Published in final edited form as:
Exp Neurol. 2013 September ; 247: 328–341. doi:10.1016/j.expneurol.2013.03.008.

Opioid administration following spinal cord injury: Implications for pain and locomotor recovery

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Abstract

Approximately one-third of people with a spinal cord injury (SCI) will experience persistent neuropathic pain following injury. This pain negatively affects quality of life and is difficult to treat. Opioids are among the most effective drug treatments, and are commonly prescribed, but experimental evidence suggests that opioid treatment in the acute phase of injury can attenuate recovery of locomotor function. In fact, spinal cord injury and opioid administration share several common features (e.g. central sensitization, excitotoxicity, aberrant glial activation) that have been linked to impaired recovery of function, as well as the development of pain. Despite these effects, the interactions between opioid use and spinal cord injury have not been fully explored. A review of the literature, described here, suggests that caution is warranted when administering opioids after SCI. Opioid administration may synergistically contribute to the pathology of SCI to increase the development of pain, decrease locomotor recovery, and leave individuals at risk for infection. Considering these negative implications, it is important that guidelines are established for the use of opioids following spinal cord and other central nervous system injuries.

Keywords

spinal cord injury; opioid; central sensitization; opioid-induced hyperalgesia; excitotoxicity; locomotor function; glia

Neuropathic pain, resulting from injury, significantly impacts quality of life in people living with spinal cord injury (SCI) (Harden & Cohen, 2003; Wetering et al., 2010; Cairns et al., 1996 Celik et al., 2012). Unfortunately, however, approximately one-third of people with a spinal cord injury will experience this severe or excruciating pain within 5 years of injury (Siddall et al., 2003), compared to an estimated 1% of people in the general population experiencing the same pain characteristics (Dieleman et al., 2008). Moreover, this aberrant pain is very difficult to treat (Heutink et al., 2012). Clinicians are currently faced with a trial-and-error approach to pain management after SCI.

Opioids are considered to be among the most effective treatments for neuropathic pain, and are commonly trialed for analgesic efficacy. In the long term, approximately 20% of people

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will discontinue opioid treatment (Moore & McQuay, 2005), because of significant side effects (reviewed in Dellemijn, 1999; Cruccu, 2007; Dworkin et al., 2007), but even short-term trials may interact with spinal injury and impact recovery. For example, there is novel, experimental evidence showing that the therapeutic use of opioids in the acute phase of SCI (Day 1–7 post injury) can inhibit locomotor recovery (Hook et al., 2009, 2010, 2011; Woller et al. 2012). Yet, there are currently no guidelines for opioid administration, regarding timing and duration of use, following injury. As opioids are administered immediately for the treatment of pain resulting from SCI, this issue must be further explored.

Based on a comprehensive review of the literature, we propose that opioids and SCI may have synergistic effects on neuronal and glial function that adversely affect locomotor recovery, the development of pathological pain, and general health. Evidence from the literature suggests that excitotoxicity and glial activation are exacerbated by opioid administration, which can negatively affect the vulnerable cellular environment of the injured spinal cord to increase cell death and reduce recovery of function. Aberrant glial activation and hyperexcitability of dorsal horn neurons (the development of central sensitization) have also been implicated in the development of pain after spinal injury (Hulsebosch, 2008; Gwak et al., 2012; Gwak & Hulsebosch, 2011).

This paper reviews the molecular changes associated with both SCI and opioid administration, highlighting the characteristics that are common to both phenomena. We first outline changes induced by SCI, focusing on neuronal and glial function. Using the same strategy, we review opioids and molecular changes underlying opioid-induced analgesia, as well as pathologies associated with repeated opioid use. Finally, we review literature suggesting that administration of opioids after a spinal cord injury can contribute to the pathology of SCI. Throughout this discussion, we emphasize the need to better understand how opioids affect the cellular and molecular environment of the injured cord. Indeed, the data suggest that opioid treatment in the acute phase of injury might lead to augmented pain and loss of locomotor function after SCI, as well as concerns for overall health.

SPINAL CORD INJURY

This section will review the neuronal and glial consequences of SCI as they pertain to the loss of locomotor function and the development of pain. Specifically, SCI results in a number of consequences that can lead to cell death, excitotoxicity, and central sensitization. Each of these consequences contributes to decreased locomotor function and the development of pain following the initial trauma. As these are immediate consequences of SCI, this review focuses primarily on the acute phase of SCI; defined here, for the rodent model, as days 1–7 immediately following the injury.

Neuronal Effects of Spinal Cord Injury

Excitotoxicity—Excitotoxicity refers to the death of cells resulting from an excessive exposure to glutamate, a major excitatory neurotransmitter in the CNS, or overstimulation of glutamate receptors (Olney, 1969; Olney, 1970). In SCI, cell death resulting from trauma induces the release of glutamate from primary afferent and injured dorsal horn neurons into the dorsal horn of the spinal cord. Glutamate levels peak 15-minutes after injury, remain elevated for an hour, and return to normal over a period of 1.5 hours (Vera-Portocarrero et al., 2002; Liu et al., 1991; McAdoo et al., 1999; Xu et al., 1998). Studies have shown that the extracellular concentrations of glutamate reached post injury are capable of inducing functional impairments when administered to intact animals (Xu et al., 2005). In the intact animal, however, glutamate is typically regulated by neurons and astrocytes (Tsai et al., 2012; Matos et al., 2012) with excess levels being removed from the synaptic cleft in a

matter of milliseconds (Clements et al., 1992). As a result of trauma, release of glutamate into the dorsal horn causes increased activation of NMDA receptors (NMDARs) and AMPA receptors (AMPARs), allowing an influx of calcium ions to the postsynaptic cell. This increased activation of NMDARs has been implicated in excitotoxic cell death following experimental injury. Indeed, administration of an NMDAR antagonist, or other agents that block glutamate receptors, soon after injury improves functional outcome following SCI (Faden et al., 1988; Faden et al., 1990; Gómez-Pinilla et al., 1989; Mills et al., 2000; Mills et al., 2001; Wrathall et al., 1994; Wrathall et al., 1996; Wrathall et al., 1997).

