sprouting, synaptic hyperexcitability, and disruption of inhibitory controls, these fibers shift from facilitating movement to becoming sources of pathological excitation that promote hyperreflexia and impair functional motor output [8,10,11].

This review synthesizes current evidence, drawing on preclinical mechanistic studies and, where available, clinical and translational data, to explore how proprioceptive afferents become maladaptive after SCI. We detail the structural and functional changes they undergo, the pivotal role of interneuronal dysregulation and early disuse, and the consequent impact on spasticity, motor impairment, neuropathic pain, and autonomic dysfunction. We also distinguish evidence from rodent models from findings has been demonstrated in human physiological studies, because translational gaps remain significant in this field. We evaluate existing and emerging therapeutic strategies aimed at mitigating maladaptive plasticity and redirecting the injured spinal cord's intrinsic plastic capacity toward functional recovery. A mechanistic framework for these processes is illustrated across Fig. 1, Fig. 2, Fig. 3, Fig. 4 (Ref. [12,13]), Fig. 5, Fig. 6.

The integrative framework advanced here differs from prior reviews in one specific respect. Rather than cataloguing maladaptive changes as parallel contributors, we propose that aberrant group Ia afferent activity may serve as an important upstream driver to downstream synaptic, ionic, and circuit-level changes in selected experimental models. In a rodent SCI model, continuous suppression of Ia afferent activity reduced hyperreflexia and limited maladaptive synaptic remodeling, supporting a causal contribution of afferent activity to the pathological cascade [14]. We therefore organize the mechanisms and therapeutic targets around this testable hypothesis. From this perspective, disuse-associated retention of calcium-permeable AMPA receptors [11] and impaired synaptic inhibition [15] may act as downstream or interacting processes that reinforce an initially afferent-driven disturbance, rather than as wholly in-

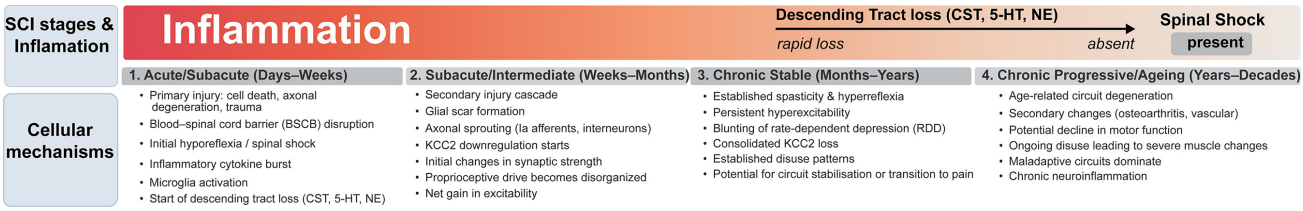


Fig. 2. Conceptual timeline of post-SCI maladaptive proprioceptive plasticity. The figure presents a proposed temporal framework organizing key cellular and circuit-level changes across approximate post-injury phases: acute/subacute (days–weeks), subacute/intermediate (weeks–months), chronic stable (months–years), and chronic progressive (years–decades). These temporal boundaries are intended as approximate conceptual ranges rather than precisely defined or universally established stages. The upper tier depicts SCI stages and the inflammatory microenvironment. The lower tier shows the phase-specific cellular and circuit mechanisms active during that window, from initial sprouting and PIC unmasking through to KCC2 loss and interneuronal dysfunction, tracing how these mechanisms accumulate over time to produce chronic spasticity and neuropathic pain. CST, corticospinal tract; GABA, gamma-aminobutyric acid; KCC2, potassium-chloride cotransporter 2; RDD, rate-dependent depression; SCI, spinal cord injury; 5-HT, serotonin; NE, norepinephrine.

dependent lesions. This framework motivates attention to interventions that act at or near the afferent source, alongside strategies intended to restore inhibitory control. Its generalizability across injury models and to human SCI remains to be established.

2. The Normal Proprioceptive System: Architecture and Function

To appreciate the pathological changes that occur after SCI, it is useful to first define the organization and function of the intact proprioceptive system. Proprioception, the sense of self-movement and body position, is primarily mediated by large-diameter, rapidly conducting sensory afferents originating from specialized mechanoreceptors in muscles, tendons, and joints [16,17].

2.1 Peripheral Afferents and Receptors

● Group Ia afferents: Originating from primary endings of muscle spindles, these fibers are highly sensitive to the rate of change in muscle length and provide the afferent input to the monosynaptic stretch reflex. They are among the largest and fastest-conducting sensory fibers in the peripheral nervous system.

● Group II afferents: Arising primarily from secondary endings of muscle spindles, these fibers respond mainly to static muscle length and contribute to the regulation of posture and sustained muscle activity.

● Group Ib afferents: Originating from Golgi tendon organs (GTOs) within muscle tendons, these fibers encode muscle tension or force and contribute to force-dependent regulation of motoneuron activity through spinal interneuronal circuits [16].

The sections that follow focus principally on group Ia and Ib pathways because SCI-specific evidence concerning structural remodeling and synaptic function of group II afferents remains limited. The contribution of group II afferents to post-SCI spasticity and motor dysfunction therefore remains an important area for further investigation.

2.2 Central Integration and Spinal Circuitry

Upon entering the spinal cord via the dorsal roots, proprioceptive afferents project to both the dorsal horn and the ventral horn, engaging key neuronal populations. The structural organization of these long-range and local proprioceptive pathways, including spinocerebellar projections, provides the anatomical substrate for the coordinated sensorimotor loops that are disrupted after SCI [17,18].

● Alpha motoneurons: Group Ia fibers make direct monosynaptic connections with α-motoneurons, enabling rapid reflexive contractions. This monosynaptic reflex arc is the substrate of the clinically assessed tendon jerk reflex.

● Ia inhibitory interneurons: Mediate reciprocal inhibition, ensuring that antagonist muscles relax during agonist contraction, a prerequisite for smooth, coordinated movement [19].

● Ib inhibitory interneurons: Regulate motoneuron output based on force feedback from GTOs, providing a force-dependent brake on motoneuron firing.

● Renshaw cells: Recurrent inhibitory interneurons that receive collateral input from motoneuron axons and provide recurrent inhibition to the same motoneuron pool and synergist motoneurons [16].

2.3 Supraspinal Modulation

The gain of spinal proprioceptive circuits is continuously modulated by descending pathways from the brainstem, including reticulospinal and vestibulospinal tracts, and from the cortex via the corticospinal tract (CST) [18]. These pathways provide tonic inhibitory and facilitatory input, dynamically adjusting reflex sensitivity to suit behavioral context: suppressing reflexes during voluntary movement and permitting them during postural control. Serotonergic (5-HT) and noradrenergic (NE) projections are particularly important in gating the intrinsic excitability of motoneurons via persistent inward currents (PICs), a mechanism whose disruption after SCI is a cornerstone of spasticity pathophysiology. It is this delicate balance between ex-

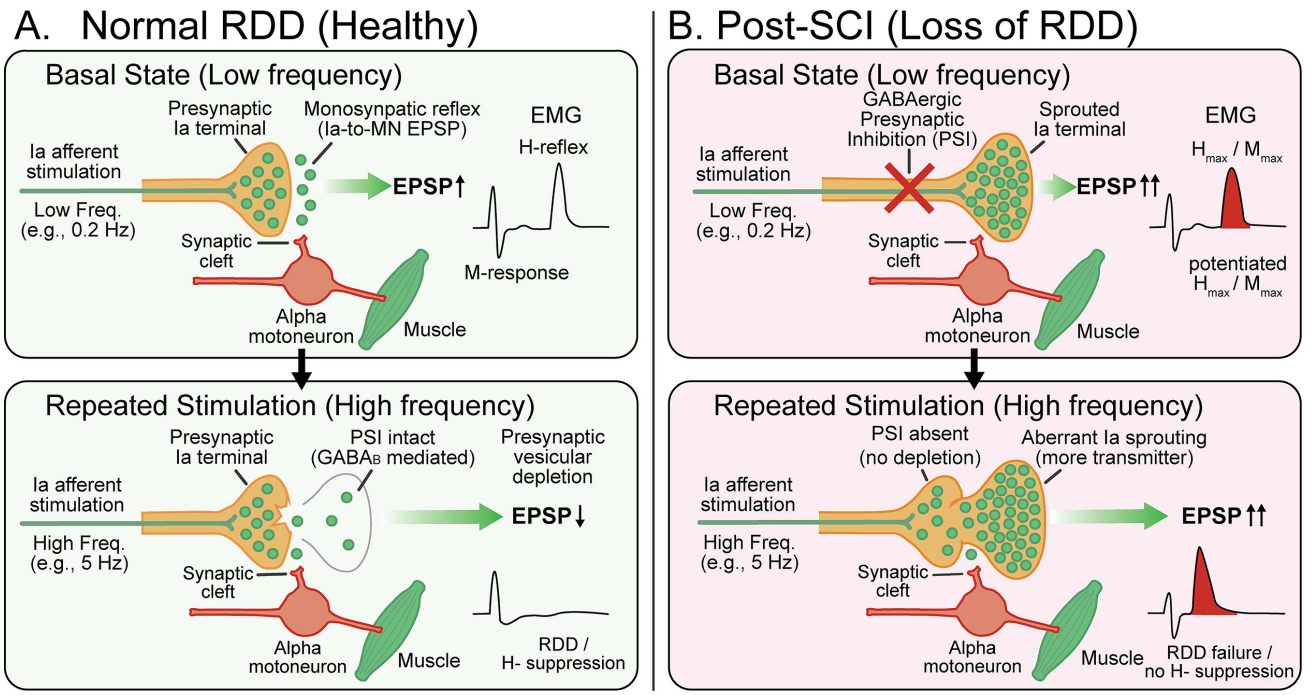


Fig. 3. H-reflex rate-dependent depression (RDD) in normal and post-SCI conditions. (A) Normal condition: the H-reflex monosynaptic circuit and the electrophysiological effect of repeated stimulation. At low frequency, the H-reflex amplitude is near-maximal. At high frequency, PSI and presynaptic vesicular depletion progressively suppress H-reflex amplitude, constituting RDD. (B) Post-SCI condition: following SCI, PSI is lost, Ia sprouting increases presynaptic glutamate release, and RAC1-mediated cytoskeletal remodeling in motoneurons disrupts the molecular substrate of RDD. Repeated stimulation fails to suppress H-reflex amplitudes; the RDD curve is flattened or absent. Example RDD curves (right panel) show a healthy blue curve (progressive amplitude depression with increasing frequency) versus a flat post-SCI red curve. PSI, presynaptic inhibition; RDD, rate-dependent depression; RAC1, Ras-related C3 botulinum toxin substrate 1.

citation and inhibition, and between descending command and sensory feedback, that is profoundly disrupted following SCI (Figs. 1,2).

