

Spinal cord injury pain: Spinal and supraspinal mechanisms

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Abstract—Altered sensations, including pain, are well-documented consequences associated with spinal cord injury (SCI). Although loss of sensory and motor functions at and below the level of injury is commonly thought to affect individuals with SCI most significantly, secondary consequences that include spasticity, bladder and bowel dysfunctions, infertility, and pain rank among the most difficult conditions to deal with following injury. Understanding the mechanisms responsible for the condition of pain requires one to appreciate the pathological, physiological, neurochemical, and molecular events associated with injury of the spinal cord parenchyma. Over the past 15 years, a systematic examination related to the pathophysiology, clinical characteristics, and treatment of pain associated with SCI has provided insights into the spinal and supraspinal mechanisms associated with the development of at- and below-level pain. In this review, experimental studies focusing on the spinal and supraspinal mechanisms associated with pain at and below level will be discussed.

Key words: central pain, cortex, excitotoxicity, inflammation, microglia, plasticity, secondary injury, sensitization, signaling pathways, synaptic plasticity, thalamus.

INTRODUCTION

Sensory abnormalities, including pain, associated with spinal cord injury (SCI) are related to the nature of the lesion, damaged neurological structures, and secondary pathophysiological changes of surviving tissue [1–3]. Although complete loss of sensory and motor functions is thought to most significantly affect individuals with spinal

injury, secondary complications that include spasticity, bladder and bowel dysfunctions, infertility, autonomic dysfunction, and pain are among the most difficult consequences to deal with following injury [4]. Over the past 15 years, a systematic examination related to the pathophysiology, clinical characteristics, and treatment of different pain conditions has provided insight into the potential mechanisms contributing to the onset and maintenance of above- and below-level pain associated with SCI [5]. The development of experimental models to study spinal injury combined with clinical studies has provided important information related to spinal and supraspinal changes contributing to the development of at- or below-level pain. At the site of injury, multicomponent excitotoxic and inflammatory cascades affect the survivability and functional state of spinal neurons. Changes in the excitability of neurons secondary to the release of inflammatory mediators

Abbreviations: 5-HT = 5-hydroxytryptamine, ACC = anterior cingulate cortex, CCK = cholecystokinin, CNS = central nervous system, EAA = excitatory amino acid, ERK = extracellular signal-regulated kinase, IL = interleukin, MAPK = mitogen-activated protein kinase, mRNA = messenger ribonucleic acid, NF- κ B = nuclear factor- κ B, NK-1 = neurokinin-1, NMDA = N-methyl-D-aspartate, NOS = nitric oxide synthase, PPD = preprodynorphin, PPE = preproenkephalin, SCI = spinal cord injury, TNF- α = tumor necrosis factor- α , VPL = ventral posterior lateral (ventroposterolateral).

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along with a decrease in local inhibitory influences and changes in descending modulation provide a permissive environment that leads to the development of spinal pain generators that contribute to the mechanism of injury-induced pain. In this review, I will discuss experimental studies that focus on the spinal and supraspinal mechanisms associated with at- and below-level neuropathic pain. Pain of musculoskeletal, radicular, visceral, or psychogenic origins all are significant in the clinical sequela of spinal injury. These pain syndromes are discussed elsewhere [6–11].

SCI PAIN: RESEARCH STRATEGIES AND EXPERIMENTAL STUDIES

A cascade of cellular, biochemical, and molecular responses to SCI is significant in producing functional changes that contribute to the onset of abnormal sensations, including pain, following spinal injury [2–3,12]. Considering the traumatic and/or ischemic insult associated with injury to the spinal cord parenchyma, one is not surprised that the pathological sequela of injury includes a wide spectrum of events that severely compromise the anatomical and functional integrity of sensory, motor, and autonomic pathways in the spinal cord. Another consideration is the physical factors, including completeness and level of injury, that correlate with pain onset. Unfortunately, few consistent predictors have been identified [1,13], although a positive relationship between the higher incidence of pain in patients with thoracolumbar and incomplete lesions has been described [14]. Several models, including mechanical trauma, isolated lesions, complete transection, chemical lesions, and ischemic injury, each with pathological components found in the human condition, have been used in the study of SCI pain [15–18]. Many of the well-documented changes associated with different SCI models progress in a rostrocaudal direction and influence not only spinal but also cortical and subcortical structures [2]. Given the wide range of pathophysiological changes associated with spinal injury, it is important to identify causal relationships between specific changes and the onset of pain as opposed to merely pointing out events occurring secondary to the injury process. Establishing these causal relationships is critical to identifying underlying mechanisms responsible for pain development.