Central Sensitization—Increased extracellular glutamate levels, and the subsequent NMDAR activation, can lead to the induction of central sensitization, one mechanism thought to underlie the development of neuropathic pain, in the spinal cord (Woolf & Thompson, 1991; Artola & Singer, 1987). Central sensitization is a phenomenon in which neurons of the spinal cord dorsal horn become hypersensitive following peripheral tissue damage, inflammation, or injury to the CNS. This hypersensitivity continues even in the absence of the triggering stimulus (Woolf, 1983; Woolf, 2007; Woolf, 2011), and shares many of the molecular changes that have been described for long-term potentiation (e.g. Ji et al., 2003). Briefly, the release of glutamate resulting from SCI activates NMDARs, and subsequently allows for the influx of Ca^{2+}, which then activates downstream intracellular kinases. This includes activation of adenylyl cyclase (AC), protein kinase A (PKA), protein kinase C (PKC), and/or calcium/calmodulin-dependent kinase II (CaMKII). Through these cascades, mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK are phosphorylated. The phosphorylation of CREB (cyclic adenosine monophosphate (cAMP) response element-binding), a downstream target of ERK1/2, p38 MAPK, and CaMKII, is important in regulating transcription and maintaining central sensitization. Connecting this molecular pathway with functional implications, Crown et al. (2005) showed that animals with signs of neuropathic pain following SCI had an increased expression of pCREB. This increase was not seen in injured animals free of neuropathic symptoms, or in control animals (Crown et al., 2005). Furthermore, inhibition of p38 MAPK at 35 days post injury reversed established mechanical allodynia and decreased hyperexcitability in dorsal horn neurons in contused SCI subjects (Crown et al., 2008). These behavioral studies implicate central sensitization in the development and maintenance of pain following SCI.

Glial Effects of Spinal Cord Injury

Endothelial cells are damaged as a result of the initial trauma, producing hemorrhage, initially in the grey matter, which spreads over time to the surrounding white matter. The damage compromises the blood-spinal cord barrier allowing for an infiltration of inflammatory cells (Bareyre & Schwab, 2003) and disruption in blood flow to the surrounding areas, which results in oxygen and nutrient deprivation. The hemorrhage and resulting edema also contribute to secondary damage in the spinal cord, a process further exacerbated by the infiltration of immune cells. The immune response begins with the infiltration of neutrophils, monocytes, macrophages, microglia, and lymphocytes. This immune activation, while necessary following injury, is often detrimental (Schwartz, 2003). The effects of immune activation will be discussed in this section, with a focus on microglia and astrocytes.

Aberrant Glial Activation—In the CNS, glia are present in numbers greater than neurons. In addition, astrocytes and microglia express many of the same receptors and release many of the same factors (transmitters, reactive oxygen species, etc.) as neurons, marking them as prime candidates in the development of neuropathic pain and neuronal hyperexcitability following injury (Gwak & Hulsebosch, 2011; Pineau & Lacroix, 2007;

Porter & McCarthy, 1997; Wang et al., 2009; Jarvis, 2010). In fact, a persistent, dysfunctional glial reaction, termed “gliopathy” (Hulsebosch, 2008), is thought to contribute to central pain following injury (Costigan et al., 2009).

Normally, microglia are present in a resting state, but the presence of an activating factor (e.g. interleukin (IL)-6, adenosine triphosphate (ATP), substance P, fractalkine) results in a morphological and functional change (Gwak et al., 2012; Hulsebosch et al., 2009; Soulet & Rivest, 2008). Microglia are activated within minutes of CNS injury and initially function to remove debris and damaged cells (Kreutzberg, 1996; David et al., 1990; Avellino et al., 1995; Fleming et al., 2006; Carlson et al., 1998). However, these cells can remain activated for weeks to months following injury and contribute to continued damage and cell death via the release of glutamate, ATP, calcitonin gene-related peptide (CGRP), pro-inflammatory cytokines, reactive oxygen species (ROS), nitric oxide (NO, and proteases (Kreutzberg, 1996; Aloisi, 2001; Dong & Benveniste, 2001; Fleming et al., 2006; Carlson et al., 1998; Chao et al., 1995; Lieberman et al., 1989; Priller et al., 1995; Rischke & Krieglstein, 1991; Stanley et al., 1994; Svensson et al., 1993). Several of these factors (e.g. increased extracellular glutamate, pro-inflammatory cytokines) have been associated with the development of pain via sensitization of sensory circuits (Bennett et al., 2000a, b; Detloff et al., 2008).

Astrocytes also play a dual role in SCI, becoming activated within 24 hours of SCI, and remaining active for months to years (Schnell et al., 1999; Popovich et al., 1997) following injury. In the initial stages of injury, astrocytes play a crucial role in restricting inflammation and protecting neurons (Hu et al., 2010; Bradbury et al., 2002). Moreover, astrocytes are responsible for glutamate homeostasis, thus preventing excitotoxicity under normal circumstances (Lepore et al., 2011). However, astrocytes migrate to the lesion area and form a scar, which is thought to impair axonal regeneration (Hu et al., 2010; Bradbury et al., 2002). Activation of astrocytes also leads to the activation of MAPK pathways. These pathways can activate the nuclear transcription factor, NF-κB (nuclear factor κB), which subsequently results in increased production of pro-inflammatory cytokines, chemokines, prostaglandins, NO, free radicals, neurotoxins, and excitatory amino acids (Hameed et al., 2010). These substances, as with those released from microglia, are pain-mediating and, in a cyclic manner, contribute to continued neuronal hyperexcitability following injury (Detloff et al., 2008; Hulsebosch et al., 2009; Keane et al., 2006; Scholz & Woolf, 2007; Vallejo et al., 2010).