Fig. 1 contrasts the intact proprioceptive circuit with its maladaptive post-SCI state, marking the specific changes at the afferent terminal, in the interneuronal network, and at the motoneuron. Fig. 2 places these changes on a timeline, from the acute inflammatory phase through the chronic stages, summarizing a proposed temporal framework in which these changes may emerge and accumulate across post-injury stages.

3. Maladaptive Structural Plasticity of Proprioceptive Afferents

The loss of descending supraspinal input after SCI creates a permissive environment for structural reorganization within the spinal cord. Proprioceptive afferents, endowed with a constitutive capacity for axonal growth, are particularly prone to this maladaptive rewiring [20]. Most available mechanistic evidence comes from animal models; the extent of analogous structural reorganization in the human spinal cord remains an area of active investigation.

3.1 Aberrant Sprouting of Ia Afferents

Degeneration of CST axons following SCI denervates regions of spinal gray matter, particularly the dorsal and intermediate laminae. In response, intact axons, including proprioceptive afferents, undergo reactive sprouting, forming new synaptic connections onto vacant postsynaptic sites [10,20]. Although such sprouting may initially appear as compensatory, available evidence indicates that it may also be aberrant and functionally disruptive.

Key rodent evidence for this process was provided by Tan et al. [10], who demonstrated that selective CST lesions in rats induce significant sprouting of VGlut1-positive proprioceptive afferent terminals onto spinal motoneurons. Critically, this anatomical rewiring correlated directly with a reduction in rate-dependent depression (RDD) of the H-reflex, a widely used electrophysiological indicator of spinal hyperexcitability, supporting an association between afferent structural remodeling and spinal hyperreflexia in this model. The molecular mechanisms driving this process involve reactive microgliosis and astrogliosis. Microglia activated by CST injury release pro-inflammatory cytokines and brain-derived neurotrophic factor (BDNF), creating a neuroinflammatory milieu permissive for af-

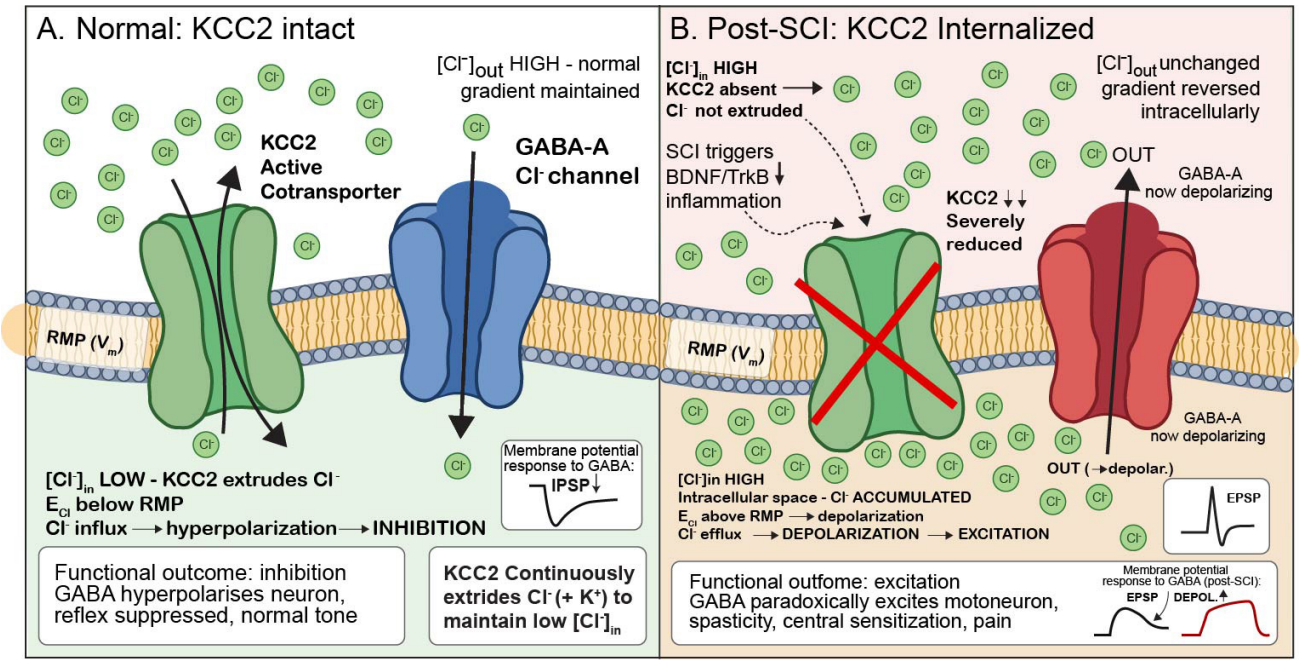


Fig. 4. KCC2 internalization and the chloride shift after SCI, with molecular drivers. (A) Normal: Active KCC2 extrudes Cl^- and K^+, maintaining low intracellular Cl^- concentrations. The chloride equilibrium potential (E*Cl*) is generally more negative than the resting membrane potential (RMP), supporting hyperpolarizing GABAergic inhibition. (B) Post-SCI: KCC2 downregulation and internalization impair chloride extrusion, leading to intracellular Cl^- accumulation and a depolarizing shift in E*Cl* relative to RMP. When E*Cl* becomes more positive than RMP, GABA-A receptor activation may produce depolarizing responses, contributing to spinal hyperexcitability and spasticity [12,13]. The schematic illustrates these changes qualitatively and does not represent universal physiological values. GABA, gamma-aminobutyric acid; KCC2, potassium-chloride cotransporter 2; SCI, spinal cord injury; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; Vm, resting membrane potential.

ferent sprouting [21]. The newly formed synapses are functionally potent but lack corresponding presynaptic inhibitory inputs, effectively amplifying reflex pathways in a manner unchecked by normal presynaptic inhibition. Comparable VGlut1 sprouting has not been directly has been supported by clinical physiological evidence in the human spinal cord after SCI; however, indirect electrophysiological evidence, such as the frequently observed loss of H-reflex RDD in clinical SCI populations [6,22], is consistent with this mechanism.

The structural consequences of Ia sprouting extend beyond simple synapse multiplication. Indeed, the functional impact of this central reorganization is compounded by a loss of signal quality at the source: traumatic and neurotoxic injury produces complex functional impairment of Ia muscle proprioceptors, with diminished and desynchronized sensory encoding that degrades the quality of the proprioceptive signal independent of sprouting [23]. At the synaptic level, the normally precise spatial distribution of VGlut1-positive synapses on motoneuron dendrites, which provides the substrate for graded sensorimotor integration, is disrupted after nerve injury, with reorganization that distorts the spatiotemporal pattern of Ia-motoneuron connectivity [24]. Recent work has further revealed that aberrant sprouting recruits astrocytic remodeling: alterations in glutamate transporter 1 (GLT-1) expression in tripartite synapses formed by sprouted Ia terminals, astrocyte processes, and motoneuron dendrites correlate directly with the degree of SCI-induced hyperreflexia [25], implicating glial-synaptic co-remodeling as an amplifier of proprioceptive malfunction that extends beyond purely neuronal reorganization (Fig. 3).

At the molecular level, cytoskeletal remodeling mediated by the Rho GTPase RAC1 in motoneurons has been identified as a key molecular driver of the loss of H-reflex RDD. Conditional RAC1 knockout in motoneurons restored RDD after SCI in rodents [26], revealing a tractable molecular target within the sprouting-hyperreflexia pathway. Clinically, the H-reflex and its rate-dependent depression have been proposed as useful electrophysiological markers of spinal reflex excitability in SCI; their relationship to clinical spasticity is informative but not one-to-one; changes in H-reflex amplitude and the H/M ratio track spasticity course across the injury continuum [22], providing a translational bridge between the preclinical molecular evidence and patient monitoring.

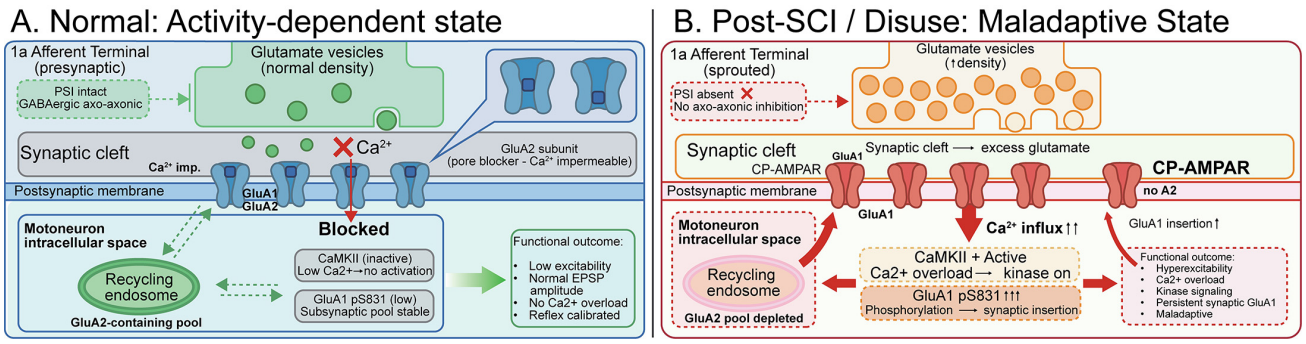


Fig. 5. Disuse-induced AMPA receptor trafficking at the Ia afferent–alpha motoneuron synapse after SCI. (A) Normal uninjured state: Synaptic AMPARs predominantly contain the GluA2 subunit, rendering them Ca^{2+}-impermeable. Bidirectional recycling endosomal trafficking maintains appropriate receptor composition. CaMKII activity is low, and GluA1 pS831 phosphorylation is limited. Functional outcome: calibrated EPSP amplitude, no excessive Ca^{2+} influx, and normal reflex excitability. (B) Post-SCI/disuse state: Loss of weight-bearing activity and proprioceptive drive promotes CaMKII activation and GluA1 pS831 phosphorylation, facilitating synaptic accumulation of GluA2-lacking, Ca^{2+}-permeable AMPARs (CP-AMPARs). Increased Ca^{2+} influx further activates CaMKII, creating a self-reinforcing feedback loop that may contribute to persistent maladaptive synaptic plasticity and hyperexcitability. AMPAR, AMPA-type glutamate receptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CP-AMPAR, calcium-permeable AMPA receptor; EPSP, excitatory postsynaptic potential; GluA1/A2, AMPA receptor subunits; PSI, presynaptic inhibition; pS831, phosphorylation at serine 831; SCI, spinal cord injury; CK2, casein kinase 2.