Selecting effective behavioral measures used to assess mechanical and thermal sensibilities following injury is

another challenge in the study of different injury-induced pain conditions. Most behavioral measures used in the study of SCI pain have historically relied on reflex-based responses to peripheral stimuli. Nociceptive reflexes, like tail-flick and hindpaw withdrawal, are regulated by segmentally organized spinal mechanisms and are present in spinalized animals. Lick and guard responses to nociceptive input depend on spino-bulbo-spinal circuits and are present in decerebrate animals [19]. The study of excitability changes of spinal sensory and motor neurons at the level of injury can therefore be evaluated with reflex-based assessment strategies. Unfortunately, enhancement of flexion/withdrawal reflexes (i.e., the spastic syndrome) can be dissociated from the conditions of at- and below-level pain in cases of subtotal SCI [20–21]. The challenge of studying these types of pain, therefore, lies in using appropriate behavioral measures that engage neural substrates responsible for the pain condition being evaluated. If one assumes that below-level pain depends on activation of cortical structures, then to study this type of pain requires behavioral measures that rely on cortical activation. Behavioral outcomes fitting this criterion include operant tasks that rely on cortical involvement for processing sensory information, decisions based on environmental contingencies, and initiation of behavioral responses to nociceptive stimuli [22]. A major misconception in the study of below-level pain is the belief that sensory stimuli delivered to dermatomes below the level of a lesion to evoke reflexive responses qualify as an evaluation of below-level pain. Acceptance of the differences and limitations between responses obtained with operant- versus reflex-based behavioral measures is a major challenge in the study of SCI pain, especially studies related to the evaluation of at- versus below-level pain [22].

In recent years, the systematic study of SCI pain has led to significant advances in understanding specific changes that contribute to developing and maintaining at- and below-level pain. In the following sections, a brief review of some of the more significant contributions is presented.

“CENTRAL INJURY CASCADE” OF SCI

An important factor in determining potential mechanisms of pain following spinal injury relates to understanding the cascade of pathological, biochemical, and molecular events initiated by ischemic or traumatic insult to the cord. Significant structural damage to the spinal cord

parenchyma leads to the reorganization of spinal circuits that integrate, locally process, and transmit sensory information. Ischemic or traumatic insult also changes the expression of chemical mediators that maintain homeostatic balance between inhibitory and excitatory circuits. Equally significant is the disruption of cellular events affecting signaling, transduction, and survival pathways of spinal neurons. Collectively, these events profoundly affect the excitability and functional properties of spinal sensory neurons and ultimately affect evoked and resting sensibilities. Primary and secondary pathophysiological events associated with injury are part of a central injury cascade that initiates pain-related behaviors following injury [12]. Different components of this hypothetical cascade are

shown in **Figure 1** and include anatomical, neurochemical, excitotoxic, and inflammatory events that have an interdependent relationship and collectively create an environment responsible for changing the functional (physiological) state of spinal sensory neurons leading to the expression of different clinical conditions (e.g., allodynia, hyperalgesia, spontaneous pain). I should mention that it is unlikely that events associated with the onset of SCI pain occur in sequence. Since many contributing factors potentially influence the excitability of central neurons and thus the onset of pain, they most likely do not occur in a programmed sequential fashion. On the contrary, some events associated with the central cascade are more likely occurring simultaneously and the interaction and escalation