The adverse consequences of glial activation include the development of neuropathic pain and cell death following SCI. Following injury, p38 MAPK is phosphorylated in microglia, astrocytes, and neurons (Crown et al., 2008). Activation of p38 MAPK, can phosphorylate NMDARs, leading to maintained hyperexcitability (Hulsebosch, 2008), and subsequently neuronal and glial death (Crown et al., 2006). Depending on the numbers of NMDARs being activated, this hyperexcitability can also lead to a loss of GABAergic cells, contributing to a loss of inhibitory tone and the development of neuropathic pain. Indeed, an increased expression of p-p38 is seen in animals experiencing neuropathic pain resulting from SCI, but not in their pain-free counterparts (Crown et al., 2006). Moreover, inhibiting the action of p38 MAPK reduces neuropathic pain symptoms in a contusion model (Crown et al., 2008). Similarly, administration of propentofylline (PPF), which blocks activation of both microglial and astrocytes, for the first 7 days after injury decreased dorsal horn neuron hyperexcitability and mechanical allodynia following a hemisection of the spinal cord (Gwak et al., 2008). Together, these results demonstrate a role of glia in the development of pain following SCI.

Aberrant glial activation may also contribute to the loss of locomotor function after SCI. Liu et al. (2008) found that administration of IL-1β on days 1–3 following SCI leads to impaired locomotor recovery. IL-1β is expressed within 15-min following injury in a rodent model of SCI, and is one of the first cytokines released by activated microglia (Kim et al., 2006; Pineau & Lacroix, 2007). Experimental evidence indicates IL-1β can induce apoptosis by phosphorylation of p38 MAPK, activating the pro-apoptotic caspase-3 cascade (Mika, 2008; Springer et al., 1999). Apoptosis, a programmed cell death, leads to the release of pro-inflammatory cytokines and induces migration of immune cells to the injury site (Kang et al., 1997; Seino et al., 1997; Desbarats et al., 2003; Letellier et al., 2010). Furthermore, cytokines, such as IL-1β, can activate both cytochrome c and caspase-9, which, together, lead to the activation of caspase-3 (Springer et al., 1999; Sekhon & Fehlings, 2001). Cell death initiates the release of pro-inflammatory cytokines, NO, and reactive oxygen species (Block & Hong, 2005; Min et al., 2003, 2004; Cho et al., 2011), causing further, sustained activation of microglia, enhancing the pro-inflammatory environment of the injured spinal cord, and affecting locomotor recovery after SCI.

Toll-like Receptors—Toll-like receptors (TLRs), a collection of ~12 single transmembrane receptors, are normally expressed on microglia (among numerous other neuronal and non-neuronal cells) and, in response to inflammation, are expressed on astrocytes. TLRs are believed to activate pathways similar to those activated by IL-1, eventually leading to the activation of NF-κB, and resulting in the production of pro-inflammatory cytokines (e.g. IL-1β and TNFα). A role for this pathway is well established in the initiation and maintenance of chronic pain (Milligan & Watkins, 2009). In particular, the TLR4 pathway has been well defined (see Hutchinson et al., 2011; Hameed et al., 2010; Nicotra et al., 2012). Blocking TLR4 receptors prevent and reverse neuropathic pain in an experimental setting (Bettoni et al., 2008, Hutchinson et al., 2007, 2008, 2010, Tanga et al., 2005). In these studies, rats experiencing neuropathic pain were treated with a TLR4 antagonist and showed decreased thermal hyperalgesia and mechanical allodynia (Bettoni et al., 2008). In addition, TLR4 KO animals or animals treated with TLR4 antisense oligodeoxynucleotide prior to an L5 nerve transection did not develop neuropathic pain (Tanga et al., 2005).

In addition to effects on neuropathic pain, ligand binding to TLR4 results in activation of phosphoinositide 3-kinase (PI3K) and Akt, which can lead to apoptosis. Indeed, Kigerl & Popovich (2009) have shown that TLRs activate a number of signaling cascades, which affect the pathophysiology of secondary injury processes in an SCI model. For example, after SCI TLR4 function appears to be necessary for locomotor recovery. In fact, TLR4 knockout mice showed increased, abnormal demyelination and astrogliosis relative to wild-type mice following SCI (Kigerl et al., 2007). This demyelination led to decreased locomotor function following injury, indicating that normal TLR4 function is necessary to mediate inflammation after SCI. Together, these effects demonstrate the complex nature of TLR4 signaling: blockade of the receptor is beneficial for neuropathic pain, but detrimental to recovery of locomotor function.

Summary

Following SCI, there is a loss of neurons and an aberrant activation of glia that can contribute to the loss of locomotor function and the development of pain. How locomotor function and pain are affected by opioids following SCI, however, has yet to be fully examined.

