Review

The feasibility of acupuncture on post-spinal cord injury treatment

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Abstract

Spinal cord injury (SCI) simultaneously causes multiple and interrelated pathophysiological disorders throughout the nervous system, hindering the development of effective treatment strategies. Mechanistically, SCI triggers excitatory signaling activation, downregulation of the inhibitory system, neuronal death, followed by the development of new synaptic circuits and reorganization, leading to chronic neurological dysfunctions and mental disorders. Therefore, a simultaneous treatment strategy, known as overlapping treatment, is needed. Over decades, both preclinical and clinical studies have established that acupuncture treatment offers neuroprotection, pain attenuation, improvement of functional recovery, and promotes reward behaviors, suggesting potential roles of acupuncture in post-SCI treatment. Recently, the importance of overlapping treatment has been recognized in developing effective treatments for post-SCI pathophysiology. However, there has been no systematic study investigating the role of acupuncture in various SCI pathophysiology. In this review, we briefly address the mechanisms of post-SCI pathophysiology and discuss the potential therapeutic effects of acupuncture, suggesting its feasibility as a treatment for post-SCI pathophysiology.

Keywords: Acupuncture, neuropathic pain, neurological recovery, overlapping treatment, spinal cord injury

1. Introduction

Spinal cord injury (SCI) can cause sensory, motor, autonomic, and endocrine dysfunctions that directly or indirectly impact quality of life. SCI-induced neurological dysfunctions are often accompanied by emotional and motivational disorders, contributing to a relatively high suicide rate among SCI patients (Betthauser et al., 2022; Shabany et al., 2022; Watson et al., 2022). Long-lasting neurological dysfunctions after SCI result from maladaptive neurochemical and neuroanatomical reorganization at both spinal and higher nervous system levels. However, effective treatments for these neurological dysfunctions remain elusive (Brown et al., 2022; Hudson & Grau, 2022; Zhang et al., 2022a). Due to the multi-level and interrelated nature of neurological dysfunctions caused by SCI, a simultaneous treatment strategy, known as 'overlapping treatment', is needed.

SCI affects neurological function throughout the entire nervous system, including the spinal cord, brainstem, thalamus, and cortex, with spatial and temporal processes observed in humans and other animals (Defrin et al., 2022; Kang et al., 2020; Liu et al., 2023b; Takata et al., 2023). To explore potential therapies for SCI-induced pathophysiology, research groups have used rodent models of SCI. Enhanced excitatory signaling and inflammation, neuronal death, suppression of inhibitory pathways, and reorganization of synaptic circuits due to axon degeneration or regeneration have been implicated (Heutink et al., 2011; Kupfer & Formal, 2022; Mei et al., 2022; Zhou et al., 2021). First-line pharmacological treatments for post-SCI pathophysiology include anti-inflammatory agents such as methylprednisolone, calcium/sodium channel inhibitors (e.g., pregabalin, gabapentin,

riluzole, lamotrigine, or amitriptyline), inhibitory receptor agonists (gamma-aminobutyric acid, GABA, opioid), and enzymes for inhibiting growth factors (chondroitin sulfate proteoglycans, CSPGs) (Kupfer & Formal, 2022). However, long-term and high-dose pharmacological treatments are associated with tolerance and mental disorders, leading to adverse effects and dissatisfaction with psychological or psychiatric disorders (Mei et al., 2022; Zhou et al., 2021). Although cell-based engineering approaches promote functional recovery in post-SCI settings, their clinical applicability is limited by a lack of understanding of action mechanisms in various SCI pathophysiological processes. Against this backdrop, alternative or supplemental non-pharmacological therapeutics may be needed to address post-SCI pathophysiology.

Acupuncture treatment for SCI-induced sensory, motor, and mental disorders has shown therapeutic efficacy and few side effects in both rodent and human SCI studies (Heutink et al., 2011; Jiang et al., 2014; Walker & Dreher, 2020). Acupuncture targets endogenous opioids, GABA, glutamate, reactive oxygen species (ROS), mitogen-activated protein kinase (MAPK), and proinflammatory pathways, which play key roles in SCI-induced sensory/motor dysfunction, inflammation, neuronal death, and various other pathophysiological processes. In this review, we briefly address the underlying mechanism of post-SCI pathophysiology and the potential of acupuncture as an overlapping post-SCI treatment. Given the wide use of acupuncture treatment for various diseases, we focus solely on the potential overlapping treatments of acupuncture for traumatic SCI-induced pathophysiology in this review.

2. Spinal cord injury pathophysiology

After SCI, neurons and glial cells immediately and persistently increase extracellular levels of excitatory signaling substances, including glutamate, reactive oxygen species (ROS), adenosine triphosphate (ATP), proinflammatory cytokines, and cations, while inhibitory substances such as GABA, serotonin (5-HT), and noradrenaline (NE) are decreased in the spinal dorsal horn (Bringans et al., 2022; Munteanu et al., 2022; Stefanova & Scott, 2022; Zhang et al., 2022b). This imbalance between excitatory and inhibitory substances can easily lead to enhanced neuronal activity, excitotoxicity, apoptosis, and inflammation, all of which are involved in post-SCI pathophysiology (Fan et al., 2022; Mech et al., 2022; Quadri et al., 2020; Stewart et al., 2022).