3.2 Failed Central Integration of Regenerated Afferents

A clinically relevant paradox further complicates the picture. Even successful peripheral regeneration of proprioceptive afferents after injury often fails to restore function. Rodent work by Haftel et al. [27] demonstrated that after peripheral nerve crush and regeneration, group Ia afferents successfully reinnervated muscle spindles and resumed normal firing responses to stretch at the peripheral level. However, the central stretch reflex circuit remained profoundly and persistently silent. This finding implies a powerful central suppression of the regenerated input, likely mediated by persistent presynaptic inhibitory mechanisms or a failure to reconnect with appropriate postsynaptic partners in the ventral horn. This phenomenon underscores that restoring peripheral anatomy alone is insufficient for functional recovery; active neurobiological support of central integration is required. The translational relevance of this finding to human SCI rehabilitation has not been directly established.

4. Maladaptive Plasticity: Hyperexcitability and Disinhibition

Beyond structural rewiring, a coordinated suite of plastic alterations renders the proprioceptive–motor system chronically hyperexcitable, transforming it into a generator of pathological output in the absence of appropriate descending control [6,28].

4.1 Unmasking of Persistent Inward Currents

A central change post-injury is the emergence of unmodulated PICs, sustained depolarizing currents mediated by L-type calcium channels (CaV1.3) and persistent sodium channels (NaV1.6) [29,30]. In the intact spinal cord, PICs are tightly gated by descending 5-HT and NE inputs, which facilitate their activation only during purposeful movement. After SCI, the loss of these descending monoaminergic inputs unmasks PICs, allowing them to be readily recruited by even minor afferent inputs, including aberrant proprioceptive signals, and to generate sustained plateau potentials that directly contribute to prolonged, uncontrolled muscle spasms [29,30,31]. Rodent sacro-caudal spinal cord preparations have been instrumental in characterizing the ionic basis of these currents: persistent sodium conductances contribute critically to the initial ramp phase, while L-type calcium currents sustain the plateau [32].

The functional consequence for spasm generation has been documented in detail in both rodent and human studies. In rodents, activation of PICs in α-motoneurons converts brief synaptic inputs, including those from aberrantly sprouted Ia afferents, into prolonged, self-sustaining bursts of motoneuron firing [29,31]. Clinically, this is mirrored in humans with SCI through the temporal facilitation of spastic stretch reflexes. When two stretch stimuli are delivered in close succession, the second produces a disproportionately amplified H-reflex, providing indirect electrophysiological evidence of motoneuron bistability [33,34]. Changes in sensory-evoked synaptic activation of motoneurons after SCI in humans further corroborate the rodent mechanistic framework: the magnitude and duration of excitatory synaptic drive onto motoneurons are significantly altered in chronic SCI, consistent with unmodulated PIC amplification of afferent input.

A comprehensive contemporary review of PIC evidence in human motoneurons, combining H-reflex triangulation, motor unit recordings, and paired-motor-unit tech-

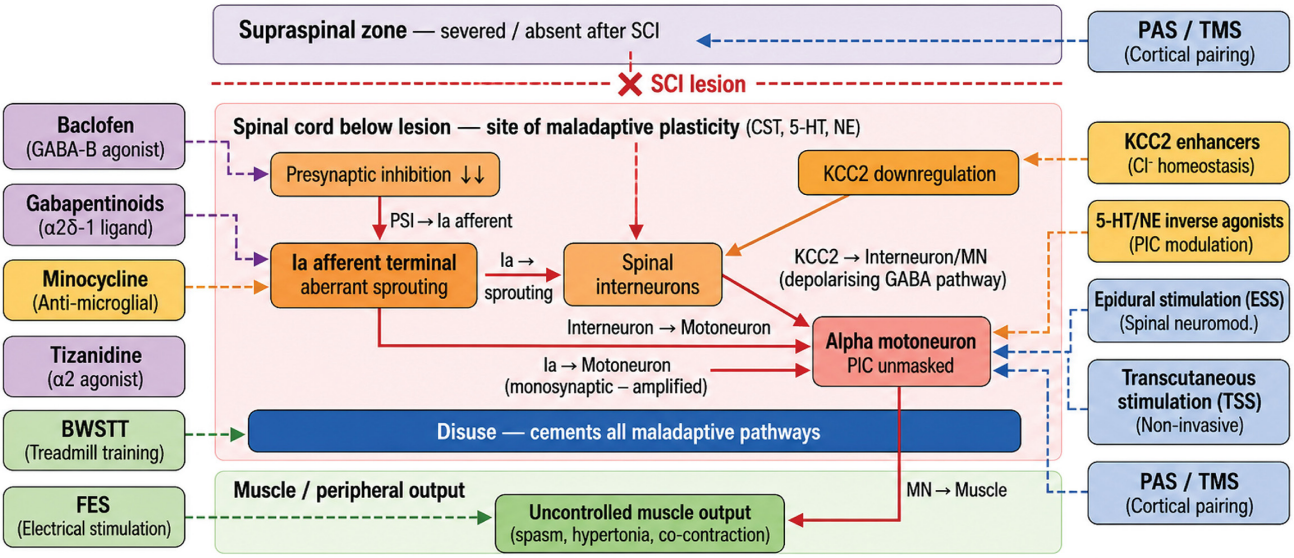


Fig. 6. Therapeutic targets mapped onto the post-SCI maladaptive proprioceptive circuit. The circuit diagram illustrates maladaptive changes following loss of supraspinal input, including reduced presynaptic inhibition, Ia afferent sprouting, altered spinal interneuronal signaling, KCC2 downregulation, and α-motoneuron hyperexcitability, leading to uncontrolled muscle output. Disuse is shown as an amplifier of these maladaptive pathways. Therapeutic modules are positioned at their principal sites of action and color-coded by class: established pharmacology (purple: baclofen, gabapentinoids, tizanidine); emerging pharmacology (yellow: minocycline, KCC2 enhancers, 5-HT/NE inverse agonists); activity-dependent interventions (green: BWSTT, FES); and neuromodulation (blue: ESS, TSS, PAS/TMS). Dashed lines indicate the principal sites of therapeutic action. Evidence levels for each intervention are detailed in Section 8. BWSTT, body weight-supported treadmill training; CST, corticospinal tract; ESS, epidural spinal stimulation; FES, functional electrical stimulation; GABA, gamma-aminobutyric acid; KCC2, potassium-chloride cotransporter 2; MN, motoneuron; PAS, paired associative stimulation; PIC, persistent inward current; PSI, presynaptic inhibition; TMS, transcranial magnetic stimulation; TSS, transcutaneous spinal stimulation; 5-HT, serotonin; NE, norepinephrine; α2δ-1, alpha-2-delta-1 auxiliary subunit.

niques, confirms that PICs are present and tonically active in humans with SCI, and that their magnitude correlates with clinically measured spasticity severity [35,36]. Computational modeling of ionic mechanisms underlying motoneuron bistability has further clarified how the interaction between persistent sodium currents, L-type calcium currents, and inhibitory conductances determines whether a motoneuron enters a self-sustaining firing state [37]. This framework predicts that restoring inhibitory conductance is as important as reducing excitatory current density for reversing pathological bistability, a prediction with direct therapeutic implications.

4.2 Loss of Supraspinal Inhibitory Tone and Activity-Dependent Potentiation

The brainstem and cortex provide tonic inhibitory modulation to spinal circuits via descending pathways to prevent hyperactive reflexes. SCI severs this brake, creating a state of net excitation in spinal circuits below the lesion. Without supraspinal modulation, activity-dependent strengthening of proprioceptive synapses proceeds unchecked, resulting in a pathological form of synaptic potentiation that contributes directly to hypertonia and clonus [6].

4.3 Diminished Spinal Inhibitory Mechanisms

Local inhibitory controls within the spinal cord are impaired at multiple distinct levels.

Reduced presynaptic inhibition (PSI). GABAergic axo-axonic synapses that normally suppress glutamate release from proprioceptive afferent terminals are significantly diminished after SCI [6]. This allows greater glutamate release per arriving action potential, amplifying synaptic drive onto α-motoneurons and contributing to hyperreflexia. Consistent with these findings, clinical electrophysiological studies using D1 inhibition, in which conditioning stimulation of the common peroneal nerve suppresses the subsequent soleus H-reflex and thereby provides an indirect measure of presynaptic inhibition of Ia afferent input, have documented altered presynaptic inhibition after SCI [6].

potassium-chloride cotransporter 2 (KCC2) internalization and the chloride shift. The potassium-chloride cotransporter KCC2 is significantly downregulated in spinal neurons post-SCI [12]. KCC2 is essential for maintaining low intracellular chloride concentrations that support hyperpolarizing inhibitory postsynaptic potentials. Its internalization causes a buildup of intracellular Cl^- and shifts the chloride equilibrium potential (E_{Cl}) to a depolarizing

direction. Now GABA- and glycine-gated chloride channels can paradoxically depolarize rather than hyperpolarize neurons, converting inhibitory synapses into excitatory ones [12,13]. This ionic transformation also occurs along the pain pathways. KCC2 internalization in spinal dorsal horn circuits impairs GABAergic inhibition of nociceptive processing, contributing to central sensitization and neuropathic pain comorbidity [7,13]. At the molecular level, the injury-triggered biochemical cascade begins with the rapid internalization of functional KCC2 from the neuronal membrane. This clearance is facilitated by the accelerated lateral diffusion and de-clustering of the transporter away from active synaptic domains. Ultimately, calpain-mediated proteolytic degradation of the protein permanently may contribute to the intracellular chloride shift in the subacute period, making early pharmacological protection of KCC2 a highly rational therapeutic strategy [38]. Pro-excitatory receptor and channel phenotype changes in deafferented lumbar motoneurons after spinal cord transection, including upregulation of GluN2B-containing NMDA receptors and HCN channels, further compound the ionic excitability shift that follows KCC2 internalization [39]. This is illustrated schematically in Fig. 4. The ionic plasticity resulting from KCC2 internalization and associated changes shares mechanistic underpinnings with pathologies in traumatic brain injury (TBI) and epilepsy, emphasizing that KCC2-based interventions may have utility beyond SCI. Notably, recent evidence explains that not all forms of post-SCI hyperreflexia are equally dependent on KCC2 loss. After corticospinal tract lesions specifically, hyperreflexia reflects primarily changes in Ia afferent circuit connectivity rather than KCC2-mediated disinhibition [40], indicating that different SCI lesion types may require distinct therapeutic targeting of these two mechanisms. While direct measurement of intracellular chloride in human spinal neurons is not feasible, reduced efficacy of GABAergic pharmacotherapy in chronic SCI is clinically consistent with this ionic transformation [6]. The magnitude, cellular distribution, and functional consequences of KCC2 dysregulation in human SCI remain uncertain; this mechanism should therefore be interpreted primarily on the basis of preclinical evidence.