ADMINISTRATION OF OPIOIDS

Three classic opioid receptors, the μ-opioid receptor (MOR), δ-opioid receptor (DOR), and κ-opioid receptor (KOR) have been identified and are located throughout regions of the brain, brainstem, spinal cord, and periphery on both presynaptic (e.g. afferent fibers), postsynaptic (e.g. dorsal horn neurons), and glial cells (Pert & Snyder, 1973a, b; Simon, 1973; Terenius, 1973; Yaksh, 1997; Pert et al., 1973; Atweh & Kuhar, 1977a, b, c; Arvidsson et al., 1995; Besse et al., 1990a, b; 1991; Fields et al., 1980; Mansour et al., 1987; reviewed by Yaksh & Noueihed, 1985; Hutchinson et al., 2011; Stein et al., 1989). Traditionally, opioid receptor agonists are known for their analgesic (antinociceptive) and rewarding, hedonic properties. This is evidenced by their frequent use in the treatment of pain, and the common occurrence of abuse following recreational or therapeutic use. There is emerging evidence, however, that opioid administration affects neuronal and glial systems to produce pathology (Machelska, 2011). For instance, the continuous administration of morphine can lead to the development of pain sensitization known as opioid-induced hyperalgesia (OIH; Mao, 2002; Lee et al., 2011). Opioid-induced hyperalgesia results from prolonged administration of opioids, which paradoxically produces hyperalgesia, expressed as an increased sensitivity to a noxious stimulus. In addition, studies suggest opioid administration negatively affects locomotor function (e.g. Hemstapat et al., 2009; Headrick et al., 1995; Caudle & Issac, 1987; Faden, 1990). The mechanisms mediating these effects, as with SCI, can fall under two broad categories: neuronal- or glial-mediated effects. In this section, evidence supporting these claims will be reviewed.

Neuronal Effects of Opioid Administration

Kappa Opioid Mediated Excitotoxicity—Experimental evidence suggests agonists for the KOR can have detrimental effects on locomotor function by inducing central sensitization. For instance, it is known that intrathecal administration of either dynorphin or intrathecal dynorphin A (2–17), a stable metabolite of dynorphin, induces a lasting paralysis in intact rats (Headrick et al., 1995, Caudle & Isaac, 1987; Faden, 1990; Faden & Jacobs, 1984; Przewlocki et al., 1983; Hemstapat et al., 2009). The paralysis and loss of tail flick reflex resulting from dynorphin activity are NMDAR-dependent (Caudle & Isaac, 1987; Long et al., 1987; Faden & Simon, 1988; Faden, 1992; Woods & Zangen, 2001; Hemstapat et al., 2009), and treatment with a selective, noncompetitive NMDAR antagonist prior to dynorphin administration lessens resultant paralysis (Bakshi et al., 1992). This result implicates NMDAR in producing the negative effects. In this manner, dynorphin is leading to paralysis via excitotoxicity.

In support of this, data suggest that dynorphin increases excitatory amino acid levels, and augments NMDAR-mediated neurotoxicity through impaired/ reduced glutamate reuptake (Mao et al., 2002; Bakshi et al., 1990; Faden, 1992; Woods & Zangen, 1987; Rothman & Olney, 1987; Choi, 1992). Similarly, dynorphin potentiates NMDA currents (Lai et al., 1998) and increases internal calcium ion concentrations, leading to enhanced neuronal loss. These effects are blocked by the NMDAR antagonist -(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine hydrogen maleate (MK-801) (Hauser et al., 1999). These experiments suggest that dynorphin, like morphine, is producing locomotor deficits through an NMDA-mediated mechanism.

Kappa opioids have also been found to impact spinal plasticity. For example, following a complete transection of the spinal cord, uncontrollable nociceptive stimulation disrupts NMDAR-mediated plasticity (Grau et al., 2006; Joynes et al., 1995; Joynes et al., 2004; Liu et al., 2005). This effect is blocked by pre-administration of a kappa-opioid antagonist (nor-BNI), but not by a MOR or DOR antagonist (Joynes & Grau, 2004). Similarly, treatment with the kappa-opioid receptor agonist GR89696 prevents spinal learning (a behavioral

index of spinal plasticity), while MOR and DOR agonists have no effect (Washburn et al., 2008). Moreover, kappa opioid agonists have been shown to inhibit long-term potentiation, a lasting enhancement in synaptic transmission thought to underlie learning and memory (Caudle et al., 1994; Caudle et al., 1997; Terman et al., 2000; Terman et al., 1994). Together, these findings suggest that kappa opioids can negatively influence neuronal survival, with implications for the development of pain following opioid administration as well.

Opioid-Induced Hyperalgesia—Opioid-induced hyperalgesia (OIH) has been observed following administration of intrathecal (i.t.) morphine (Mao et al., 1995), a fentanyl bolus (Célèrier et al., 2000), and with repeated heroin administration (Célèrier et al., 2001). Moreover, increasing the dose of the opioid does not relieve this pain; instead, relief requires a seemingly contradictory decrease in the dose (see Lee et al., 2011). While the causal mechanisms for OIH are still largely unknown, the glutamatergic system and increased spinal dynorphin have emerged as important mediators (Mao et al., 2002; Silverman, 2009; Lee et al., 2011; Mayer et al., 1999).

For the glutamatergic system, the development of OIH is related to increased NMDAR activation stemming from 1) increased NMDAR excitability and 2) increased glutamate availability. It is known that glutamate can cause persistent activation of NMDA receptors, leading to pathological pain (Jacquet, 1988; Raigorodsky & Urca, 1987; Mao & Price, 1994; Laulin et al., 2002). Ironically, repeated exposure to morphine increases NMDAR channel activation (Harris et al., 1996; Croul et al., 1998; Mao & Mayer, 2001). Extended morphine administration is thought to contribute to NMDAR excitability via upregulation of PKCγ (Lim et al., 2005). Increased PKC activation is involved in the removal of the Mg^{2+} block from the NMDAR channel, facilitating NMDAR activation (Chen & Huang, 1992; Woolf & Salter, 2000; Mao et al., 1995), and significantly resembling the mechanisms implicated in central sensitization after SCI. Furthermore, it has been demonstrated that MORs are naturally associated with the NMDAR-1 subunit (Rodríguez-Muñoz et al., 2012). Morphine-induced increases in PKC break this association, leading to NMDAR-mediated decreases in analgesia (Rodríguez-Muñoz et al., 2012). In support of this, treatment with an NMDA antagonist enhances morphine analgesia (Mehta et al., 2011).