The most crucial signaling cascade in post-SCI pathophysiology is the glutamate signaling pathway. The increase in glutamate and activation of its receptors after SCI affect inter- and intra-cellular signaling (Diaz-Ruiz et al., 2007; Leem et al., 2010; Tai et al., 2021). However, the inhibitory neurotransmitter GABA, which counters the effects of glutamate-induced excitation, is also increased after SCI, albeit only transiently; GABAergic transmission is decreased in the chronic phase after SCI (Drew et al., 2004; Meisner et al., 2010; Mills et al., 2001). Therefore, a loss of balance between these two neurotransmitters may play a significant role in post-SCI pathophysiology. The activation of membrane ion channels, such as calcium and sodium channels, and the inhibition of potassium channels, accelerates post-SCI pathophysiology. For example, the activation of the alpha2delta subunit of the calcium channel modulates the activity of pain signaling pathways after SCI (Zeng et al., 2013). The effects of inhibiting the alpha2delta1 subunit using gabapentinoids, which are first-line treatments for SCI-induced neuropathic pain, demonstrate the importance of calcium channels in post-SCI (Liu et al., 2011). Several previous studies have shown that SCI upregulates calcium/sodium channels, whereas potassium channels are downregulated (Boroujerdi et al., 2011; Boulenguez et al., 2010; Hains et al., 2003a). Intracellular signaling by proinflammatory cytokines, MAPK, and protein kinases pathways are key components of the inflammatory process and apoptotic response after SCI (Kawabata et al., 2010; Zhang et al., 2020). Moreover, SCI-induced neuronal loss and the degeneration, or regeneration of axons and their terminals (e.g., GABAergic neuronal death and sprouting of primary afferent fibers) lead to maladaptive synaptic reconstructions that result in sensorimotor, bladder, and endocrine dysfunctions (Krupa et al., 2022; Muller et al., 2022; Whittemore et al., 2022). Finally, SCI-induced chronic neurological dysfunction causes emotional disorders characterized by decreased motivation and high rates of anxiety and depression (Sanguinetti et al., 2022).

Because acupuncture can inversely modulate all the pathophysiological mechanisms discussed above, it may be a useful treatment for SCI patients. However, no systematic studies have been conducted to confirm this.

3. Mechanism of acupuncture

3.1 Acupoint

Acupoints refer to specific points on the body where acupuncture needles are inserted. The optimal depth for needle insertion, which varies depending on the patient's overall condition, is crucial for ensuring both safety and effectiveness during acupuncture treatment (Chou et al., 2011; Goh et al., 2014; Lin et al., 2013). However, findings from functional magnetic resonance

imaging (fMRI) studies suggest that deeper needle insertion tends to have a more pronounced effect on brain activity (Zhang et al., 2007).

Acupoints are primarily composed of mast and fat cells, blood vessels, muscle tissues, elastic and collagen fibers, and primary afferent nerve fibers. Upon needle insertion, various signaling molecules, including glutamate, neuropeptides, serotonin (5-HT), norepinephrine (NE), and proinflammatory cytokines, are activated (Hsiao et al., 2022; Kim et al., 2017; Li et al., 2015), all of which play crucial roles in mediating post-SCI pathophysiology.

Stimulation of acupoints through manual or electrical means activates signaling pathways that connect peripheral nerves with higher nervous system. Acupoints typically exhibit lower electrical resistance and higher electrical conductance compared to other regions of the body, although these properties may vary depending on factors such as age and sex (Chamberlin et al., 2011; Fan et al., 2018b; Ma, 2021).

Additionally, acupoints contain elevated levels of cations, including calcium, potassium, copper, and zinc ions, while the levels of anions, such as chloride ions, are relatively lower (Lee et al., 2022; Yan et al., 2009). Although neural acupuncture units represent a novel concept, their anatomical and functional distinctions from traditional acupoints remain unclear (Zhang et al., 2012).

3.2 Principle of acupuncture

Acupuncture needles are strategically inserted into specific acupoints to elicit desired stimulation, as documented in studies by Langevin et al. (2001) and Zhou & Benharash (2014). Repeat stimulation of these points may be necessary to achieve optimal therapeutic outcomes, as observed in research by Park et al. (2010a). There are two primary methods of acupuncture stimulation widely utilized in clinical practice.

Manual acupuncture (MA) involves mechanical stimulation through techniques such as vibration, twirling, and flicking of the inserted needle. In contrast, electroacupuncture (EA) combines mechanical and electrical stimulation. Following acupuncture treatment, peripheral primary afferent fibers, including myelinated A fibers and unmyelinated C fibers, activate pathways projecting to higher nervous system centers via the spinal cord (Kagitani et al., 2010; Li et al., 2004).

EA has emerged as a predominant treatment modality for various pathophysiological conditions, both in animal models and clinical trials (He et al., 2022). It offers advantages in terms of frequency, duration, and amplitude, resulting in greater activation of descending inhibitory pathways involving opioidergic, GABAergic, and monoaminergic systems. Acupuncture generally suppresses excitatory intracellular protein kinases and proinflammatory cytokine pathways across the nervous system (Du et al., 2019; Lai et al., 2022).

Furthermore, acupuncture activates surrounding connective tissues, nerve fibers, and immune cells, thereby modulating neural signaling through the regulation of specific molecular expressions. This modulation creates micro-environmental changes that help mitigate hyperexcitability-induced chronic pain. In summary, by providing adequate stimulation to specific acupoints, acupuncture can prevent, alleviate, or attenuate the progression of various post-SCI disorders through its multifaceted effects on neurons and immune cells. Thus, acupuncture holds promising potential as an overlapping treatment approach for a wide range of post-SCI conditions.