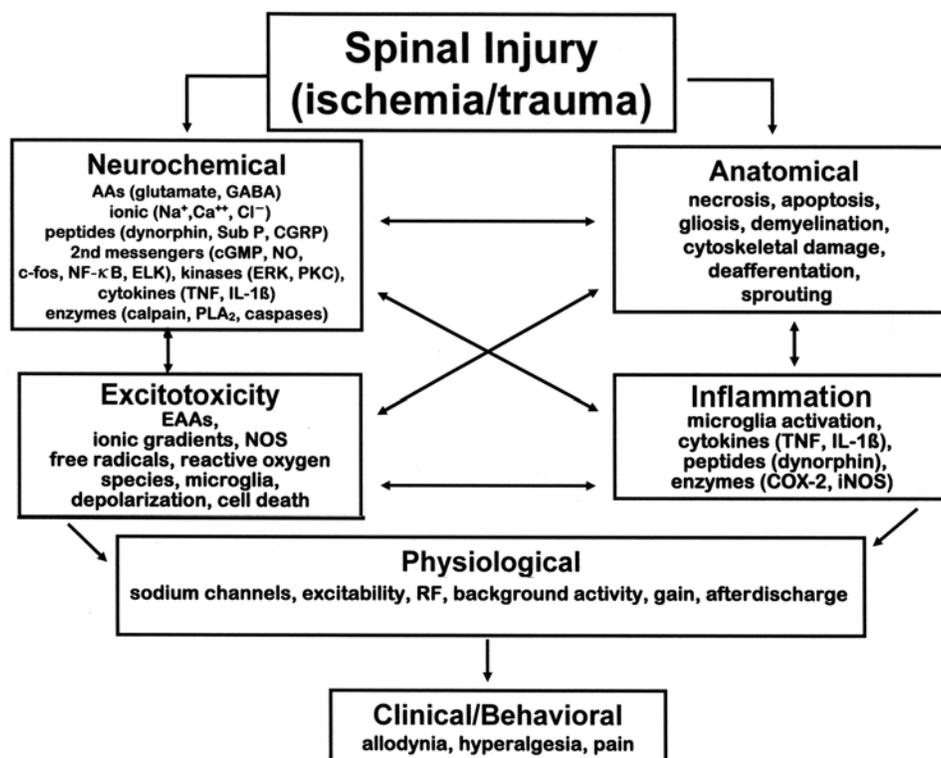


Figure 1.

Interactive components of the central injury cascade that contribute to development of pain following spinal injury. Evidence supporting involvement of this cascade comes from results of clinical and preclinical experimental studies (see body text for details). Four major components of the cascade (neurochemical, excitotoxicity, anatomical, and inflammation) are interactive and collectively result in creation of an environment within the cord resulting in physiological changes in spinal and supraspinal neurons. End point of the cascade is onset of clinical and behavioral symptoms, e.g., allodynia, hyperalgesia, and pain. AAs = amino acids, cGMP = cyclic guanine monophosphate, CGRP = calcium gene-related peptide, COX-2 = cyclooxygenase-2, EAAs = excitatory amino acids, ERK = extracellular signal-regulated kinase, GABA = gamma-aminobutyric acid, IL-1 β = interleukin-1 β , iNOS = inducible nitric oxide synthase, NF- κ B = nuclear factor kappa B, NO = nitric oxide, NOS = NO synthase, PKC = protein kinase C, PLA₂ = phospholipase A₂, RF = receptive field, Sub P = substance P, TNF = tumor necrosis factor. *Source:* Reprinted by permission from Elsevier Science Pub. Co. This figure was published in Pain: Handbook of Clinical Neurology, Vol 81. Yezierski R. Pain following spinal cord injury: Central mechanisms. Amsterdam (the Netherlands): Elsevier Science Pub. Co; 2006.

of events over time create an environment for changes to occur in the functional properties of central neurons, including enhanced responses to peripheral stimuli and/or spontaneous discharges.

Changes in the level of neuronal excitability, denervation supersensitivity, inactivation/activation of cell signaling pathways, and glial-neuronal interactions are all part of the injury cascade that ultimately contributes to the onset of abnormal sensory processing. Since the introduction of the central injury cascade and its role in the initiation of SCI pain, significant progress has been made in understanding many of the individual events associated with each major component. The general construct, however, of interactive injury processes working in concert to produce a permissive environment for functional changes in spinal neurons leading to abnormal clinical/behavioral symptoms remains a viable working model for the onset and maintenance of different injury-induced pain conditions [3,23].

Critical events in the aftermath of SCI include the transient elevation in excitatory amino acids (EAAs) and the production of potentially toxic mediators, e.g., cytokines, reactive oxygen species. EAAs are well-documented to have an important role in neuronal death associated with stroke, hypoxia-ischemia, and traumatic brain injury [24]. Similarly, research supports injury-induced glutamate neurotoxicity in the secondary pathology of ischemic and traumatic spinal injury [25–26]. Using an excitotoxic model of SCI that simulates injury-induced elevations in EAAs, Plunkett et al. found an upregulation of messenger ribonucleic acids (mRNAs) for interleukin (IL)-1 β , cyclooxygenase-2, nitric oxide synthase (NOS), and death-inducing ligands CD-95 and tumor necrosis factor- α (TNF- α)-related apoptosis-inducing ligand [27]. Upregulation of mRNA for TNF- α and dynorphin along with the activation of transcription factors nuclear factor- κ B (NF- κ B) and ELK-1 has also been reported following SCI [28–30]. Activation of the NF- κ B family of transcription factors is significant given its involvement in the inducible regulation of more than 150 genes involved in inflammatory, proliferative, and cell death responses that regulate transcription factors, inflammatory processes, cell survival, and membrane excitability. Importantly, a number of the secondary messengers, receptors, and ionic channels upregulated in response to central nervous system (CNS) injury are important in determining the functional state of spinal sensory neurons. For example, upregulation of sodium channels has been linked to the onset of changes in