In addition, repeated morphine administration can lead to the downregulation of spinal glutamate transporters, which increases glutamate availability (Lim et al., 2005). This additional glutamate availability, along with NMDAR excitation, increases NMDAR activation (Mao et al., 2002; Harris et al., 1996; Croul et al., 1998; Mao & Mayer, 2001). Activation of the NMDAR, through hyper-excitation, as discussed in the previous section, has been shown to produce pain and neuronal cell death by apoptosis (Mao et al., 1992; Mao et al., 1997).

In experimental models, NMDAR activation also increases the pro-apoptotic element Bax, and decreases the anti-apoptotic element Bcl-2, leading to apoptosis (Mao et al., 2002). Similar apoptotic elements, namely, adenylyl cyclase (AC), cAMP, and PKA (Nestler & Aghajanian, 1997), are elevated following repeated morphine administration (Nakamura et al., 2003). Of particular importance to cell survival, it has been shown that inhibiting the activity of cAMP and PKA attenuates the downregulation of spinal glutamate transporters (Lim et al., 2005), thus decreasing glutamate dysregulation. These results suggest that repeated exposure to morphine, by increasing glutamate levels and activating cAMP and PKA, contributes to apoptosis, occurring, primarily, in neurons in lamina I-II of the spinal cord dorsal horn (Mao et al., 2002). Furthermore, the repeated administration of morphine induces the expression of MAPK (von Zastro et al., 2003; Zhang et al., 2008), an effect that was also attenuated by AC or PKA inhibition (Lim et al., 2005), suggesting opioids, as

found for SCI, activate MAPK pathways to contribute to pain and apoptosis. Overall, prolonged morphine administration can initiate neuronal apoptosis, with implications for both locomotor function and the development of pain.

A role of spinal dynorphin, an endogenous ligand for the KOR (Zhang et al., 1998), has also been established in OIH (Mao, 2002; Lee et al., 2011). Sustained opioid administration results in increased spinal levels of dynorphin (see Vanderah et al., 2001). Dynorphin is often pronociceptive (Cho & Basbaum, 1989; Caudle & Isaac, 1988; Kajander et al., 1990; Wang et al., 2001; Dubner & Ruda, 1992), and, via a non-opioid mechanism, results in the release of excitatory amino acids (Faden, 1992). Faden (1992) demonstrated that administration of both the opioid-active dynorphin 1–17 and the opioid inactive dynorphin 2–17 result in similar levels of glutamate and aspartate release in intact rats, which are not blocked by opioid receptor antagonists. This glutamate release, as outlined previously, can lead to the development of pain (Vanderah et al., 2000) via the induction of central sensitization.

Glial Effects of Opioid Administration

As with SCI, opioid administration has effects at both a neuronal and glial level. The effects of opioids on glia are mediated by binding to both classic and non-classic opioid receptors. On the classic side, microglia express kappa- (Chao et al., 1996; for review see Bidlack et al., 2006) and mu-opioid receptors (Chao et al., 1997; Dobrenis et al., 1995). In addition, opioids bind to non-classic toll-like receptors present on microglia, astrocytes, and neurons.

Aberrant glial activation—Microglial activation resulting from classic opioid receptor binding yields the same consequence as microglia activation resulting from SCI. Both cause the release of pro-inflammatory cytokines IL-1, IL-6, and tumor necrosis factor alpha (TNFα) (see; DeLeo & Yezierski, 2001; Milligan et al., 2001; Watkins et al., 2001a, b). The endogenous release of IL-1 β, TNFα, and IL-6 has been demonstrated to oppose the analgesic effects of opioid administration, leading to reduced opioid efficacy (Hutchinson et al., 2008b).

Similarly, astrocytes express mu-, delta-, and kappa-opioid receptors (Eriksson et al., 1990; Dobrenis et al., 1995; Thorlin et al., 1998) and, when activated, can release excitatory amino acids, NO, ROS, pro-inflammatory cytokines, chemokines, and prostaglandins (Raghavendra et al., 2002; Kreutzberg, 1996; Aloisi, 2001; Dong & Beveniste, 2001; DeLeo et al., 2004; Hutchinson et al., 2011). Following repeated systemic morphine administration, there is an increase in both glial fibrillary acid protein (GFAP) expression, indicative of increased astrocyte expression, and activation of proinflammatory cytokines in the lumbar spinal cord (Raghavendra et al., 2002; Song & Zhao, 2001). The release of pro-inflammatory cytokines (from microglia or astrocytes) further stimulates microglia to produce more pro-inflammatory cytokines, leading to mechanical hypersensitivity (allodynia) and further glial activation (Johnston et al., 2004; White et al., 2007; Watkins et al., 2001a; Scholz & Woolf, 2007). The effects of this opioid-induced glial activation can influence neuronal and non-neuronal cells and have implications for pain transmission and morphine analgesic efficacy (for review see O'Callaghan & Miller, 2010; Sweitzer & DeLeo, 2011).

TLR's—Exogenous opioids have also been demonstrated to bind in a non-classic fashion to the TLR4 receptor. Effects mediated by this receptor, in general, oppose the classic analgesic properties of opioid administration (Hutchinson et al., 2008 a, b, c), an effect that can be reversed by the administration of a TLR4 inhibitor (Hutchinson et al., 2010). Binding

of an agonist to this receptor activates signaling pathways similar to those of IL-1β, and is involved in the development of neuropathic pain, as discussed in the previous section.