3.3 The differences between EA and electrical stimulation

Numerous types of electrical stimulation have been employed for SCI treatment, collectively known as spinal cord stimulation or neuromodulation (Karamian et al., 2022). These modalities include epidural spinal cord stimulation (eSCS), transcutaneous spinal cord stimulation (tSCS), repetitive transcranial magnetic stimulation (rTMS), transcutaneous electrical nerve stimulation (TENS), transcutaneous spinal direct current stimulation (tsDCS), and functional electrical stimulation (FES). Research studies, such as those by Barss et al. (2022), Krishnan et al. (2019), Rahman et al. (2022), and Sivaramakrishnan et al. (2018), have demonstrated the safety and efficacy of these approaches in addressing various symptoms associated with SCI, including pain, locomotion difficulties, bladder dysfunction, and autonomic disorders.

Moreover, these electrical stimulation methods are minimally invasive, enhancing their appeal as therapeutic options for SCI patients. While EA targets specific acupoints, neuromodulation stimulates skin and muscle fibers at extended levels of the spinal cord. Consequently, acupuncture offers a more targeted approach compared to neuromodulation. However, both approaches have their respective merits and can contribute to the long-term management of SCI.

4. Post-SCI pathophysiology and opposite roles of acupuncture

SCI upregulates signaling molecules and pathways in both peripheral and central nervous systems, while

acupuncture has been shown to effectively mitigate this activity (He et al., 2022; Lai et al., 2022), thereby improving post-SCI pathophysiology recovery.

4.1. Excitatory signaling

4.1.1 Glutamate

After SCI, there is a significant increase in the production of excitatory signaling molecules, particularly glutamate, in synaptic clefts, a hallmark of post-SCI pathophysiology. Glutamate binds to various glutamate receptors (GluRs), including N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (KA) receptors, as well as metabotropic GluRs, leading to a massive influx of calcium ions and subsequent excitotoxicity (Liu et al., 1999; Tufan et al., 2008; Xu et al., 2004). Animal studies have demonstrated that inhibiting GluRs is an effective approach for treating post-SCI pathophysiology (Gaviria et al., 2000; Kim et al., 2012).

In one study, EA at specific acupoints inhibited NMDA (NR2B) receptor activity at Zusanli (ST36) and Shangjuxu (ST37) acupoints, while EA at Dazhui (GV14) and Mingmen (GV4) acupoints inhibited AMPA (GluR1) receptor activity in the spinal dorsal horn (Chen et al., 2022; Liu et al., 2017). Furthermore, EA at Zusanli (ST36) and Sanyinjiao (SP6) acupoints enhanced the antinociceptive effects of ketamine, an NMDA receptor blocker (Huang et al., 2004). However, repeated and prolonged EA may lead to tolerance due to a decrease in glutamate transporters (Cui et al., 2016). Overall, these findings suggest that EA can suppress aberrant glutamate-mediated signaling, potentially inhibiting SCI-induced excitotoxicity and exerting neuroprotective effects, thus attenuating central neuropathic pain (CNP) following SCI.

4.1.2 Reactive oxygen species

Following SCI, there is an overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are metabolic byproducts implicated in synaptic transmission. This ROS overproduction contributes to neuronal hyperexcitability, inflammation, and neuronal cell death in the damaged spinal dorsal horn (Lee et al., 2021; Sabirzhanov et al., 2019; Savikj et al., 2019; Slater et al., 2022). In the nervous system, abundant polyunsaturated fatty acids are susceptible to ROS interactions. ROS-mediated lipid peroxidation, induced by intracellular Ca^{2+}-mediated sensory signaling pathways, generates 4-hydroxynonenal (HNE)/2-propenal, activating caspases and the p38-MAPK signaling pathway, key players in apoptosis (Visavadiya et al., 2016; Wang et al., 2016).

However, EA at specific acupoints, including Mingmen (GV4), Shuigou (GV26), Renzhong (DU26), and Fengfu (DU16), significantly reduces ROS-mediated oxidative stress and MAPK activity post-SCI, enhancing antioxidant activity and functional recovery (Cheng et al., 2020; Choi et al., 2012; Dai et al., 2021). A quantitative meta-analysis revealed that acupuncture increases the expression of major antioxidants, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Zhao et al., 2022). These findings collectively suggest that EA can inhibit ROS-mediated signaling, thereby promoting functional recovery after SCI.

4.1.3 Apoptosis

SCI-induced neuronal death, primarily through apoptosis, is a major pathophysiological process leading to neuroanatomical reorganization and exacerbated loss of inhibitory synaptic circuits, such as GABAergic circuits (Hwang et al., 2016; Rafati et al., 2008). The influx of massive Ca^{2+} following SCI stimulates neural cell apoptosis (Liu et al., 2023a). However, EA can inhibit neuronal apoptosis. For instance, acupuncture at specific acupoints, including Shuigou (GV26) and Yanglingquan (GB34), attenuates the activity of caspase-3, tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), nitric oxide synthase (NOS), and matrix metalloproteinase-9 (MMP-9), thus preventing neuronal apoptosis post-SCI (Choi et al., 2010). Additionally, acupuncture at Jizhong (GV6) and Zhiyang (GV9) acupoints activates anti-apoptotic signaling via B-cell lymphoma (Bcl)-2 and Bcl-3 (Liu & Wu, 2017). Furthermore, at Dazhui (GV14) and Mingmen (GV4) acupoints, it enhances phosphatidylinositol-3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway activity, while reducing phosphatase and tensin homolog (PTEN) and caspase-3 levels (Li et al., 2020). EA at multiple acupoints also inhibits the mitochondrial apoptotic pathway by activating the PI3K/Akt and extracellular signal-regulated protein kinase (ERK) 1/2 signaling pathways in a rabbit model of SCI (Renfu et al., 2014). Finally, EA at Jiaji (EX-B2) enhances locomotion by promoting autophagy and reducing necroptosis, crucial in the cell loss and tissue damage post-SCI (Hongna et al., 2020). Collectively, these findings suggest that EA can effectively inhibit neuronal apoptosis, thereby promoting functional recovery after SCI.