Altered reciprocal inhibition. Circuits mediating Ia-mediated reciprocal inhibition between agonist and antagonist muscles become dysfunctional after SCI, often leading to pathological co-contraction [19]. This inability to selectively inhibit antagonist muscles impedes coordinated movement and contributes to the characteristic stiffness of SCI spasticity. Human electrophysiological studies have documented impaired reciprocal inhibition in individuals with SCI [6].

5. The Pivotal Role of Interneuronal Dysfunction

While changes in primary afferents and motoneurons are critical, the interneurons that form the computational circuitry of the spinal cord are key integrators of sensorimotor function. Their dysfunction after SCI is a central hub of maladaptive plasticity, a major convergence point through which diverse pathological changes produce the clinical syndrome of spasticity [6,28,41]. The evidence in this section derives predominantly from rodent models; human translational data are noted where available.

5.1 The Excitatory–Inhibitory Imbalance

The functional integrity of spinal motor circuits relies on a precise and dynamic balance between excitation and inhibition. SCI disrupts this balance. The loss of descending inhibitory control disproportionately disinhibits excitatory interneuronal circuits while simultaneously reducing excitatory drive to inhibitory interneurons, creating a bidirectional shift toward net excitation [6,41]. Experimental studies have demonstrated that removal of GABAergic inhibition facilitates polysynaptic A-fiber-mediated excitatory transmission in the superficial spinal dorsal horn, highlighting the importance of inhibitory control in regulating spinal sensory processing [42]. Critically, a recent challenge to the purely excitocentric view of spasm generation suggests that muscle spasms after SCI may arise primarily from changes in motoneuron intrinsic excitability and from synaptic inhibition failure, rather than from elevated excitatory synaptic drive alone [15]. This finding, consistent with computational modeling of bistability [37,43], suggests that restoring inhibitory conductance is as crucial as reducing excitatory current for preventing pathological motoneuron firing. Analogous spontaneous hyperexcitability in the human spinal cord would be consistent with clinical observations of hyperreflexia, but it has not been directly quantified.

5.2 Altered Excitability of Sensory-Responsive Interneurons

Rodent studies suggest that selected spinal interneuron populations develop altered excitability following SCI. In a mouse model of chronic spinal transection, bursting interneurons in the deep dorsal horn exhibited increased responsiveness to dorsal root stimulation and prolonged burst durations compared with the acute injury stage [44]. Their activity preceded and correlated with prolonged ventral root responses, suggesting a potential contribution to long-lasting reflex spasms. However, these findings do not establish a generalized increase in excitatory synaptic activity across spinal interneuron populations. Indeed, recent evidence indicates that muscle spasms after chronic SCI are associated with impaired synaptic inhibition and enhanced motoneuron persistent inward currents, without a corresponding increase in sensory-evoked excitatory synaptic currents onto motoneurons [15]. These findings suggest that circuit-specific alterations in interneuronal responsiveness, together with impaired inhibitory control, contribute to pathological reflex activity after SCI.

5.3 Impaired Spinal Inhibitory Signaling

Spinal inhibitory mechanisms are also compromised following SCI, although the underlying changes vary across neuronal populations and spinal circuits. In a rat SCI model, Lu et al. [13] demonstrated that downregulation of KCC2 in lumbar superficial dorsal horn neurons alters chloride homeostasis and attenuates GABAergic inhibitory synaptic transmission, contributing to abnormal sensory processing. Separately, Mahrous et al. [15] demonstrated impaired sensory-evoked synaptic inhibition in chronic SCI models, supporting a role for reduced inhibitory control in muscle spasm generation. Together, these findings indicate that SCI can reduce the effectiveness of spinal inhibition through multiple mechanisms. However, they do not directly establish reduced spontaneous activity or loss of tonic-firing inhibitory interneurons. Thus, impaired inhibitory signaling, rather than generalized suppression of inhibitory interneuron firing, represents a more accurate description of the available evidence.

5.4 Neurotransmitter Phenotype Switching

One of the most remarkable forms of interneuronal plasticity following SCI, demonstrated in rodent models, is the switching of neurotransmitter phenotype in adult spinal interneurons. Bertels et al. [45] showed that a defined population of interneurons, including Tlx3- and Shox2-positive cells in dorsal and intermediate laminae, can undergo a switch from a glutamatergic to a GABAergic/glycinergic phenotype after injury. Counterintuitively, the resultant increase in inhibitory synapses onto α-motoneurons correlated with increased paralysis and spasticity in rodent models, likely because these aberrant connections disrupt the precisely patterned temporal sequences of excitation and inhibition required for coordinated motor output. This phenomenon is age-dependent in rodents; neonatal SCI does not induce the phenotype switch. Whether comparable phenotype switching occurs in the adult human spinal cord after SCI has not been established, and this mechanism should be considered a preclinical finding pending translational validation.

Two cautions temper the clinical reading of this finding. First, it derives from a rodent model, and the dependence of the switch on injury severity and completeness has not been systematically tested. Whether it occurs after the incomplete contusion injuries that predominate in human SCI, as opposed to severe or complete lesions, is unknown. Second, the reported association between increased inhibitory synapses and worse motor function is counterintuitive and may reflect disruption of circuit-specific timing and connectivity rather than a simple increase in global inhibition. For both reasons the phenotype switch should be read as a preclinical observation whose clinical relevance provides a rationale for validation in graded, clinically representative injury models and, ultimately, in human tissue.

5.5 Monoaminergic Dysregulation and Constitutive Receptor Activity

The loss of descending 5-HT and NE projections has complex, time-dependent effects on spinal interneurons and motoneurons. Acutely, their loss contributes to spinal shock, the transient depression of all spinal reflex activity. In the chronic injury state, spinal neurons below the lesion undergo denervation supersensitivity. Rodent studies demonstrate that constitutive (ligand-independent) activity of 5-HT2B/2C and α1-adrenergic receptors facilitates persistent inward currents in motoneurons and contributes to prolonged muscle spasms after SCI [46,47]. In a human pharmacological study, D'Amico et al. [48] demonstrated that cyproheptadine, an inverse agonist of 5-HT2/α1 receptors, reduced long-lasting reflex responses in individuals with chronic SCI, whereas a neutral antagonist had no significant effect in participants with motor-complete injuries. These findings provide indirect clinical evidence that constitutive monoamine receptor activity contributes to persistent inward current-mediated muscle spasms after SCI. Importantly, this constitutive receptor activity persists after incomplete SCI and is not normalized by chronic selective serotonin reuptake inhibitor (SSRI) fluoxetine treatment or baclofen, indicating that it represents an independent and pharmacologically tractable target that existing drugs do not address [49]. At the mechanistic level, 5-HT2 receptor activation amplifies PICs by facilitating persistent sodium conductance [50], providing a direct molecular link between serotonergic denervation supersensitivity and the motoneuron excitability changes documented after SCI. Further modulating the excitability of proprioceptive afferents, extrasynaptic α5GABA-A receptors on Ia afferent terminals produce a tonic depolarizing current that modulates the gain of sodium channel activation [51]. Their contribution to afferent hyperexcitability after loss of appropriate inhibitory tone warrants further investigation. Although human pharmacological findings support a contribution of constitutive monoamine receptor activity to post-SCI spasms [48], direct confirmation of the underlying receptor mechanisms and clinical efficacy of selective inverse agonists require further investigation.

These interneuronal changes map onto distinct clinical features. Loss of descending inhibitory tone and hyperexcitability of excitatory interneurons may lower the threshold for reflex activation and thereby contribute to hyperreflexia and stimulus-triggered spasms. Impaired inhibitory interneuron function and reciprocal inhibition may permit broader reflex spread and contribute to clonus and agonist–antagonist co-contraction. KCC2 loss and the resulting failure of postsynaptic inhibition contribute both to spasticity and to the central sensitization that associated with neuropathic pain, although the relative contribution of each mechanism in human SCI remains unresolved. Table 1 (Ref. [6,12,13,15,38,41,44,45,46,47,48]) summarizes these

Table 1. Key interneuronal changes and mechanisms contributing to spasticity after SCI.

Interneuronal change	Mechanism	Consequence	Evidence level/Ref.
Loss of descending inhibitory tone	Disinhibition of excitatory INs; unchecked synaptic potentiation	Net spinal hyperexcitability; hyperreflexia	Rodent + clinical electrophysiology [6,41]
Altered bursting interneuron responsiveness	Enhanced dorsal root-evoked responses and prolonged bursting in deep dorsal horn interneurons	Prolonged reflex responses; potential contribution to muscle spasms	Rodent [44]
Impaired spinal inhibitory signaling	Reduced sensory-evoked inhibitory efficacy	Reduced inhibitory control; increased susceptibility to muscle spasms	Rodent [15]
KCC2 internalization	Depolarizing shift in E_{Cl}; GABAergic channels become excitatory	Loss of genuine postsynaptic inhibition; central sensitization	Rodent evidence; clinically inferred [12,13,38]
Evidence level	Unmodulated 5-HT2 and NAα1 receptors; PIC re-activation	Sustained plateau potentials; long-lasting spasms	Rodent mechanistic evidence [46,47]; human pharmacological evidence [48]
Neurotransmitter phenotype switching	Glu→GABA switch in $Tlx3^+$/$Shox2^+$ INs; aberrant inhibitory synapses	Disrupted E/I patterning; paralysis	Rodent evidence only [45]

IN, interneuron; sEPSC, spontaneous excitatory postsynaptic current; AMPAR, AMPA receptor; PIC, persistent inward current; RDD, rate-dependent depression; KCC2, potassium-chloride cotransporter 2; E/I, excitatory–inhibitory; 5-HT, serotonin; NAα1, noradrenergic alpha-1 receptor; Glu, glutamatergic; GABA, GABAergic.

changes, their mechanisms, and the level of evidence supporting each.

6. The Confluence of Mechanisms: From Plasticity to Pathology

The maladaptive changes in afferents, interneurons, and motoneurons do not occur in isolation; they interact synergistically and reinforce one another to produce the complex clinical syndromes observed after SCI. Table 2 (Ref. [6,10,11,12,19,23,24,25,27,29,30,35,37,38,45,52,53,54]) summarizes these changes across structural, synaptic, cellular, ionic, and systems levels, with their functional consequences and characteristic clinical signs.