Importantly, the glial expression of TLRs has been repeatedly documented, but it is also known these receptors (e.g. TLR2, TLR4, and TLR9) exist on neurons. Indeed, the neuronal expression of TLR2 is increased following extended morphine treatment (Li et al., 2010). Moreover, this TLR has been implicated in regulating neuronal apoptosis following morphine administration (Li et al., 2009). A study conducted by Li et al. (2009) demonstrated that overexpression of TLR2 in cell culture increased the number of apoptotic cells. Moreover, overexpression of β-arrestin, which negatively regulates activation of TLRs, inhibited the morphine-induced increase in the number of apoptotic cells (Li et al., 2009). Apoptosis occurs through the caspase-3 pathway, a pathway primarily involved in neuronal apoptosis. These results demonstrate that TLRs can have neuronally-mediated and glial-mediated effects that can affect pain and locomotor function following administration.

Summary

Acting through many of the same mechanisms discussed in the SCI section, opioid administration can contribute to functional pathologies. With prolonged administration, opioid-induced hyperalgesia develops via an NMDA-mediated mechanism, and counters morphine-induced analgesia. In addition, kappa-opioid receptor agonists induce detrimental effects on locomotor function (paralysis) in an NMDA-dependent manner. Furthermore, opioids are capable of influencing immune cell trafficking and chemokine/cytokine activity, activating many of the pathways discussed in respect to SCI-induced glial activation. Activation of these pathways can lead to the development of pain, and apoptosis. In the following section, the clinical implications of these shared mechanisms will be discussed.

Experimental Evidence for Synergistic Interactions between Opioids and SCI

From the previous sections, it becomes evident that several of the key cellular players involved in SCI are similarly activated following opioid administration (Table 1). For instance, SCI and opioid administration can lead to the release of excitatory amino acids, such as glutamate, which can lead to the development of pain and locomotor deficits. In addition, SCI and opioid administration modulate immune activation. Here, we will present data demonstrating that either a single administration or repeated administration of opioids following spinal injury can have adverse effects on recovery of locomotor function, pain, and general health.

Locomotor Function

Restoration of locomotor function has been a primary focus of research in SCI, and, while outside the scope of this review, there is a vast literature concerning strategies directed at this goal (Sandner et al., 2012; Sharma et al., 2011; Tohda & Kuboyama, 2011, Gilbert et al., 2011; Côté et al., 2011). There is, however, limited data examining the effects of opioid treatment on recovery of locomotor function. An early study by Faden and colleagues (1981) found the administration of an opiate antagonist, naloxone, 45-minutes after injury improved recovery from an experimental spinal contusion injury in cats, indicating a role of endogenous opioids in the pathology of injury. As discussed in the previous sections, dynorphin has been implicated in these motor deficits. The effects of exogenous opioid administration on locomotor function, however, have subsequently received little attention. This section will review existing literature on excitotoxicity and immune activation following injury as it relates to locomotor function, and will demonstrate the additional negative impact of opioid administration on recovery of locomotor function after SCI.

Neuronal Effects—In the preceding sections, the contribution of excitatory amino acids (e.g. glutamate, aspartate) to the pathology of SCI was outlined. In the acute phase of SCI, there is an increase in cell death mediated, in part, by these increased glutamate levels and NMDAR activation. Similarly outlined, was the activation of NMDARs via a morphine-induced downregulation of glutamate transporters within the dorsal horn of the spinal cord. Separately, either source of increased glutamate, as discussed previously, can lead to excitotoxic cell death. In the acutely injured spinal cord, however, the elevated levels of glutamate return to normal within 1.5 hours, and it is thought that, while dying cells can continue to release glutamate over days, the levels are not high enough to contribute significantly to excitotoxicity (McAdoo et al., 2005). However, by acting together to increase glutamate levels, it is possible SCI and opioid administration in the early phase of injury can exacerbate and sustain neuronal (Lepore et al., 2011; Nottingham & Springer, 2003) and/or oligodendrocytic (Xu et al., 2004; McTigue, 2008; Almad et al., 2011) cell death, which could undermine recovery of locomotor function following injury.

An exacerbation of cell death following morphine administration has been demonstrated in several studies conducted in our laboratory (Hook et al. 2007, 2009, 2011). In our initial study, we hypothesized that morphine might block the impaired locomotor recovery seen in previous studies with the administration of uncontrollable nociceptive stimulation after a moderate contusion injury (Grau et al., 2004). To test this, we administered systemic morphine before the onset of nociceptive electrical stimulation. Morphine did not block the negative effects of this stimulation, and, more surprisingly, further attenuated locomotor performance. In a follow-up study, it was found that intrathecal (i.t.) morphine, administered once, 24-hours after injury, significantly undermined recovery of locomotor function, even 3 weeks after administration (Hook et al., 2009). Histology revealed an increased lesion size in morphine-treated animals (Hook et al., 2007). Vehicle-treated animals did not show this increased lesion size, suggesting that the loss of neurons was the result of morphine treatment.

While the single administration of morphine in our studies (Hook et al. 2007, 2009) was not directly linked to either cell death or increased glutamate levels, other evidence suggests morphine could cause neuronal loss. For instance, repeated morphine administration, as outlined in the previous section, has been shown to induce apoptosis in the spinal cord (Atici et al., 2004; Mao et al., 2002). Further, morphine causes toxicity in neuronal cultures (Turchan-Cholewo et al., 2006). An NMDA-mediated role has been established in both of these effects. While these effects have previously only been observed with repeated morphine treatment, the rats studied are typically free of injury. As outlined, however, SCI also leads to release of glutamate and activation of NMDARs. After SCI, therefore, cell loss may be exacerbated or compounded by the administration of morphine. Thus even a single morphine administration in the acute phase of a spinal contusion injury may lead to an increase in cell death mediated by excitotoxicity, resulting in a morphine-induced reduction in locomotor recovery. It is crucial this issue be examined in further detail as it has serious implications for the use of opioids in the acute phase of SCI.