neuronal excitability and the onset of abnormal sensations following SCI [31].

Other pathological, biochemical, and molecular changes associated with SCI include afferent sprouting in distant segments [32], upregulation of vanilloid receptor expression [33], changes in expression of metabotropic glutamate receptors [34], activation of protein kinases and transcription factors associated with the mitogen-activated protein kinase (MAPK)-signaling pathway [35], increased NR1 serine phosphorylation of the N-methyl-D-aspartate (NMDA) receptor [36], changes in galanin immunoreactivity [37], and increased expression of c-fos mRNA [30,38–39]. Although each of these events is considered part of the central injury cascade, causal relationships with the expression of chronic pain behaviors have not been established.

MECHANISMS OF SCI PAIN

Over the past 15 years, several mechanisms have been proposed to explain the condition of pain following SCI, including (1) loss of spinal inhibitory mechanisms [17,40], (2) presence of pattern generators within the injured cord [40–42] and supraspinal relay nuclei [43], (3) synaptic plasticity [2], (4) spinal and supraspinal microglia activation [44], and (5) changes in cell-signaling pathways at spinal and supraspinal sites [35,45]. In spite of evidence that cellular or axonal loss following injury predisposes individuals to at- or below-level pain, separating these regionally distinct categories of pain is important (from the standpoint of therapeutic strategies) and considering each as separate, although potentially related conditions. For example, the expression of pain after SCI follows a progressive sequence from at- to below-level pain, suggesting the existence of interactive mechanisms for these two pain conditions [46]. The temporal profile of different pain conditions raises the possibility that abnormal neural activity (spinal and supraspinal) associated with at-level pain may be a predisposing condition in below-level pain development. This relationship might be an important factor in the design of preventive and/or therapeutic strategies.

DYNAMIC PROGRESSION OF CENTRAL INJURY CASCADE

The dynamic longitudinal progression of tissue damage should be considered in the pathological changes associated

with spinal injury. The functional and behavioral significance of this progression is evidenced by the use of neuroprotective agents shown to limit the spread of injury as well as the expression of different pain-related behaviors [47]. These results led to the proposal of a “spatial threshold” in which a critical distance of tissue damage must occur for pain behaviors to develop (**Figure 2**). This concept evolved from a series of studies in which an approximately 5 mm distance in the dorsal horn gray matter was required for the expression of a spontaneous pain-like behavior (i.e., excessive grooming) [47–49]. From this follows a critical determinant that expression of pain following SCI may include both specific injury-induced anatomical and functional events along with the progressive longitudinal spread of pathophysiological changes within the cord [2,48]. Identifying the mechanisms responsible for the dynamic spread of injury may therefore help researchers develop neuroprotective interventions to use as preventive strategies for different pain conditions.

The spatial threshold hypothesis was tested by Yu et al. using selective neuroprotective agents following SCI [47],

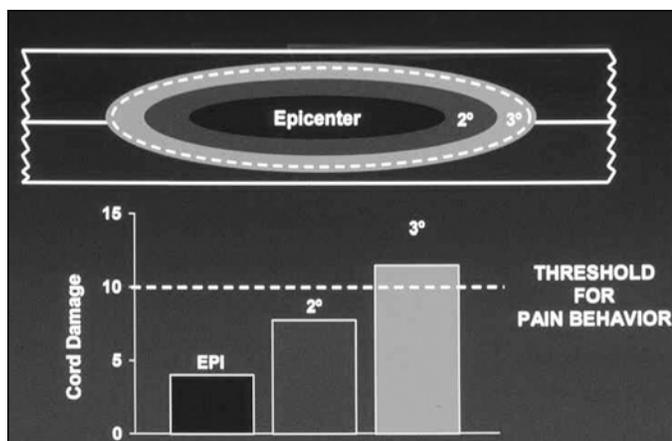


Figure 2.