4.1.4 Glial activation and inflammation

Glial cells, including astrocytes, microglia, and oligodendrocytes, play crucial roles in synaptic structure and transmission within the nervous system.

SCI-induced glial activation can lead to hypertrophy and the release of gliotransmitters, influencing local synaptic transmission primarily in the spinal dorsal horn due to the short branches of activated glial cells (Gaudet & Fonken, 2018; Gwak et al., 2017). EA has been shown to inhibit glial activation and modulate neuron-glia interactions (Gong et al., 2020; Yan et al., 2023; Zhang et al., 2022c). EA-induced glial inhibition and pain relief may involve the release of interleukin-10 (IL-10), an anti-inflammatory cytokine. The analgesic effects of EA, particularly at the Sanyinjiao (SP6) and Yanglingquan (GB34) acupoints, are blocked by spinal IL-10 antibodies, underscoring the role of the IL-10 pathway in EA-induced analgesia (Dai et al., 2019).

EA, particularly at the Zusanli (ST36) acupoint, inhibits astrocytic and microglial activation, resulting in decreased expression of glial fibrillary acidic protein (GFAP) and CD11b, markers of astrocytes and microglia, respectively. This leads to reduced levels of MMP-9, MMP-2, TNF-α, IL-1β, and chemokines (Chen et al., 2020). Interestingly, acupuncture exhibits bidirectional effects on macrophages during inflammation. EA at GV acupoints enhances the activity of M2 macrophages, which suppress inflammation and support tissue repair, while also increasing the levels of anti-inflammatory molecules such as IL-10 and neurotrophin-3 (NT-3). Conversely, it decreases the expression of M1 macrophages, thereby reducing the inflammatory response (Zhao et al., 2017).

Additionally, EA at specific acupoints, including Yaoyangguan (GV3), Dazhui (GV14), Zusanli (ST36), and Ciliao (BL32), suppresses the Ras homologous (Rho) small GTPase/Rho-associated protein kinase (Rho/ROCK) signaling pathway, attenuates the inflammatory response, and promotes axonal growth post-SCI (Hong et al., 2021). Moreover, EA at Jiaji (EX-B2) and other acupoints inhibits astrocytic activation and glial scarring, facilitating hindlimb motor function recovery after SCI (Liu et al., 2013a). By inhibiting glial activation and inflammatory processes, EA reduces tissue damage and promotes functional recovery following SCI.

4.1.5 Excitatory intracellular signaling

The MAPK family, along with protein kinase A/C (PKA/PKC), cyclic adenosine monophosphate (cAMP), calcium/calmodulin-dependent protein kinase (CaMKII), and oxidative stress, are key players in excitatory intracellular signal transduction pathways implicated in post-SCI pathophysiology (Bai et al., 2023; Cheng et al., 2022; Fakhri et al., 2022). Pharmacological interventions targeting these pathways have shown promise in promoting functional recovery and alleviating central neuropathic pain (CNP) (Canavan et al., 2022; Flack et al., 2022). Acupuncture has demonstrated efficacy in inhibiting activity within these same signaling pathways.

For instance, EA applied at the Shuigou (GV26) and Yanglingquan (GB34) acupoints effectively inhibits astrocyte-mediated c-Jun N-terminal kinase (JNK) signaling and microglia-mediated p38MAPK/ERK signaling in patients experiencing SCI-induced neuropathic pain (Choi et al., 2012; Lee et al., 2013). Additionally, EA at the GV acupoints activates peripheral afferent nerves, leading to the release of calcitonin gene-related peptide (CGRP) and the upregulation of alpha-CaMKII. This, in turn, promotes the release of neurotrophin-3 (NT-3) and facilitates functional recovery following SCI (Xu et al., 2021).

Collectively, these findings suggest that EA has the potential to attenuate excitatory intracellular signaling pathways and enhance functional recovery in individuals with SCI.

4.2. Descending pain inhibitory pathways

Descending inhibitory pathways, including opioidergic, GABAergic, and monoaminergic systems (e.g., adrenergic, serotonergic, and dopaminergic pathways), play a pivotal role in regulating pain signaling within the spinal dorsal horn (Bannister & Dickenson, 2017; Kwon et al., 2014). Activation of these pathways can induce spinal analgesia across various pathophysiological conditions (Kucharczyk et al., 2022; Nemoto et al., 2022; Otsu & Aubrey, 2022; Tinnermann et al., 2022).

Acupuncture has been shown to effectively activate descending inhibitory pathways, thereby modulating pain perception (Ma et al., 2022). Additionally, acupuncture can engage ascending pathways that project to inhibitory centers in the brain stem (e.g., amygdala [AMG]) and midbrain structures (e.g., periaqueductal gray [PAG]), as well as cortical regions like the anterior cingulate cortex (ACC) (Duan et al., 2020; Murotani et al., 2010; Xu et al., 2022; Zhang et al., 2018).