6.1 The Pathophysiology of Spasticity

Spasticity in SCI is not a single entity but a collection of distinct, mechanistically separable symptoms [3,6].

Velocity-dependent hypertonia, primarily driven by hyperexcitable stretch reflexes. Loss of RDD, reduced PSI, and unmodulated PICs indicate that the stretch reflex circuit fails to habituate to repeated muscle stretch, resulting in sustained, velocity-dependent resistance to passive movement. Clinical and kinematic assessments of this component include the Modified Ashworth Scale and Pendulum Test, respectively [2,3].

Clonus, self-sustaining, rhythmic oscillatory contractions (most commonly at the ankle) resulting from a combination of hyperexcitable stretch reflexes, impaired reciprocal inhibition, and the cyclic activation and deactivation of plateau potentials within the α-motoneuron pool [30,37].

Muscle spasms, involuntary, often powerful contractions mediated primarily by the unmasking and hyperexcitability of PICs, which transform brief afferent inputs (from bladder distension, cutaneous stimulation, or joint movement) into sustained motoneuron output. Aberrant afferent sprouting and hyperexcitable interneuronal circuits amplify and broadly distribute these inputs, often triggering flexor or extensor spasms across multiple muscle groups simultaneously. The contribution of synaptic inhibition failure is equally critical: spasm amplitude correlates with the degree of inhibitory synaptic depression, not merely with excitatory drive [10,15,29,31].

6.2 Impairment of Voluntary Motor Function

Maladaptive proprioceptive plasticity actively impedes voluntary motor recovery beyond simply producing positive symptoms. Aberrant synaptic connections formed through sprouting create pathological reflex pathways that compete with and overwhelm residual voluntary descending commands [10,11]. Pervasive loss of fine-grained inhibitory control produces co-contraction of agonist and antagonist muscles, resulting in stiff, metabolically inefficient movements. Furthermore, severely disrupted sensory feedback ascending from maladapted proprioceptors means that motor commands are issued without accurate real-time knowledge of limb position or generated force, fundamentally impairing coordination and dexterity [55].

6.3 Contribution to Neuropathic Pain

The neural pathways underlying pain and motor dysfunction overlap substantially with proprioception. Cen-

Table 2. Summary of key maladaptive proprioceptive changes and their functional consequences.

Level	Specific mechanism	Functional consequence	Clinical sign	Evidence/Ref.
Structural	Aberrant Ia sprouting (VGlut1$^+$ terminals on α-motoneurons; astrocytic GLT-1 co-remodeling)	Amplified monosynaptic reflex arc	Hyperreflexia; spasms	Rodent [10,24,25]
Structural	Ia proprioceptor impairment after injury	Degraded sensory signal quality	Impaired coordination	Rodent [23]
Structural	Microglial-mediated afferent synaptogenesis into sympathetic circuits	Pathological rewiring of autonomic pathways	Autonomic dysreflexia	Rodent [52]
Structural	Failed central integration of regenerated afferents	Loss of functional proprioceptive feedback	Impaired coordination	Rodent [27]
Synaptic	Loss of PSI	Enhanced glutamate release per AP	Hyperreflexia; reduced RDD	Rodent + clinical [6]
Synaptic	CP-AMPAR upregulation (disuse-induced; calcineurin/CK2 dysregulation)	Enhanced synaptic strength; Ca^{2+} influx; excitability loop	Spasticity; impaired recovery	Rodent [11,53,54]
Cellular	Alpha motoneuron PIC hyperexcitability (CaV1.3, NaV1.6)	Sustained plateau potentials; prolonged firing	Muscle spasms	Rodent + clinical [29,30,35,37]
Cellular	Interneuron phenotype switching (Glu→GABA in Tlx3$^+$/Shox2$^+$ cells)	Aberrant inhibitory synapses disrupting motor patterning	Impaired coordination; paralysis	Rodent only [45]
Ionic	KCC2 internalization (calpain-mediated; BDNF/TrkB dysregulation); depolarizing E*Cl* shift	GABAergic synapses become excitatory	Loss of inhibition; central sensitization	Rodent; clinically inferred [12,38]
Systems	Loss of reciprocal inhibition	Agonist–antagonist co-contraction	Stiffness; inefficient movement	Rodent + clinical [19]

AP, action potential; CP-AMPAR, calcium-permeable AMPA receptor; KCC2, potassium-chloride cotransporter 2; PIC, persistent inward current; PSI, presynaptic inhibition; RDD, rate-dependent depression; Glu, glutamatergic; GABA, GABAergic; GLT-1, glutamate transporter 1.

tral sensitization, a key neurobiological mechanism of chronic neuropathic pain, shares foundational pathologies with spasticity: hyperexcitability of dorsal horn neurons, glial activation, neuroinflammatory cytokine release (TNF-α, IL-1β), and KCC2 internalization [56,57]. Maladaptive changes in large-diameter, low-threshold mechanoreceptors can lead to their aberrant activation of nociceptive pathways, a phenomenon termed tactile allodynia, in which light touch is perceived as painful. Thus, the same plastic processes that cause a light touch to trigger a muscle spasm can simultaneously cause that touch to be experienced as pain, illustrating the unified pathobiology of two of the most debilitating post-SCI complications.

6.4 Autonomic Dysreflexia

Autonomic dysreflexia (AD) is a potentially life-threatening condition affecting individuals with SCI at or above the T6 level, characterized by episodic, uncontrolled sympathetic reflex discharge triggered by stimuli below the injury level. AD extends the principle of maladaptive plasticity into autonomic circuits: sprouting of somatic and visceral afferents into sympathetic interneuronal circuits, combined with the hyperexcitability of these interneurons, leads to uncontrolled sympathetic surges causing severe hypertension. Rodent evidence implicates microglial-mediated synaptogenesis as a key driver of this pathological rewiring of sympathetic preganglionic neurons in the thoracic spinal cord [52], underscoring that maladaptive plasticity is a spinal cord-wide process with systemic consequences. Clinical correlates of AD with aberrant spinal plasticity have been documented, but the precise cellular mechanisms in humans remain less well characterized.

A point of clarification concerns the trigger. The afferent drive that initiates autonomic dysreflexia is nociceptive and visceral, most often arising from bladder or bowel distension, rather than proprioceptive, and proprioceptive afferents are not established as direct triggers of these episodes. The relevance of autonomic dysreflexia to this review lies instead in shared cellular mechanisms: afferent sprouting into denervated circuits, interneuronal hy-

perexcitability, and loss of inhibitory control are the same processes that drive maladaptive plasticity in somatic motor circuits, now expressed in the autonomic domain.

7. The Impact of Disuse: Cementing Maladaptive Pathways

The early period following SCI is typically characterized by enforced immobilization and profound sensorymotor deprivation. Rodent evidence, reviewed in this section, suggests that disuse is not a passive state but an active driver of maladaptive plasticity that can solidify pathological changes and create a self-reinforcing cycle that can hinder long-term recovery [11,58]. The translational relevance of these rodent findings to the timing of early human rehabilitation is discussed in Section 8.

7.1 Disuse-Induced Hyperexcitability: The Maladaptive Memory Trace

A study by Morioka et al. [11] demonstrated in a rodent thoracic SCI model that hindlimb unloading restricted to only the first two weeks post-injury induced a persistent and disproportionate hyperexcitability in lumbar spinal circuits. This disuse-induced hyperexcitability enhanced spasticity and limited long-term locomotor recovery, even after normal weight-bearing activity was subsequently resumed. This finding suggests that the early post-injury period is a critical window during which disuse consolidates a maladaptive memory trace into the synaptic architecture of the spinal cord, one that is resistant to later modification. Complementary work in aged mice shows that hindlimb unloading alters spinal motoneuron morphology and excitability even without SCI, and that exercise with sensory stimulation can partially reverse these changes [59], suggesting that disuse-driven plasticity mechanisms are broadly conserved and that the vulnerability of the motoneuron pool to unloading may be amplified in older individuals following SCI. Whether an analogous critical window of equivalent temporal sensitivity exists in humans has not been directly demonstrated, though the principle is clinically supported by the general observation that early rehabilitation is associated with better functional outcomes [55].

7.2 Molecular Mechanisms of Disuse-Induced Synaptic Plasticity

Morioka et al. [11] identified specific synaptic alterations in rodents that favor chronic hyperexcitability following disuse. Early post-SCI disuse promotes phosphorylation of the GluA1 subunit of AMPA receptors at the serine-831 (pS831) site, a modification that facilitates synaptic trafficking and retention of calcium-permeable AMPA receptors (CP-AMPARs) lacking the GluA2 subunit. CP-AMPARs have significantly higher single-channel conductance than their GluA2-containing counterparts and permit Ca^{2+} influx upon activation, which further potentiates synaptic strength through calcium-dependent signaling cascades (notably CaMKII activation) in a positive feedback loop.

The molecular regulation of synaptic AMPAR composition after injury involves multiple converging pathways. Nerve injury broadly promotes a shift toward GluA2-lacking, Ca^{2+}-permeable receptors in spinal cord circuits [53], and this shift is regulated upstream by a reciprocal interaction between calcineurin and casein kinase 2 (CK2) kinases acting through the auxiliary subunit α2δ-1 in spinal excitatory neurons [54]. Disruption of this calcineurin/CK2 balance after SCI likely sustains the aberrant synaptic insertion and retention of CP-AMPARs independently of the pS831 phosphorylation pathway. Together, these converging mechanisms create a durable molecular barrier to adaptive recovery. A comprehensive review confirms that AMPAR-selective modulators capable of reversing GluA2-lacking receptor accumulation represent a mechanistically plausible therapeutic class that remains underexplored [60]. This mechanism is illustrated schematically in Fig. 5. Direct evidence for pS831-GluA1 accumulation at human spinal synapses after SCI is not yet available; this mechanism should be regarded as a preclinical finding with strong therapeutic implications.

7.3 Functional and Behavioral Consequences of Early Disuse

Rodent models of early disuse following SCI demonstrate significantly poorer locomotor outcomes on open-field assessments (Basso-Beattie-Bresnahan scale), irregular and arrhythmic stepping patterns, reduced interlimb coordination, and increased hindlimb rigidity in gait analysis [11]. Swimming assessments reveal classic spastic postures, including extended, rigid hindlimbs that are quantitatively more severe and persistent in the disuse group. These rodent findings provide mechanistic support for the clinical imperative of early rehabilitation, even if the precise temporal parameters of the critical window in humans require further investigation.