Progression of events associated with central injury cascade from epicenter (EPI) of ischemic, traumatic, or excitotoxic insult in spinal cord leads to conditions responsible for expression of abnormal sensations, including pain. Ultimate extent of injury and/or area of cord influenced by different components of injury cascade expands to include 2° and 3° areas of injury. Amount of cord damage will continue to expand until it exceeds a spatial threshold required for onset of pain behavior. *Source:* Reprinted by permission from Elsevier Science Pub. Co. This figure was published in *Progress in brain research: Nervous system plasticity and chronic pain*, Vol 129. Yeziarski R. Pain following spinal cord injury: Pathophysiology and central mechanisms. Amsterdam (the Netherlands): Elsevier Science Pub. Co; 2006.

including agmatine (NMDA antagonist and NOS inhibitor), IL-10, and cyclosporine A (immunosuppressant). The results of this study showed a delayed onset of spontaneous pain behavior and reduced neuronal loss in the spinal cord of animals treated with neuroprotective agents compared with those treated with saline [47]. Treatment of pain after onset with these same compounds compared with treatment of saline significantly reduced pain behaviors and neuronal loss. These results showed for the first time that administration of neuroprotective agents significantly affected injury-induced spontaneous pain behaviors. Collectively, these results support the conclusions that (1) the expression of pain behaviors depends on a critical distance of neuronal injury along the longitudinal axis of the cord [2,47] and that (2) neuroprotective strategies targeting selected components of the central injury cascade may prevent the progression of pathological conditions that express pain following SCI [2]. Further support for these conclusions is the result of transplant studies in which adrenal chromaffin cells were used to prevent and/or reverse the expression of injury-induced pain behaviors [50–52]. Adrenal chromaffin cells are known to produce several neuroactive substances, including those with neuroprotective properties [53]. The possibility that neuroprotective strategies could conceivably worsen pain by providing an environment for the survival of dysfunctional nociceptive pathways should be considered a caveat of using this strategy of intervention.

One should note that sex, strain, and gonadal hormones also exert significant influences on the onset and progression of spontaneous pain behaviors following SCI [48]. For example, the development of pain-like behaviors following excitotoxic spinal injury in male rats of three different strains and ovariectomized female rats is related to the rostrocaudal spread of a specific pattern of neuronal loss in the dorsal horn [48]. Animals treated with estradiol develop severe pain behaviors, whereas those treated with progesterone have delayed onset and attenuated severity and progression of these behaviors [48]. The fact that sex, strain, and hormonal effects influence the temporal profile of pain behaviors and, more importantly, the longitudinal spread of neuronal damage following injury suggests an additional level of complexity regarding endogenous neuroprotective and neurodegenerative mechanisms in the CNS. Consistent with these observations are other reports describing age, sex, and strain factors contributing to differences in prevalence and severity of pain following SCI [13,54–55]. Unraveling the key components of the complex variables associated with SCI may help researchers

develop novel strategies for controlling spinal injury and its clinical consequences.

EMERGENCE OF SPINAL AND SUPRASPINAL PAIN GENERATORS

The initial onset of at-level changes in sensitivity to mechanical and thermal stimuli is believed to reflect, in part, a loss of inhibitory tone within the injured cord [17,56–57]. Loss of inhibition enhances recruitment of surrounding neurons and increases the spread of abnormal at-level sensations, including pain. Coincident with reduced local inhibition is the emergence of a pain-generating mechanism. Evidence supporting this concept led to the proposal that not all postinjury pains are due to noxious input; some may be due to changes in firing patterns, including burst activity and long afterdischarges, of neuronal pools adjacent to an injury site [40]. Evidence consistent with a pain-generating mechanism following injury include (1) the existence of hyperactivity in the spinal cord and thalamus of patients with SCI [43,58–59], (2) effectiveness of local anesthetics in alleviating pain when delivered to the injured cord [41,60], and (3) sensitization and prolonged afterdischarges of spinal sensory neurons following SCI [25,31,42,61–62]. The involvement of this neuronal pain-generating mechanism as a component of the spinal and supraspinal mechanisms of SCI pain is also supported by results of pharmacological studies [63–64]. For example, lidocaine and ketamine, two drugs that reduce membrane excitability and glutamate receptor activation, effectively attenuate SCI pain [65–66]. Efforts to increase inhibition with either baclofen or propofol are also effective [32,67]. The anti-convulsant lamotrigine that blocks sodium channels involved in hyperexcitability is also suggested to be effective in patients with SCI with spontaneous and evoked pain [68] as is the anticonvulsant pregabalin [69].