In addition to the effects of exogenous morphine treatment, studies have suggested that the endogenous KOR agonist, dynorphin, plays a role in the pathology of SCI (Krumins & Faden, 1986). Faden & Jacobs (1984) conducted a series of experiments in which they administered dynorphin peptides intrathecally and quantified the effects on motor function. They found dose-dependent decrements in motor function produced by dynorphin-(1–17), dynorphin-(1–13), dynorphin-(1–8), and α-neo-endorphin. This hindlimb paralysis was evident within 10 minutes of administration, and was not blocked or reversed by naloxone administration (Faden & Jacobs, 1984). Further studies demonstrated that spinal levels of dynorphin increase with the severity of SCI (Faden et al., 1985), and following prolonged

morphine administration (Mao et al., 2002). Moreover, inflammatory pain, such as that resulting from SCI, results in upregulation of spinal dynorphin (Nahin et al., 1989; Ruda et al., 1988; Przewlocki et al., 1992). As addressed in the previous section, dynorphin has been shown to produce negative effects (e.g. paralysis) through activation of the NMDAR. Together, these results suggest that increases in dynorphin expression levels following repeated opioid administration may be additive to those produced by SCI, and contribute to decreased locomotor recovery through NMDAR-mediated effects.

Overall, repeated morphine administration has been shown to increase NMDAR activity, induce apoptosis, and increase spinal levels of dynorphin. SCI, similarly, induces these same changes. Until now, these interactions have largely been overlooked, which is surprising considering the frequency of opioid use following SCI. From the evidence presented, it can be hypothesized that opioid administration in the early phase following injury contributes to the pathology of injury, resulting in decreased locomotor recovery. SCI, alone, may leave the spinal cord environment primed to a negative response to opioid administration, thus allowing synergistic effects. If this is the case, even a single opioid administration in the acute phase of injury may contribute to attenuated recovery of locomotor function, as demonstrated by Hook et al. (2007, 2009). These detrimental effects, however, may not stem from a single mechanism. Experimental evidence is needed to fully understand the effect of opioid administration on recovery of locomotor function following SCI.

Glial Effects—From the discussion in previous sections, it is evident that SCI activates an immune response and opioid administration can induce glial activation. Whether activated by opioid administration or SCI, microglia are also known to induce inflammatory responses and are thought to contribute to neurodegeneration. Minocycline treatment has, in fact, been shown to attenuate the number of morphine-induced apoptotic cells in the lumbar spinal cord by increasing anti-apoptotic elements (Hassanzadeh et al., 2011). Moreover, treatment with minocycline prior to and continuing for 7 days following a chronic constriction injury attenuated increased dynorphin levels in the DRG (Mika et al., 2010). Together, these studies suggest that inhibition of microglial activation following SCI and opioid administration may preserve locomotor function by reducing apoptosis. Accordingly, clinical use of minocycline is currently being tested in a phase I clinical trial for safety and efficacy in the treatment of SCI (see Gensel et al., 2011; CTID: NCT00559494). Importantly, this treatment may also be effective in pain relief (Cho et al., 2011).

IL-1β, a pro-inflammatory cytokine released from microglia has also been identified as a key player affecting locomotor function following SCI (Nesic et al., 2001). While it has been demonstrated that IL-1β levels increase as a result of injury, exacerbating these levels produces further trauma. Indeed, increasing the levels of IL-1β by administering intrathecal IL-1β for 3 days following SCI undermined recovery of locomotor function (Liu et al., 2008). Similarly, morphine administration has been shown to increase spinal levels of IL-1β in contused rats, relative to vehicle controls (Hook et al., 2011). As with the application of IL-1β, increased IL-1β levels resulting from morphine administration yielded an attenuation of locomotor recovery (Hook et al., 2011). Antagonizing the IL-1 receptor before morphine administration blocked morphine-induced locomotor deficits in SCI rats (Hook et al., 2011). It cannot be said for certain, however, that IL-1β is leading to these detrimental effects without evidence of functional IL-1β activity (e.g. inflammasome or caspase-1 activity; see Schroder & Tschopp, 2010), an issue that must be addressed in future studies.

Neural and immune consequences of SCI and opioid administration contribute to decreased locomotor function following injury. The timing (hours or weeks later), duration (single or repeated administration), route (intravenous, intrathecal, oral, subcutaneous), or dose of opioid administered could interact differently with the pathology of SCI depending on the

phase (acute (days 1–7), subacute (days 7–14), chronic (14+ days post injury)) or severity of injury. For example, in contrast to data demonstrating that morphine administration beginning 24-hours after injury undermines recovery of locomotor function (Woller et al., 2012), data indicate that morphine administration does not negatively affect locomotor function when administration begins 2 weeks following injury (Woller et al., in prep). This would suggest that there are windows in which morphine can be administered without negative consequences on locomotor function. These effects need to be fully examined in order to determine when opioid administration is more/less detrimental to the injured spinal cord.

Pathological Pain

Repeated opioid treatment can lead to tolerance, addiction, and enhanced pain through neural and immune interactions (Dworkin, 2007; Moalem & Tracey, 2006; Schomberg & Olson, 2012). While opioids are commonly known for their analgesic properties, evidence indicates that opioids can also contribute to the development of paradoxical pain with prolonged exposure (Wen et al., 2011; Przewlocki & Przwelocka, 2001). The following section will discuss how opioids can interact with SCI to influence the development of pain following injury. This has been studied, generally, in two categories: pain occurring as the result of central sensitization and as the result of gliopathy. As previously discussed in this review, opioids can also interact with and contribute to the development of each of these phenomena. Indeed, many of the mechanisms proposed to negatively impact locomotor function also underlie the development of pain following SCI. In this section, the development of pain from the standpoint of central sensitization and aberrant glial activation, resulting from injury and opioid administration, will be reviewed.