7.4 The Competition for Plasticity and the Imperative of Early Intervention

Rodent evidence indicates that the spinal cord possesses a finite and time-limited capacity for plasticity, particularly during the acute and subacute post-injury period. Disuse creates an environment permissive to nociception- and inflammation-driven maladaptive plasticity [58,61]. Appropriate, task-specific proprioceptive input, such as that generated during stepping, is necessary to drive adaptive plasticity that supports motor recovery. Early rehabilitation thus represents a time-sensitive neurobiological intervention aimed at competitively occupying the injured spinal cord's plastic capacity before maladaptive pathways consolidate, rather than a purely supportive measure [11,61].

8. Therapeutic Strategies: Countering Maladaptation and Promoting Recovery

The recognition that spasticity and motor impairment are driven by active and mechanistically defined maladaptive processes transforms the therapeutic framework: the goal shifts from simple symptom suppression to the rational modulation of spinal plasticity. Current strategies operate at multiple levels of the neural axis. This section distinguishes established symptomatic treatments from mechanistically promising emerging interventions and from speculative future directions. The therapeutic landscape is mapped onto the maladaptive circuit in Fig. 6. Table 3 (Ref. [6,12,14,48,58,60,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87]) summarizes the strategies discussed below, grouped by evidence tier.

Before turning to specific interventions, it is worth separating what is established in humans from what rests on rodent data alone, because the two carry different weights for therapeutic decisions. Several functional correlates of the maladaptive circuit have been demonstrated in people with SCI, including impaired H-reflex rate-dependent depression, reduced measures of presynaptic inhibition, altered reciprocal inhibition, and motoneuron excitability consistent with persistent inward current activity. These findings provide important translational support for the framework but do not by themselves establish the same cellular and structural mechanisms demonstrated in rodent models. Reduced H-reflex rate-dependent depression is commonly reported in chronic SCI and is consistent with impaired spinal inhibitory control, although its magnitude varies across individuals and experimental protocols. Reduced presynaptic inhibition measured by D1 methods, and impaired reciprocal inhibition are all documented in clinical populations [6,19,22]. Persistent inward currents are present and tonically active in human motoneurons, and their magnitude tracks clinically measured spasticity [33,34,35,36]. On the therapeutic side, epidural stimulation, transcutaneous spinal stimulation, and paired associative stimulation have all shown benefit in controlled human studies, including randomized and Level I evidence [70,75,76,77,83], and timing-dependent corticospinal-to-spinal synergies have been demonstrated intraoperatively and noninvasively in humans [88,89]. Other mechanisms central to the framework remain rodent-only at present: direct measurement of VGlut1 afferent sprouting, quantified KCC2 downregulation, CP-AMPAR and pS831-GluA1 accumulation, neurotransmitter phenotype switching, and constitutive monoamine receptor activity have not been examined in human tissue [10,11,12,45,46,47,48,49]. The emerging tools in Section 8.5, including DREADDs, engineered chloride extrusion, and selective Ia afferent suppression, are at an early preclinical stage [14,84,85,87]. We therefore present the established pharmacological and neuromodulatory options as current clinical choices, the mechanistically targeted pharmacology as promising but unproven, and we identify human validation of the rodent-only mechanisms as a priority in the Conclusions.

8.1 Established Pharmacological Interventions

The following agents represent the current clinical standard of care for SCI spasticity, with established evidence from clinical trials and long-term clinical use.

8.1.1 GABAergic Agents

Baclofen: A GABA-B receptor agonist and the cornerstone of pharmacological spasticity management. Baclofen acts presynaptically on primary afferent terminals to reduce glutamate release (via inhibition of Ca^{2+} influx) and postsynaptically on interneurons and α-motoneurons to enhance inhibition (via increased K^+ conductance and hyperpolarization), thereby suppressing hyperreflexia and spasms. Mechanistically, baclofen also directly suppresses PICs in spinal motoneurons in chronic spinal rat models, reducing both the amplitude of plateau potentials and the duration of PIC-sustained firing, providing a mechanistic basis for its anti-spasm efficacy beyond simple presynaptic inhibition [62]. Intrathecal baclofen (ITB) achieves higher spinal concentrations with lower systemic exposure and is reserved for severe refractory cases. Limitations include sedation, muscle weakness, cognitive blunting, risk of dangerous withdrawal, and potential impairment of residual voluntary motor function.

Benzodiazepines (e.g., diazepam): Positive allosteric modulators of GABA-A receptors that increase Cl^- channel opening frequency in response to GABA. Their pronounced sedative, amnestic, and dependence-inducing properties limit their utility in long-term SCI rehabilitation. Importantly, their efficacy as GABAergic agents is partially compromised in the post-SCI state by KCC2 internalization, which shifts the chloride equilibrium potential and may reduce the hyperpolarizing effect of GABA-A activation [12,13].

8.1.2 Alpha-2 Adrenergic Agonists

Tizanidine: Acts on presynaptic α2-adrenergic receptors in the spinal cord to inhibit excitatory neurotransmitter release, and on postsynaptic receptors to hyperpolarize interneurons and α-motoneurons. It provides effective reduction of spastic tone and spasm frequency with a distinct side effect profile (dry mouth, sedation, hepatotoxicity risk requiring monitoring). Clinical evidence supports efficacy equivalent to baclofen for spasticity reduction [63].

8.1.3 Ion Channel Modulators

Gabapentin and pregabalin: Although primarily indicated for neuropathic pain, these agents bind with high affinity to the α2δ-1 auxiliary subunit of voltage-gated calcium channels on primary afferent terminals and interneurons, reducing presynaptic Ca^{2+} influx and neurotransmitter release. Their efficacy for central neuropathic pain

Table 3. Therapeutic strategies for targeting maladaptive proprioceptive plasticity after SCI.

Strategy class	Example(s)	Proposed mechanism of action	Evidence level	Key references
Established pharmacology	Baclofen (GABA-B agonist); ITB	Pre/postsynaptic inhibition; direct PIC suppression	[Established clinical]	[6,62]
Established pharmacology	Tizanidine (α2 agonist)	Inhibits presynaptic excitatory neurotransmitter release; postsynaptic hyperpolarization	[Established clinical]	[63]
Established pharmacology	Gabapentin/pregabalin (α2δ-1 ligand)	Reduces presynaptic Ca^{2+} influx; neurotransmitter release from afferents and INs	[Established clinical (neuropathic pain)]	[64]
Novel pharmacology	KCC2 enhancers (CLP290); KCC2-upregulating biologics	Restores Cl^- homeostasis; reverses depolarizing E*Cl*; restores genuine GABAergic inhibition	[Preclinical]	[12,65,66]
Novel pharmacology	AMPAR modulators (CP-AMPAR negative allosteric modulators)	Reverses GluA2-lacking AMPAR accumulation; reduces Ca^{2+} influx and CaMKII loop	[Preclinical]	[60]
Novel pharmacology	5-HT/NAα1 inverse agonists	Suppresses constitutive receptor activity; reduces PIC-dependent spasms	[Preclinical mechanistic evidence; preliminary human pharmacological evidence]	[48]
Activity-dependent	BWSTT	Task-specific proprioceptive normalization; KCC2 restoration via BDNF/TrkB (rodent); counter-disuse CP-AMPAR correction (rodent)	[Clinical case series; mechanism preclinical]	[67,68,69]
Activity-dependent	FES	Large-amplitude proprioceptive and cutaneous feedback; maintains muscle bulk; counters disuse atrophy	[Established clinical practice]	[58]
Neuromodulation	ESS; TSS	Tonic spinal circuit facilitation; recruitment of inhibitory INs; KCC2-dependent chloride homeostasis restoration (TSS, rodent)	[Established/Emerging clinical; KCC2 mechanism preclinical]	[70,73,74,75,76]
Neuromodulation	PAS/TMS	STDP-driven strengthening of surviving CST connections	[Emerging clinical]	[77,78,79,80,81,82,83]
Future directions	DREADDs; Ia afferent modulation; NO/KCC2 engineering; BCIs; cell transplants	Circuit-selective inhibitory restoration; Ia-source suppression; engineered chloride extrusion; neural bypass	[Emerging preclinical]	[14,71,72,84,85,86,87]

BWSTT, body weight-supported treadmill training; CST, corticospinal tract; DREADD, Designer Receptor Exclusively Activated by Designer Drug; E/I, excitatory–inhibitory; ESS, epidural spinal stimulation; FES, functional electrical stimulation; IN, interneuron; KCC2, potassium-chloride cotransporter 2; PAS, paired associative stimulation; PIC, persistent inward current; TMS, transcranial magnetic stimulation; TSS, transcutaneous spinal stimulation; 5-HT, serotonin; NAα1, noradrenergic alpha-1 receptor; ITB, intrathecal baclofen.

after SCI is supported by a meta-analysis of randomized controlled trials, which found reductions in pain and pain-related sleep interference [64]. Evidence for a direct effect on spasticity and hyperreflexia in SCI is more limited, although their action on afferent and interneuronal calcium channels provides a plausible mechanism. Gabapentinoids may therefore be particularly useful when neuropathic pain is the primary treatment target and spasticity coexists, as is common in chronic SCI [7].

8.2 Mechanistically Promising Emerging Pharmacological Interventions

The following targets emerge directly from the mechanistic framework outlined in Sections 3–7. Evidence is predominantly preclinical; human translation is at early stages, and claims of efficacy should be interpreted cautiously.

KCC2 enhancers: Compounds that upregulate or restore functional expression of KCC2 represent among the most mechanistically rational strategies in development. KCC2 has been formally identified as a druggable spinal target whose pharmacological enhancement could restore genuine hyperpolarizing GABAergic inhibition in the SCI spinal cord [65]. By restoring intracellular chloride homeostasis, KCC2 enhancers aim to reverse the depolarizing shift in E_{Cl} and reestablish authentic inhibitory postsynaptic potentials at GABAergic and glycinergic synapses. Preclinical rodent work established proof of concept with CLP290, demonstrating significant amelioration of spasticity and neuropathic pain [12]. Most recently, Bilchak et al. [66] demonstrated in a chronic SCI rat model that KCC2 enhancers normalize H-reflex responses and produce meaningful improvements in locomotor function, providing the most rigorous current preclinical evidence for this class. Exercise itself is a physiological KCC2 enhancer: chloride homeostasis is partially restored by treadmill training in rodent SCI models through a BDNF/TrkB-mediated mechanism that upregulates KCC2 expression, and this restoration correlates mechanistically with the exercise-induced reduction in spasticity [67,68]. This exercise-KCC2 link provides a neurobiological rationale for combining pharmacological KCC2 enhancers with activity-dependent rehabilitation in a synergistic protocol. Human translation of direct KCC2 pharmacology remains unresolved.