Importantly, discovering the involvement of spinal lamina I neurons in the pain-generating mechanism was a major step in understanding the mechanism of SCI pain. Evidence for this finding comes from clinical observations showing focal hyperactivity in the superficial dorsal horn of the injured cord [58]. Microcoagulation of these hyperactive areas significantly decreased pain [58,70]. Additional support for the involvement of this region in generating pain was evidence that eliminating neurokinin-1 (NK-1) receptor-expressing neurons in the superficial dorsal horn prevents and/or reverses spontaneous pain

behavior after excitotoxic spinal injury [71]. This study provided the first evidence suggesting NK-1 receptor-expressing neurons are a critical component of the spinal mechanism responsible for developing injury-induced at-level pain.

Although significant clinical and preclinical evidence supports the involvement of an abnormal pain generator in SCI pain, support also exists for a role of supraspinal structures, e.g., diencephalon, in this mechanism. The contribution of dysfunctional input from the injured cord along with effects of deafferentation (secondary to the death of spinal projection neurons), sprouting of undamaged fibers, and/or the functional unmasking of nonfunctional local connections could help develop focal generators and/or amplifiers of abnormal discharges in supraspinal structures [3,43,72]. Thus, SCI pain may be expressed when portions of supraspinal targets are deprived of spinal input from at or below the level of injury. Instead, these targets are activated by abnormal (spontaneous or evoked) activity originating from spinal regions above the injury level [3].

Another potential contribution to the pain-generating mechanism is the role of descending bulbospinal monoaminergic pathways. Through a mechanism of descending facilitation, these pathways have been shown to be involved in initiating and maintaining neuropathic pain [73–74]. A role in pain development following SCI is suggested by studies showing anatomical and functional changes in serotonergic (5-hydroxytryptamine [5-HT]) pathways following SCI [75–77]. Further support for these changes come from studies showing facilitation of at-level pain by the 5-HT₃ receptor [78] and attenuation of injury-induced pain behaviors and excitability of dorsal horn neurons with spinal transplantation of 5-HT precursor cells [79–80].

ALTERNATIVE SENSORY PATHWAYS IN THE INJURED SPINAL CORD

Although researchers generally agree that interruption of the spinothalamic tract contributes to SCI pain and specifically to below-level pain, interruption of other pathways and/or abnormal activity in alternative sensory systems may also participate in the expression of below-level pain [72,81]. Below-level pain, for example, may involve lesions of the dorsal columns, because pain associated with syringomyelia is reported to be more prevalent when a central cavity expands to involve dorsal pathways [82]. Similarly, animal models have shown that interruption of

the dorsal or dorsolateral columns increases the incidence of overgrooming/autotomy after peripheral nerve injury and that allodynia/hyperalgesia is frequently observed in response to stimulation caudal and ipsilateral to dorsolateral column lesions in monkeys [83]. These results suggest that damage to dorsal spinal pathways may be important in producing SCI below-level neuropathic pain.

Although reduced temperature and pain sensations have been used to support the involvement of damaged spinothalamic connections in developing central pain, recent evidence showed that neuronal hyperexcitability is also important in developing below-level pain. Furthermore, loss of spinothalamic function did not appear to predict this type of pain [84]. This work complements previous magnetic resonance imaging findings showing that patients with below-level pain have larger gray matter lesions than patients without pain [63]. Additional evidence supporting this conclusion comes from studies showing that anterolateral cord lesions result in evoked pain caudal to spinal injury only when gray matter is involved [20] and spontaneous pain behavior can be elicited with spinal lesions restricted to the gray matter [18]. Below-level pain may therefore be expressed when portions of sensory-processing targets are deprived of input from classic pain pathway(s) and are indirectly activated by other sources of alternative input from a dysfunctional neuronal core (i.e., pain-generating mechanism) rostral to the injury site [3].

SIGNALING PATHWAYS AND SYNAPTIC PLASTICITY

Another potential mechanism contributing to chronic pain following spinal injury is synaptic plasticity in the brain and spinal cord. An important discovery in the mechanism of acute pain is found in the construct of central sensitization and together with long-term changes in spinal connectivity represents a potential mechanism for persistent pain [85–86]. The changes associated with central sensitization are believed to contribute to alterations in excitability of spinal neurons and ultimately to the development of spinal, and possibly supraspinal, pain generators/amplifiers.