In the context of SCI, recent studies have indicated a reduction in spinal neurons projecting to the PAG, suggesting impairment of descending inhibitory pathways (Brown et al., 2022). It's important to note that these descending pathways interact with relay sites and exert their effects synergistically.

4.2.1 Opioid

Descending opioidergic pathways play a crucial role in spinal inhibition, with EA serving as a modulator of this system. EA activates the opioidergic system, triggering the release of endomorphins, enkephalins, beta-endorphins, and dynorphins in an intensity-dependent manner (Cabyoglu et al., 2006; Han, 2003). Moreover, it can activate opioid receptors in a frequency-dependent manner.

Low-frequency (2 Hz) EA, applied at acupoints like Zusanli (S36) and Sanyingjiao (SP6), exerts its analgesic effects through μ- and δ-opioid receptors, whereas high-frequency (100 Hz) EA acts via κ-opioid receptors in rat spinal cords (Chen & Han, 1992). Additionally, EA at 2 and 60 Hz at acupoints like Baihui, Santai, Ergen, and Sanyangluo induces the release of met-enkephalin and β-endorphin in the higher nervous system of goats, while 100 Hz EA prompts the release of dynorphin-A in the spinal dorsal horn (Cheng et al., 2012).

Furthermore, the analgesic effects of EA are partially mediated by orphanin FQ (OFQ), an endogenous opioid peptide (Fu et al., 2007; Lu et al., 2010). Collectively, these findings suggest that EA-induced activation of the opioidergic system facilitates spinal inhibition through descending inhibitory pathways.

4.2.2 GABA

GABA serves as a pivotal inhibitory neurotransmitter, and the loss of spinal GABAergic inhibition is a significant mechanism in SCI pathophysiology. SCI induces the downregulation of GABAergic inhibitory tone by promoting GABAergic cell death, reducing the expression of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD; GAD65 and GAD67), and increasing GABA transporters (Bhagwani et al., 2022; Gwak et al., 2008). In the spinal dorsal horn, GABAergic interneurons receive inputs from peripheral and descending inhibitory pathways, primarily originating in the PAG. Upon activation, these neurons release GABA, exerting inhibitory effects through GABAA and GABAB receptors.

EA enhances spinal GABAergic function by upregulating GABA receptors in the spinal dorsal horn (Jiang et al., 2018; Wang et al., 2020). Low-frequency (2 Hz) EA at Zusanli (ST36) inhibits neuropathic pain by activating GABAA and GABAB receptors in the spinal cord (Park et al., 2010c). Similarly, both low- (2 Hz) and high-frequency (100 Hz) EA at acupoints like Zusanli (ST36) and Yanglingquan (GB34) suppress neuropathic pain by increasing GABAA receptor expression in the spinal dorsal horn (Li et al., 2022). In another study, both low- (2 Hz) and high-frequency (100 Hz) EA at Zusanli (ST36) and Sanyinjiao (SP6) acupoints alleviated pain through modulation of the GABAA receptor (Silva et al., 2011).

Overall, these findings suggest that EA can effectively enhance spinal GABAergic function following SCI.

4.2.3 Monoamine descending inhibitory pathways

4.2.3.1 Adrenergic Pathways

Adrenergic and noradrenergic pathways originate primarily from the raphe nuclei (RN), locus coeruleus (LC), and PAG regions, including areas A1–A7. The LC, containing a significant cluster of noradrenergic cells, interacts with the PAG, amygdala, and hypothalamus. Noradrenergic projections to the spinal cord, known as coeruleospinal pathways, express adrenergic receptors, particularly the α2-adrenoceptor, which are widely distributed in the brain and spinal cord, contributing to spinal antinociception (Proudfit & Clark, 1991; Rodriguez-Palma et al., 2022).

Both low-frequency (4 Hz) and high-frequency (100 Hz) EA at Zusanli (ST36) acupoints increase the expression of c-Fos and dopamine β-hydroxylase/tyrosine hydroxylase (DBH/TH)-expressing neurons in the LC, while low-frequency (2 Hz) EA at the same acupoint inhibits them by decreasing TH expression (Lee & Beitz, 1993; Park et al., 2010a), indicating frequency-dependent modulation of LC activity. Moreover, EA at Zusanli (ST36) inhibits the activity of spinal dorsal horn neurons by affecting α2- and β-adrenoceptors in presynaptic terminals, as well as inhibiting postsynaptic neurons in the spinal dorsal horn (Choi et al., 2015). Activation of the α2-adrenoceptor promotes motor function recovery by suppressing the expression of pro-inflammatory cytokines such as IL-1β, TNFα, and IL-6 after SCI (Gao et al., 2019).

These findings collectively suggest that EA influences noradrenergic pathways and may contribute to pain relief and locomotor recovery following SCI.

4.2.3.2 Dopaminergic Pathways

In the midbrain, clusters of dopaminergic (DAergic) neurons are found in the ventral tegmental area (VTA), substantia nigra (SN), and hypothalamus (areas A8–A16), with the hypothalamic region (A11) representing a significant descending inhibitory pathway projecting to the spinal cord (Koblinger et al., 2014). Dopamine signaling in the spinal cord is crucial for regulating locomotion, micturition, and pain, while in the higher nervous system, dopamine is integral to the reward

system (Puopolo, 2019; Qiao et al., 2021; Sharples et al., 2014). SCI suppresses D1 receptor-mediated ERK 1/2 activation in the PAG, a key component of dopamine-mediated antinociception (Meyer et al., 2009; Voulalas et al., 2017).