AMPAR modulators: Given the central role of CP-AMPAR accumulation at Ia-motoneuron synapses in disuse-driven maladaptive plasticity, selective AMPAR modulators, particularly negative allosteric modulators of GluA2-lacking CP-AMPARs, represent a mechanistically compelling emerging therapeutic class [60]. Targeting the upstream kinase dysregulation (calcineurin/CK2 imbalance) that may contribute to CP-AMPAR insertion may offer additional pharmacological entry points [54].

5-HT and NE inverse agonists: Drugs that selectively suppress the constitutive activity of denervation-supersensitized monoamine receptors could theoretically dampen PIC-driven spasms with high specificity, without affecting baseline neurotransmission or residual motor function [48]. This constitutive receptor activity persists after incomplete SCI and is not normalized by SSRIs, making inverse agonists a potentially distinct therapeutic class [49]. While the underlying mechanisms have been established primarily in rodent models, human pharmacological findings provide indirect evidence that constitutive 5-HT2/α1 receptor activity contributes to muscle spasms after SCI [48]. However, the clinical efficacy and safety of selective inverse agonists require further investigation.

Anti-neuroinflammatory agents (e.g., minocycline): Minocycline, a tetracycline with microglial activation-inhibiting properties, has shown promise in preclinical SCI models in reducing afferent sprouting and circuit hyperexcitability by attenuating the neuroinflammatory milieu [21]. Its therapeutic window is narrow, with the greatest efficacy when administered early post-injury before sprouting is consolidated. Phase II clinical data are emerging but remain heterogeneous.

8.3 Activity-Dependent Interventions: Harnessing Use-Dependent Plasticity

These strategies harness the principle that the injured spinal cord retains substantial plasticity and can be shaped by controlled, patterned sensory input to guide reorganization toward functional recovery [55,58]. Evidence ranges from strong preclinical to established clinical for the core modalities. A recent systematic review and meta-analysis of combination therapy approaches, integrating pharmacological, rehabilitative, and neuromodulatory strategies in rodent SCI models, indicates that multimodal combinations produce significantly greater motor recovery than any single intervention alone [90], supporting the rationale for combining interventions reviewed in this section.

Body weight-supported treadmill training (BWSTT): The paradigmatic activity-dependent plasticity intervention for SCI. Rhythmic, task-specific proprioceptive and cutaneous input during assisted stepping normalizes spinal circuit excitability, promotes recovery of reciprocal inhibition, enhances post-activation depression, and counters disuse-driven CP-AMPAR accumulation by providing activity-dependent synaptic normalization. A critical mechanistic insight is that BWSTT decreases spasticity in part by restoring KCC2 expression and chloride homeostasis through the BDNF/TrkB pathway [67,68]. This identifies a specific molecular target whose enhancement by concurrent pharmacotherapy could amplify the anti-spastic benefit of locomotor training. Early clinical case studies reported improvements in locomotor function in people with SCI following BWSTT [69], while a systematic review and meta-analysis of animal SCI models found that rehabilitation-based interventions improve motor recovery, particularly when combined with other therapeutic approaches [90].

Robotic exoskeletons: Wearable robotic devices provide consistent, precisely controlled proprioceptive input during assisted ambulation, promoting use-dependent plasticity with greater consistency than manual-assisted therapy. FDA-authorized powered exoskeleton systems, including ReWalk and Ekso GT, are available for rehabilitation in selected individuals with SCI [91,92]. Evidence for functional improvement is emerging; parameter sensitivity, including training dose, speed, and assistance level, remains an active area of research.

Functional electrical stimulation (FES): Application of electrical currents to paralyzed muscles to generate functional contractions (FES-cycling, FES-assisted stepping, FES hand grasp) generates large-amplitude proprioceptive and cutaneous feedback, maintaining muscle bulk, preventing disuse atrophy, and promoting beneficial activity-dependent plasticity. FES is an established clinical rehabilitation standard [58].

Combined motor cortex and spinal neuromodulation: Preclinical rodent work suggests that combining motor cortex stimulation with spinal cord stimulation produces additive or synergistic effects on CST axon growth, synaptic plasticity, and functional motor recovery that exceed either intervention alone [93], providing mechanistic support for the multimodal neuromodulatory protocols that are emerging in clinical SCI rehabilitation.

An important mechanistic rationale linking activity-dependent therapy to neurotransmitter homeostasis is the BDNF–KCC2 axis: both exercise and pharmacological BDNF delivery upregulate KCC2 expression in spinal neurons via TrkB receptor activation [61,68], directly reversing the ionic dysregulation that converts inhibitory to excitatory signaling. Furthermore, locomotor recovery after SCI depends in part on the reconstitution of constitutive serotonergic receptor tone in spinal locomotor circuits; [8] this finding provides a neurobiological mechanism through which monoaminergic pharmacotherapy and activity-dependent training may be mutually facilitating.

8.4 Neuromodulatory Interventions

These approaches directly modulate spinal or cortical circuit excitability to restore functional excitatory–inhibitory balance or strengthen surviving corticospinal pathways.

Epidural spinal stimulation (ESS): Implantation of electrode arrays over the dorsal surface of the spinal cord represents perhaps the most transformative intervention in recent SCI rehabilitation. ESS has enabled individuals with clinically complete motor paralysis to execute voluntary stepping and standing movements when stimulation is active [70], likely by restoring a tonic facilitatory state in dormant spinal locomotor networks that is analogous to the facilitation normally provided by descending monoaminergic tone. ESS also potently suppresses spasticity, probably through recruitment of inhibitory interneuronal networks. Ongoing work in rodents [71,72,94,95], primates, and human systems seeks to uncover the mechanisms by which ESS yields improvement [96,97]. Clinical studies indicate that ESS combined with intensive, task-specific locomotor training can enable standing, stepping, and, in selected individuals, overground walking after chronic motor-complete SCI; however, the available evidence is based largely on small, uncontrolled studies, and larger randomized controlled trials are needed [98,99].

Transcutaneous spinal stimulation (TSS): Noninvasive delivery of alternating currents through skin electrodes over the spinal column modulates spinal circuit excitability and, when paired with voluntary effort or locomotor training, can facilitate motor output and reduce spasticity. Its noninvasive nature makes it particularly accessible for broad clinical application and home-based neuromodulatory therapy. Critically, the mechanisms of action have been clarified: multi-session TSS prevents the development of chloride homeostasis imbalance and reduces spasticity in contusion SCI rats, at least in part through KCC2-dependent mechanisms [73], providing a molecular framework for TSS efficacy that suggests its combination with pharmacological KCC2 enhancers as a rational next step. Parameter optimization also appears important; TSS delivered at alternating intensities in a contusion SCI rat model preferentially prevents spasticity development compared to fixed-intensity protocols [74], underscoring the importance of stimulation parameter selection. Clinical evidence has expanded significantly: TSS modulates spinal reflex circuit excitability in persons with SCI in a dose-dependent manner [75], and a randomized controlled trial suggests that transspinal stimulation preceding assisted step training reorganizes neuronal excitability and restores inhibitory network function in SCI participants, with improvements in both reflex measures and overground walking [76]. The overall clinical evidence base is promising but parameter-sensitive; meta-analytic synthesis across heterogeneous protocols is ongoing, and settled efficacy claims should be interpreted with caution.

Paired associative stimulation (PAS) and TMS: PAS is the most extensively clinically tested corticospinal paired-stimulation approach and is grounded in spike-timing-dependent plasticity. A TMS pulse to the motor cortex is timed with peripheral nerve stimulation so that the descending corticospinal volley and the ascending afferent volley arrive together at corticomotoneuronal synapses in the spinal cord, strengthening surviving connections through long-term potentiation (LTP)-like mechanisms; the interstimulus interval is set individually for each muscle from the F-wave minus MEP latency to ensure spinal-level convergence. The clinically dominant high-PAS variant pairs a high-intensity TMS pulse with a 100 Hz peripheral train, producing plasticity across a wider range of interstimulus intervals and greater robustness in clinical use [77]. A practical advantage is that PAS can strengthen connections to

muscles with no residual voluntary activity. The clinical evidence has grown from early proof of concept in chronic incomplete SCI [77], through case series in tetraplegic and paraplegic patients showing improved manual motor scores, hand function, walking, and functional independence [78,79], to a systematic review of 10 studies and 84 patients in which all reported motor improvement, more than 20 sessions were needed for consistent benefit, neuropathic pain often decreased, and no serious adverse events were recorded [80]; independent groups have since replicated the effect and shown that gains persist for at least six months [81,82]. Most importantly, a randomized, sham-controlled trial applied 12 weeks of high-PAS within one to four months of incomplete cervical SCI alongside conventional rehabilitation and showed a significant effect on muscles with no antigravity activity at baseline, providing the first Level I evidence for PAS and indicating that the subacute window may be its optimal application time [83]. The main limitations are the long duration of sessions, the need for clinical-grade TMS and electroneuromyography to determine the interstimulus interval, and an incompletely characterized dose-response relationship. Because it targets surviving corticospinal synapses, PAS is best suited to incomplete SCI with at least partial corticospinal tract preservation.

Paired brain and spinal cord stimulation: A conceptually distinct approach targets the convergence of descending motor and ascending sensory signals within the spinal cord itself, rather than at the cortex, to drive associative plasticity at the sensorimotor interface [100], a framework set out in a review of sensorimotor integration as a therapeutic target after CNS injury [101]. The foundational physiology was established in rats by Mishra et al. [102], who showed that pairing motor cortex stimulation with cervical epidural stimulation timed to converge in the cord produced lasting augmentation of cortical motor responses and reduced spinal thresholds, effects dependent on interstimulus timing. A parallel line showed that combining cortical and spinal stimulation, even outside the strict convergence paradigm, has been associated with corticospinal axon growth and improves forelimb recovery [93], with independent cross-laboratory replication [103]. Using precisely timed spinal cord associative plasticity (SCAP) in a rodent cervical SCI model, Pal et al. [100] then demonstrated improved forelimb sensorimotor function, normalized H-reflex modulation, and adaptive remodeling at the cervical sensorimotor interface, and the approach was extended to locomotion, where combined stimulation restored gait kinematics that neither modality achieved alone [104]. Translation to humans followed: posterior epidural stimulation targeted at the dorsal sensorimotor interface facilitated motor cortex responses in a timing-dependent manner in surgical and chronic SCI patients, exceeding anterior stimulation of the motor system alone [88], and the same timing-dependent synergy was reproduced noninvasively with TMS and transcutaneous stimulation in chronic cervical SCI [89]. Taken together, this work, spanning rodent physiology, cross-laboratory replication, preclinical therapeutic trials across forelimb and locomotor domains, and invasive and noninvasive human studies, establishes paired brain and spinal cord stimulation as a mechanistically grounded and translationally advancing strategy for strengthening sensorimotor connections at their convergence point in the spinal cord.