Events involved in producing long-term synaptic changes following injury include (1) phosphorylation of regulatory proteins, (2) positive and negative regulation of gene transcription, (3) injury-induced synthesis of proteins, (4) strengthening and weakening of synaptic connections, and (5) death or rescuing of neurons. The

contribution of this hypothetical cascade of biochemical and molecular events to the progression of Alzheimer's, Parkinson's, and cerebrovascular diseases has received much attention in recent years [87–88]. Studies focusing on mechanisms responsible for injury-induced changes similar to those just described may provide new opportunities for therapeutic approaches for managing SCI pain.

Efforts to understand the molecular events associated with spinal injury include a study where components of the MAPK-signaling pathway were evaluated [35]. Following excitotoxic spinal injury, this study showed (1) increased phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, (2) increased activation of NF- κ B and phosphorylation of ELK-1, and (3) increased gene expression for the NK-1 receptor and NR1 and NR-2A subunits of the NMDA receptor [35]. Blockade of the MAPK cascade with the MEK inhibitor PD98059 inhibited phosphorylation of ELK-1, activation of NF- κ B, and gene expression of NR1, NR-2A, and NK-1R; and prevented the development of spontaneous pain behavior. Injury-induced elevations in spinal levels of EAAs thus lead to activation of the ERK→ELK-1 and NF- κ B signaling cascade and the transcriptional regulation of receptors important to chronic pain development. Blockade of this intracellular cascade prevents the onset of injury-induced spontaneous pain behavior [35].

The results just described support the conclusion that many of the same molecular changes described as activity-dependent following peripheral nerve and tissue injury are also associated with central injury. The expression of these molecular changes suggests that the mechanism responsible for the increased excitability of neurons following spinal injury may be similar to the well-documented activity-dependent mechanism induced by damage to peripheral tissue, a mechanism resulting in activating kinase cascades and ultimately long-term changes in synaptic efficacy and neuronal excitability.

A significant contribution to initiating synaptic plasticity has been attributed to the involvement of glial elements and specifically activation of microglia [89]. In spite of the growing evidence that microglial inhibition reduces pain, prostaglandin E-2 has only recently been shown to be involved in the microglia-to-neuron signaling mechanism to induce dorsal horn sensory neurons to undergo changes in excitability [90]. Furthermore, microglia have also been shown to be activated by CCL21 (chemokine [cc-motif] ligand 21) after SCI [91]. Inhibition of microglial activation after spinal injury reduces pain-related behaviors [44,91], and treatment with minocycline or the Mac-1-SAP

immunotoxin reverses morphological changes in microglia and attenuates functional and behavioral consequences of SCI. Therefore, microglia could possibly evolve as a significant therapeutic target in preventing and treating pain associated with spinal injury.

SUPRASPINAL CHANGES ASSOCIATED WITH SCI

In addition to the well-documented spinal mechanisms of SCI pain, remote effects of injury include increased blood flow in forebrain structures [92], cortical expression of cholecystokinin (CCK) and opioid peptides [93–95], changes in the functional properties of thalamic neurons [31,42,59,96–97], and neuronal death in the cortex [98]. The involvement of these changes in SCI pain development, although not proven, is highly probable. In the study by Morrow et al. [92], significant increases in regional cerebral blood flow were found in the arcuate nucleus, hind limb region of S1 cortex, parietal cortex and thalamic posterior, and ventral posterior medial and lateral nuclei. Changes in somatosensory structures involved in pain processing complement clinical observations showing similar changes in thalamic blood flow following SCI [99], alterations in the chemical profile of ventral posterior lateral (VPL) thalamus in patients with SCI pain [100], and reports of hyperactive foci of thalamic activity in patients with SCI induced spontaneous burning pain [43]. Consistent with these clinical reports are descriptions of VPL neurons showing increased spontaneous activity, enlarged receptive fields, enhanced evoked activity, and the emergence of abnormal burst firing after experimental spinal injury [31].