EA at frequencies ranging from 6 to 21 Hz performed at Dailing (PC7) acupoints increases striatal dopamine levels. Conversely, high-frequency (100 Hz) EA performed at Dazhui (DU14) and Baihui (DU21) acupoints inhibits TNF-α and IL-1β-mediated loss of DAergic neurons in the substantia nigra (SN), indicating direct modulation of brain dopamine activity by EA (Liu et al., 2004; Shen & Lai, 2007). Recent reports suggest that activation of dopamine D1 receptors inhibits the inflammatory process and promotes neuronal survival, underscoring the beneficial effects of enhanced DAergic activity on post-SCI pathophysiology (Jiang et al., 2023).

Therefore, EA-induced modulation of DAergic activity could potentially improve sensory, motor, endocrine, and reward system function following SCI.

4.2.3.3 Serotoninergic Pathways

The nucleus raphe magnus (NRM), located in the brainstem, contains numerous serotonergic neurons. The caudal region of the NRM (B1–B3) consists of descending serotonergic pathways projecting to the spinal cord. Studies have indicated that SCI is associated with a reduction in caudal 5-HT fibers and an increase in rostral 5-HT fibers, which may contribute to the development of pain, locomotor dysfunction, and bladder dysfunction (Perrin & Noristani, 2019). EA performed at acupoints such as Changqiang (GV1), Yaoshu (GV2), Jizhong (GV6), and Zhiyang (GV9) following SCI has been shown to promote extensive regeneration of 5-HT fibers in the injured area, along with increased expression of calcitonin gene-related peptide (CGRP) and improvements in motor function (Ding et al., 2009). Although there isn't direct evidence linking EA to changes in 5-HT receptor expression, elevated spinal 5-HT levels have been associated with improved locomotor recovery and attenuation of neuropathic pain following SCI (Fouad et al., 2010; Hains et al., 2003b).

5. Acupuncture on post-SCI and reward system

Balancing the benefits and risks of long-term pharmacological treatments is crucial in managing post-SCI pathophysiology. Prolonged use of certain medications may lead to sensorimotor and neurological dysfunction, and even potential abuse, which can further impact functional recovery and exacerbate the condition. Studies have shown that patients who abuse medications after SCI often experience poorer outcomes (Harper et al., 2022).

While the focus of acupuncture research has primarily been on its effects on chronic pain, mental health disorders, and addiction through modulation of the brain's reward system (Kwon et al., 2022; Pan et al., 2022; Wang et al., 2017), less is known about its potential effects in the context of SCI. Understanding how acupuncture may influence the brain's reward pathways and its implications for SCI management could provide valuable insights into developing more holistic and effective treatment approaches.

5.1 Reward mechanism

The mesolimbic dopamine system, centered around the ventral tegmental area (VTA) and nucleus accumbens (NAc), plays a crucial role in the brain's reward circuitry. In this system, GABAergic activity within the VTA regulates dopaminergic (DAergic) activity, with dopamine levels in the NAc influencing the strength of reward signals (Lammel et al., 2014; Sackett et al., 2017). The NAc receives inputs from various cortical areas and the amygdala, which can be activated by acupuncture or nociceptive stimuli (Chang et al., 2021; Pan et al., 2022).

Chronic depletion of dopamine in the NAc, often associated with prolonged use of dopamine, can lead to heightened craving for addictive substances and exacerbate negative reinforcement mechanisms. Previous studies have indicated that SCI can induce alterations in GABAergic activity within the VTA, subsequently leading to decreased DAergic activity (Ko et al., 2018). These changes in brain networks following SCI may contribute to the dysregulation of reward processing commonly observed in individuals with SCI (Hill et al., 2018; Yague et al., 2011).

Modulating GABAergic activity within the VTA through EA could potentially mitigate dysfunction within the reward system induced by SCI. By influencing GABAergic neurons in the VTA, EA may help restore the balance of neurotransmitter activity within the mesolimbic dopamine system, thereby addressing reward dysregulation and its associated consequences in individuals with SCI.

5.2 Acupuncture and reward mechanism

In a previous study, we demonstrated that acupuncture at Shenmen (HT7) inhibited GABAergic activity in the VTA via μ-opioid receptors and increased dopamine levels in the NA; these effects were associated with a reduction in self-administration of ethanol (Yang et al., 2010). In another study, acupuncture at Shenmen (HT7)

activated VTA GABA neurons and enhanced cocaine-induced DA release in the NAc (Jin et al., 2018). These results suggest that the effects of acupuncture on addictive behavior are mediated by different pathways, depending on the substance.

We have also found that acupuncture at Shenmen (HT7) results in peripheral ulnar nerve activation and biphasic control of GABAergic activation in the VTA; these effects may be mediated by ascending sensory pathways (Chang et al., 2017). In an fMRI study, acupuncture enhanced functional connectivity in the VTA, PAG, and AMY, suggesting that it may simultaneously modulate both descending inhibitory and reward pathways (Cao et al., 2021). Taken together, the data suggest that acupuncture at specific acupoints could improve both pain and psychiatric conditions involving mesolimbic system dysfunction.