8.5 Emerging and Future Directions

The following approaches are at early preclinical or translational stages; claims regarding their efficacy in human SCI are speculative.

Optogenetics and chemogenetics (DREADDs): These tools activate or silence genetically defined neuronal populations with high precision. In SCI spasticity, preclinical work uses them to activate inhibitory interneuron populations (V1, V2b), silence hyperexcitable excitatory interneurons, and dissect the contribution of the phenotype-switched Tlx3+/Shox2+ population [84]. A dedicated review identifies adeno-associated virus (AAV)-delivered DREADDs targeting spinal inhibitory circuits as among the most promising translational avenues, with toolsets suited to non-human primate and eventual human trials [85]. Complementarily, chemogenetic stimulation of proprioceptive afferents, rather than suppression of excitatory circuits, remodels lumbar interneuron excitability and promotes motor recovery in rodents [71,72,86]. Human application remains speculative.

Ia afferent activity modulation as a therapeutic lever: A direct test of the proprioceptive plasticity hypothesis comes from a recent rodent study demonstrating that continuous suppression of Ia fiber activity, using an activity-dependent mechanism targeting hyperactive sensory neurons, significantly reduces hyperreflexia and prevents the formation of maladaptive synaptic connections in the spinal cord after injury [14]. This finding supports the central hypothesis of this review, while its generalizability across SCI models and to human SCI remains to be determined: that aberrant Ia afferent activity is a primary driver rather than a secondary consequence of post-SCI spasticity, and that targeting the afferent source represents a complementary strategy to existing interneuron- and motoneuron-focused therapies. Translation to humans will require the development of selective afferent modulation tools.

Engineered chloride extrusion systems: Moving beyond pharmacological KCC2 enhancement, a novel approach engineers nitric oxide (NO) delivery systems to upregulate KCC2-mediated chloride extrusion in inhibitory interneurons after SCI. In a rodent contusion SCI model, this approach renormalized inhibitory interneuron excitability and reduced spasticity [87]. While at an early preclinical stage, this class of engineered biological delivery

represents a potential path to more durable KCC2 restoration than small-molecule pharmacology alone.

Brain-computer interfaces (BCIs): BCIs decode movement intention from cortical neural signals and can use this information to control functional electrical stimulation, robotic devices, or spinal stimulation systems. By linking motor intention to movement-related sensory feedback, these approaches may promote activity-dependent plasticity. In a clinical proof-of-concept study, a brain–spine interface combining cortical signal decoding with epidural spinal stimulation enabled voluntary standing and walking in an individual with chronic incomplete SCI [105]. More recently, a clinical study involving three individuals with motor-complete SCI demonstrated brain-controlled lower-limb movements and assisted walking using a similar approach [106]. A separate proof-of-concept study demonstrated real-time BCI control of a robotic walking exoskeleton with bilateral sensory feedback through cortical stimulation in a participant undergoing epilepsy evaluation, providing additional evidence for the technical feasibility of bidirectional BCIs [107]. Although these findings demonstrate substantial progress in restoring stimulation-assisted voluntary motor control, broader clinical validation and long-term functional outcomes remain to be established.

Cell-based therapies: Transplantation of GABAergic interneuron progenitors aims to enhance inhibitory signaling within injured spinal circuits. Preclinical studies demonstrate that human stem cell-derived GABAergic progenitors can integrate into host spinal networks, reduce spasticity-like responses, and improve locomotor function in SCI rats [108]. Similar transplantation approaches have reduced neuropathic pain and bladder dysfunction in SCI mice [109]. These findings support the potential of cell-based therapies to restore inhibitory control, although direct restoration of E/I balance and clinical safety and efficacy remain to be established.

8.6 The Principle of Timing: The Critical Window for Intervention

A unifying and clinically actionable theme is the critical importance of early intervention [11,61]. Rodent evidence indicates that the spinal cord enters a highly plastic and malleable state immediately following injury. If this window is dominated by disuse and inflammation-driven nociception, maladaptive changes become consolidated and progressively more difficult to reverse. Conversely, introducing appropriate, task-specific sensory and motor activity as early as medically feasible can steer the plastic capacity of the spinal cord in an adaptive direction, preventing the establishment of a durable maladaptive memory trace [11,58,61]. A systematic review and meta-analysis of combination therapeutic strategies in animal SCI models confirms that multimodal approaches, combining pharmacological, rehabilitative, and neuromodulatory elements, improve motor recovery significantly beyond what any monotherapy achieves, and that timing relative to the injury significantly moderates outcomes [90]. Whether the precise temporal parameters of the critical window in rodents translate quantitatively to humans remains an important and unresolved research question. A clinical practice guideline for acute SCI suggests that rehabilitation should be initiated once patients are medically stable and able to tolerate the required rehabilitation intensity [110]. This recommendation is consistent with the mechanistic evidence reviewed here supporting appropriately tailored rehabilitation as early as medically feasible, while the optimal timing, intensity, and patient selection criteria remain to be established clinically.

9. Conclusions

The estimated 20.6 million individuals living with SCI worldwide [111] contend not only with the primary loss of motor and sensory function but with an array of secondary complications driven by active maladaptive plasticity within the injured spinal cord. This review has argued that maladaptive proprioceptive plasticity, encompassing aberrant Ia afferent sprouting, disuse-driven CP-AMPAR accumulation, KCC2 internalization and chloride dyshomeostasis, PIC hyperexcitability, and interneuronal E/I imbalance, is a mechanistically central and underappreciated driver of post-SCI spasticity and motor impairment [9,28].

A key conceptual advance highlighted by recent work is that maladaptive plasticity is not a single mechanism but a deeply interconnected set of processes that amplify one another across multiple levels of the neural axis simultaneously [11,15,40]. The challenge and the opportunity for therapeutic development lies in this multi-level nature: pharmacological interventions that target a single mechanism (e.g., KCC2 enhancement, AMPAR modulation, or inverse agonism) must ultimately be embedded within activity-dependent and neuromodulatory frameworks that provide the patterned sensory input necessary to steer the spinal cord's plastic capacity in an adaptive direction [66,68,90].

The clinical imperative for early intervention has a strong neurobiological foundation in the evidence reviewed here. Preclinical studies suggest that the early post-injury period may be particularly susceptible to disuse-driven maladaptive plasticity, providing a rationale for initiating appropriately targeted, multimodal rehabilitation as early as medically feasible [11,61]. Whether a comparable, quantitatively defined therapeutic window exists in humans remains unknown. Recent translational advances further support this direction. In preclinical SCI models, TSS has been shown to restore chloride homeostasis and reduce spasticity through KCC2-dependent mechanisms [73], whereas clinical studies demonstrate that transspinal stimulation can reorganize spinal inhibitory network function and reflex excitability in people with SCI [76]. Other emerging approaches, including chemogenetic strategies for circuit-

selective modulation of spinal inhibitory networks [85] and direct targeting of Ia afferent-driven hyperreflexia [14], remain largely preclinical. Together, these findings point toward a therapeutic framework that moves beyond symptomatic management toward mechanism-based modulation of maladaptive plasticity. Realizing this potential will require continued translation of well-defined preclinical mechanisms into rigorously tested, patient-centered interventions. Recent 2026 syntheses reinforce this multilevel, whole-neuraxis view and extend it to supraspinal contributors such as reticulospinal plasticity [112] and to the neuromodulatory management of abnormal muscle tone after SCI [113]. A 2026 randomized, sham-controlled trial adds direct human evidence that transcutaneous spinal (transspinal) stimulation delivered before step training reorganizes spinal locomotor circuits in chronic SCI, modulating soleus H-reflex phase-dependent amplitude and the reciprocal Ia and presynaptic inhibition that shape reflex output [114]. A 2026 review of upper-limb recovery after cervical SCI further situates these mechanisms within regenerative rehabilitation, where pairing cell-based repair with task-specific, activity-dependent training is proposed to steer circuit reorganization while contending with the same maladaptive plasticity described here [115].

Several translational priorities follow from this synthesis. First, human confirmation of the rodent-only mechanisms is needed, in particular VGlut1 afferent sprouting, KCC2 downregulation, and CP-AMPAR accumulation, using the electrophysiological and imaging markers that are feasible in patients. Second, the post-SCI behavior of group II afferents should be defined, since it is currently an evidence gap. Third, the timing of the critical window should be established quantitatively in humans, so that interventions can be scheduled rather than assumed. Fourth, combination protocols that pair a mechanistic pharmacology, such as a KCC2 enhancer, with activity-dependent or neuromodulatory therapy should be tested directly, since the rationale for synergy is now specific. Fifth, noninvasive neuromodulation with defined stimulation parameters should be compared across protocols, because current efficacy claims are parameter-sensitive.

Abbreviations

5-HT, 5-hydroxytryptamine (serotonin); AD, autonomic dysreflexia; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BCI, brain–computer interface; BDNF, brain-derived neurotrophic factor; BWSTT, body weight-supported treadmill training; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CP-AMPAR, calcium-permeable AMPA receptor; CST, corticospinal tract; DREADD, designer receptor exclusively activated by designer drug; E/I, excitatory–inhibitory; E*Cl*, chloride equilibrium potential; ESS, epidural spinal stimulation; FES, functional electrical stimulation; GABA, gamma-aminobutyric acid; GTO, Golgi tendon organ; ISI, interstimulus interval; KCC2, potassium-chloride cotransporter 2; NE, norepinephrine; PAS, paired associative stimulation; PIC, persistent inward current; PSI, presynaptic inhibition; RDD, rate-dependent depression; SCAP, spinal cord associative plasticity; SCI, spinal cord injury; SSRI, selective serotonin reuptake inhibitor; STDP, spike-timing-dependent plasticity; TMS, transcranial magnetic stimulation; TSS, transcutaneous spinal stimulation; TrkB, tropomyosin receptor kinase B.

Author Contributions

Conceptualization, scientific framework, original draft preparation, literature review, figure development, and supervision [AP]; literature review, scientific content evaluation, manuscript revision, and figure preparation [JRaj, JRos, GTK]; scientific framework development, literature review, and critical revision [AS]; scientific framework refinement and critical manuscript revision [GS]. Jacquelynn Rajavong, Joshua Ross, and Gavin Thomas Koma contributed equally to this work. All authors contributed to editorial changes in the manuscript. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used Claude.ai (Anthropic, San Francisco, CA, USA; https://claude.ai) in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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