In addition to these studies, Brewer and colleagues clarified changes in peptidergic transmitter systems at spinal and supraspinal levels following excitotoxic SCI [38,93–95]. Many of these changes mimic what is seen in conditions of neuropathic pain following peripheral nerve injury. Opioid precursors preproenkephalin (PPE) and preprodynorphin (PPD) increased expression in cortical regions associated with nociceptive function: PPE in the anterior cingulate cortex (ACC) and PPD in the parietal cortex. These increases occurred bilaterally following injury, and expression of PPE in the ACC and PPD in the contralateral parietal cortex were significantly higher in animals that developed spontaneous pain behaviors versus those that did not. Receptors for opioid peptides were also differentially expressed in these two groups of animals (pain vs nonpain), with expression levels being

affected throughout the medial pain system (i.e., ACC, medial thalamus, periaqueductal gray and rostroventral medulla). In addition to direct effects on opioid peptides and receptors, excitotoxic injury affects the expression of CCK, an endogenous antagonist to opioid analgesia, and several isoforms of protein kinase C, an important enzyme in the phosphorylation of opioid receptors that renders receptors unavailable for binding [101]. These effects of injury were seen throughout the medial pain system and were pronounced in animals with post-SCI pain. Together, these changes create a dysfunctional system within the endogenous pain control system. The importance of these findings is that following SCI, significant changes occur at supraspinal sites involved in pain processing, including changes in several components of the normal pain-modulation system (ligands, receptors, and second messenger for opioids).

FUTURE DIRECTIONS AND CONCLUSIONS

Clinical and experimental studies need to identify critical events responsible for the onset of mechanisms of SCI pain. Studies must continue to focus on details of different secondary events associated with the injury process in which dysfunctional spinal and supraspinal neurons emerge. These studies are essential to the design of more effective treatment strategies. Progress in understanding central pain after SCI will require clinically relevant experimental models and behavioral assessment strategies. A single mechanism solely responsible for the onset of central pain following SCI is unlikely. Depending on the nature of injury and the progression of pathological, molecular, and biochemical changes along the rostrocaudal axis of the cord, each of the mechanisms that I have discussed in this review most likely contributes to the onset of SCI pain (**Figure 3**). Continued basic and clinical research of different aspects of at- and below-level pain should help healthcare professionals better understand spinal and supraspinal mechanisms that cause these conditions.

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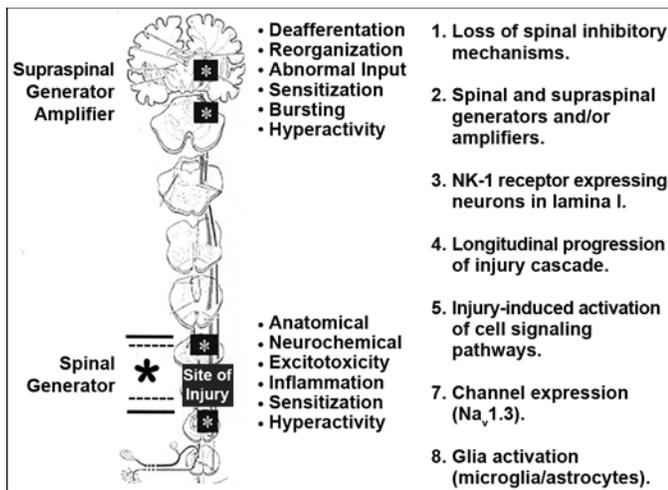


Figure 3.

Summary of different injury-induced changes associated with development of at- and below-level pain. *Spinal generators of abnormal activity evolve because of the collective impact of anatomical, neurochemical, inflammatory, and excitotoxic changes (i.e., central injury cascade) leading to increased excitability of spinal sensory neurons. Changes contributing to development of a *spinal generator include loss of intrinsic inhibitory mechanisms, longitudinal progression of events associated with spinal injury cascade, injury-induced activation of cell signaling pathways, increased expression of sodium channels, and activation of microglia and astrocytes. Development of generator/amplifier mechanism at *supraspinal levels emerge as result of deafferentation of input from spinal segments below injury level. Functional impact of this and other injury-induced changes at supraspinal levels (e.g., sprouting, unmasking of connections) results in activation of supraspinal regions by input from noninjured segments of cord and referral of pain sensations to dermatomes below injury level. *Source:* Reprinted by permission from Elsevier Science Pub. Co. This figure was published in *Pain: Handbook of Clinical Neurology*, Vol 81. Yeziarski R. Pain following spinal cord injury: Central mechanisms. Amsterdam (the Netherlands): Elsevier Science Pub. Co; 2006. SCI = spinal cord injury.

The author has declared that no competing interests exist.

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