6. Acupuncture and neurological recovery

SCI results in acute and chronic sensory, motor, bowel, autonomic, and mental dysfunctions. As described above, EA can inhibit the inflammatory response and glial activation, thereby promoting neurological recovery after SCI. Additionally, acupuncture reportedly increases the levels of growth factors, NTs, and neuropeptides, all of which play a role in neurological recovery after SCI. Although EA alone can improve walking performance (i.e., stride duration and length, as well as walking speed) in SCI rats (Escobar-Corona et al., 2017), most studies have documented neurological improvements in response to acupuncture after SCI. The treatment was combined with cell-based engineering, such as the transplantation of neural stem cells (NSCs). Notably, acupuncture promotes the differentiation, migration, and survival of transplanted NSCs, as well as functional recovery via the production of NT and neuropeptides (NT-3 and CGRP) in SCI rats (Zeng et al., 2022). These results suggest that acupuncture facilitates the reconstruction and repair of ascending and descending pathways in injured spinal cords.

In the spinal ventral horn, peripheral nerve networks (PNNs) impede the recovery of locomotion after SCI. EA stimulation of Jiaji (EX-B2) suppresses PNNs and promotes the recovery of locomotion following SCI, as indicated by the increased Basso–Beattie–Bresnahan (BBB) scores (Hu et al., 2020). Recently, it was shown that combined treatments with EA and low-frequency pulsed current stimulation (GV electroacupuncture) regulated transcriptome gene expression, resulting in nerve fiber regeneration, enhanced functional recovery after SCI (via the production of NT-3), and neuroprotective effects (Xiao et al., 2022; Zeng et al., 2022). EA performed at the Dazhui (GV14) and Mingmen (GV4) acupoints decreased SCI-induced Delta1, Presenilin1, Hes1, and Hes5 expression, resulting in locomotor improvements and neural repair (Wang et al., 2021). Additionally, performed at Yaoyangguan (GV3), Dazhui (GV14), Zusanli (ST36), and Ciliao (BL32), it promoted the recovery of hindlimb locomotion and suppressed the Rho-A and ROCKII signaling pathways (Min et al., 2017). In a recent study, EA at Mingmen (GV4) and Dazhui (GV14) inhibited miR-34a-3p and programmed cell death 6 (miR-34a-3p/PDCD6), which are proapoptotic; had neuroprotective effects on motor neurons; and promoted axonal regeneration after SCI (Ma et al., 2022). Finally, EA improved the functional recovery, and thus quality of life, of SCI patients (Tan et al., 2022). Taken together, these results suggest that EA reduces neuronal damage by regulating apoptotic pathways, thus promoting functional recovery after SCI.

7. Clinical trials of acupuncture

To relieve pain, acupuncture is increasingly popular among SCI patients, either alone or in combination with other treatments. Incomplete SCI patients tend to undergo acupuncture treatment more often than complete SCI patients, probably because an intact nervous system is important for desirable outcomes after acupuncture. Moreover, the development of neuropathic pain after SCI depends on the sparing of dorsal horn neurons (Dietz et al., 2022; Fan et al., 2018a). However, negative effects of acupuncture have also been reported, including discomfort and fatigue after long sessions. Additionally, a few patients have reported a transient increase in pain sensitivity (Nayak et al., 2001). A small comparative study involving quantitative sensory testing (QST) reported no difference in outcomes between six sessions of acupuncture and three weeks of gabapentin treatment (Chen et al., 2021), suggesting the effectiveness of acupuncture in reducing pain. However, some people believe that acupuncture treatment can cause infection, tissue damage, and even hemorrhage, although adverse effects are rarely reported and are transient (Jindal et al., 2008; Karpatkin et al., 2023; Park et al., 2010b; Xu et al., 2013). In addition, clinical trials demonstrate that long-term acupuncture treatment can facilitate bladder, sensory, and functional recovery after SCI (Liu et al., 2013b; Xiong et al., 2021). Recently, Veterans Affairs providers expressed positive attitudes toward acupuncture for pain treatment, neuroprotection, and

functional recovery after SCI (Castaneda et al., 2021; Coker et al., 2022; Huang et al., 2022).

8. Combined acupuncture therapy

In various animal models, although acupuncture has been effective as a post-SCI treatment, its efficacy was enhanced when combined with drugs or other therapies. For example, EA combined with celecoxib (an anti-inflammatory), milnacipran (a selective serotonin/noradrenaline reuptake inhibitor), gabapentin (a calcium channel inhibitor), lidocaine (a sodium channel blocker), and dexmedetomidine (an α2-adrenoceptor agonist) had stronger and longer-lasting analgesic effects in the treatment of post-SCI rats and goats via anti-inflammatory and antioxidative effects (Alvarado-Sanchez et al., 2019; Cui et al., 2017; Dai et al., 2021; Mi et al., 2008). In other studies, while EA alone attenuated pain, both inflammation and neuropathic pain were improved by EA combined with a glial activation inhibitor (fluorocitrate or propentofylline) (Liang et al., 2010; Sun et al., 2006). Moreover, combining acupuncture with antioxidant or anti-inflammatory agents may facilitate the recovery of urinary and motor functions, prevent apoptosis, reduce hydroxyl radical levels and lipid peroxidation, and have a neuroprotective effect on post-SCI (Alvarado-Sanchez et al., 2019; Ding et al., 2022b; He et al., 2021). In other studies, combining acupuncture with mesenchymal stem cells (MSCs) or adult stem cell transplantation enhanced synaptic reconstruction and functional recovery compared to acupuncture alone (Tang et al., 2020; Zeng et al., 2022). Furthermore, in those studies, the survival, proliferation, and migration of transplanted cells were facilitated by the release of CGRP and NT-3 within the injured spinal cord. In addition, EA combined with selective serotonin reuptake inhibitors (SSRIs) relieves anxiety to a greater degree than SSRIs alone (Sabbagh Gol et al., 2021). Finally, acupuncture combined with physical therapy enhances the recovery of motor and neurological functions (Regnier & Most, 2022). Taken together, the results indicate that acupuncture has synergistic effects with other treatments and could potentially reduce the drug doses required for efficacy (Regnier & Most, 2023; Zheng et al., 2023; Zhong et al., 2023).

9. Limitation and future study

As detailed above, there is growing evidence of the efficacy of acupuncture in relieving pain and enhancing functional recovery after SCI. However, while animal and clinical studies of SCI have shed light on the mechanisms underlying the therapeutic effects of acupuncture, controversy remains regarding its efficacy for SCI patients in Western countries. This situation is partly due to weaknesses in acupuncture feasibility studies, including a lack of blinding, small cohorts, and a lack of standardization. International collaborations dedicated to researching the efficacy of acupuncture therapy for SCI could be helpful in this regard (Wei et al., 2022).

In this review, we focused on mechanical and electrical acupuncture. However, other approaches exist, such as treating specific acupoints with diluted bee venom (DBV, apipuncture) (Lin & Hsieh, 2020). Bee venom has anti-inflammatory, antioxidant, and anti-apoptotic properties. Apipuncture performed at the Zusanli (ST36) and Yaoyangguan (GV3) acupoints facilitates locomotor recovery and inhibits inflammation via an increase in IL-10 after SCI (Nascimento de Souza et al., 2017). Furthermore, warm acupuncture (WA) enhances locomotor recovery via NSC proliferation, downregulation of MAPK pathways and glial activation, suggesting anti-inflammatory effects and inhibition of apoptosis after SCI (Ding et al., 2022a; Xu et al., 2019).

However, the main weakness of acupuncture treatment protocols is the difficulty in managing acupuncture patients over treatment periods that last several months, particularly in studies with extensive follow-ups. Moreover, standardized evaluation protocols are lacking; visual analog scales, numeric rating scales, and the Brief Pain Inventory have all been used to evaluate the effect of acupuncture on neuropathic pain in SCI patients (Almeida et al., 2022). Improvements in needle materials and enlarging the contact surface of the acupuncture needle can be beneficial. For example, we previously reported that EA performed at Shenmen (HT7) with an extended surface area of acupuncture needle (i.e., a "high surface area porous needle") enhanced the electrophysiological and behavioral effects as well as better outcomes in the treatment of colorectal cancer in rat models (In et al., 2016; Lee et al., 2017). We speculate that a larger surface area may be more important than deep needle insertion in improving post-SCI pathophysiology.

10. Summary

Currently, the main treatments for SCI are surgical, pharmacological, neuromodulation, and stem cell treatments (Eller et al., 2022; Fehlings et al., 2021; Geisler et al., 2023; Naro et al., 2022; Ribeiro et al., 2023). However, there is increasing scientific evidence that acupuncture can enhance these treatments. Acupuncture is a noninvasive, nonsurgical approach that can be applied immediately after SCI. However, long-term acupuncture treatment is needed to achieve desirable outcomes, and standardized protocols are

currently lacking (Huang et al., 2022). Acupuncture at acupoints containing nerve fibers, mast cells, immune substances, and muscles can modulate the physiological functions of both the peripheral and central nervous systems (Lin et al., 2022; Xiao et al., 2018). When myelinated and unmyelinated primary afferent fibers are activated by acupuncture, immune response mediators activate ascending signaling pathways. It is believed that acupuncture inhibits hyperexcitability in the nervous system by activating descending inhibitory pathways, including MAPK, protein kinase, Wnt/mTOR, and calcium-mediated intracellular signaling pathways. Additionally, it inhibits proinflammatory cytokines and oxidative stress, thus having neuroprotective effects and promoting functional recovery. Finally, it modulates activity in the brain reward system; all these actions can improve post-SCI pathophysiology.

Both preclinical and clinical studies have shown that acupuncture can improve SCI-induced pathophysiology. However, such studies have varied widely in terms of stimulation intensity, treatment duration, age of the participants, and needle insertion depth. SCI is characterized by acute, early, intermediate, and chronic phases, ultimately resulting in reorganization of the nervous system (Hachem & Fehlings, 2021; Lima et al., 2022). The death of neurons and axons at the site of injury is followed by the loss of synaptic connections, destruction of the blood barrier, and the recruitment of immune cells. Although regeneration and repair subsequently occur, the primary pathophysiological process continues, resulting in glial scar formation and enhanced pain signaling. Therefore, spatial and temporal studies will be needed to prove the effectiveness of acupuncture in post-SCI pathophysiology.

11. Conclusion

Many studies have described the physiological, neurochemical, and neuroanatomical properties of acupoints, as well as the mechanisms underlying the effects of acupuncture. SCI is characterized by complex pathophysiological processes, making it difficult to devise effective treatment strategies. A recent study suggested the potential of overlapping treatments to address the interaction between mental and physical pain (Bouchatta et al., 2022); this could be applicable to SCI patients (Griffin & Bradke, 2020). This review indicates that acupuncture can contribute to neuroprotection, pain attenuation, functional recovery, and repair of the brain reward system, which could serve as a potential overlap in post-SCI treatment.

Author Contributions

Bong Hyo Lee; design and manuscript preparation, Nam Jun Lee; data acquisition and manuscript preparation, Jonghoon Kang and Walker S. Lewis; data analysis, manuscript preparation, Young Gwak; design, manuscript edition, and approval of submission. All authors have read and agreed to the final version of the manuscript.

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Conflict of interest statement

All authors declare no conflict of interest.

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