Neuronal Effects—As discussed in the previous section, opioid administration leads to the development of opioid-induced hyperalgesia through an NMDA-mediated process (Mao, 2002; Lee et al., 2011). This means that opioids applied for the treatment of pain could, paradoxically, exacerbate pain symptoms. Importantly, SCI induces several of the same molecular changes that have been implicated in the development of OIH: increased glutamate availability, leading to increased NMDAR activation and increased dynorphin levels. Furthermore, apoptosis, resulting from NMDAR neurotoxicity, occurs after both opioid administration (Mao et al., 2002; Ram et al., 2008; Ossipov et al., 2005; King et al., 2005; Belanger et al., 2002) and SCI, and can contribute to abnormal pain sensitivity. The OIH phenomenon, however, has not been addressed following SCI. It is hypothesized that administration of exogenous opioids following SCI may synergistically enhance the development of OIH, rendering opioids less effective in the treatment of chronic pain. Moreover, the development of OIH after SCI would constitute a pain different to that which led to the initiation of opioid therapy in the first place.

Separate from opioid-induced hyperalgesia, NMDAR activation is implicated in other aspects of pain following injury. Of particular relevance to both injury-induced pain and opioid reward is the NR2B subunit of the NMDAR. The NR2B subunit is localized to the forebrain, dorsal root ganglia, and superficial lamina of the spinal cord (Wu & Zhuo, 2009). Following a contusion injury, there is no change in the expression of NR2B compared to uninjured controls (Kim et al., 2012), but repeated morphine administration induces the upregulation of NR2B expression in the spinal cord (Guo et al., 2009). Spinal NR2B subunits of the NMDAR are known to play a role in the development of central sensitization and neuropathic pain via the induction of long-term potentiation (LTP) in dorsal horn neurons (Qu et al., 2009; Pedersen & Gjerstad, 2008). This implies that, in addition to those mechanisms listed above, repeated morphine administration following SCI can increase the development of pain through an NMDA-mediated mechanism.

Glial Effects—Glial cells also play a significant role in the development and maintenance of persistent pain following CNS injury (Graeber & Christie, 2012; Graeber, 2010; Hulsebosch et al., 2009; Watkins et al., 2007, Re & Dubner, 2010; Gosselin et al., 2010; Graeber & Streit, 2010). Accordingly, 'gliopathy' is a term coined by Hulsebosch (2008; 2012) to describe aberrant, dysfunctional immune activation following CNS injury, which can contribute to the development of neuropathic pain (see Schomberg & Olson, 2012; Milligan & Watkins, 2009). Further, Suter et al. (2007) have outlined potential glial-induced mechanisms involved in pain following injury (nerve, SCI, inflammation, etc.). It is important to note that various types of pain are manifest following injury, each with unique and shared mechanisms (for review, see Hulsebosch et al., 2009). Generally speaking, however, microglia become activated in response to factors produced by damaged cells and contribute to pain states through their recruitment to the spinal cord dorsal horn. Activation of microglia is positively associated with severity of allodynia following a moderate SCI or spinal nerve ligation (Detloff et al., 2008). Similarly, opioid-dependent activation of astrocytes and microglia affects the release of excitatory amino acids, NO, ROS, pro-inflammatory cytokines, chemokines, and prostaglandins (Raghavendra et al., 2002; Kreutzberg, 1996; Aloisi, 2001; Dong & Beveniste, 2001; DeLeo et al., 2004). Glial activation alone can lead to neuronal hyperexcitability, neurotoxicity, and chronic inflammation, however, these effects, as they are initiated by SCI and interact with opioid administration, have not been examined. Evidence suggests that the two pathologies, in combination, can lead to the development of pain through shared pathways.

Glial activation-related changes in glutamate transporters, whether they stem from SCI or opioid-administration, can also lead to NMDA-mediated excitotoxic cell death following SCI (Gwak et al., 2012), and this would contribute to the development of central sensitization. Minocycline treatment, shown to be an effective treatment for neuropathic pain, prevents the downregulation of GLT-1 and glutamate-aspartate transporter (GLAST) (Nie et al., 2010), thwarting the dysregulation of glutamate and glutamate-mediated excitotoxic cell death. Thus, following SCI and opioid administration, dysregulation of glutamate levels can contribute to both deficits in locomotor recovery and the development of pain.

Pain is often studied in the absence of other pathologies, and in the absence of treatment. As outlined here, however, there is likely to be an interaction between pain treatment and pathology that would significantly alter functional outcome. Moreover, in the case of SCI, the neuronal and immune environment of the spinal cord changes with time. It is important to know how potential therapeutic agents can interact with the pathology at each stage of injury. Opioids are administered following SCI without consideration or knowledge of the consequences their administration may have on locomotor recovery or the development of pain. Clearly, there is potential for a negative interaction between opioids being used as a treatment for pain and the further development of pain. While opioids are the focus of the current review, the same idea applies to other treatments. It is important to examine how the therapy can affect the pathology of disease or injury progression. Potentially, one therapeutic agent may prove to be more effective in the early stages of injury, and another in the chronic stages. These are issues that need to be addressed, as they have serious implications on quality of life in the SCI population.

General Health Concerns

Although spinal cord injury directly damages tissue at the level of the spinal cord only, its effects are seen throughout the CNS and periphery. While the preceding review focused on the neuronal and glial consequences of injury, it should be noted that SCI also induces a number of changes that can decrease the overall health of the individual. In fact, a leading

cause of death in both acute and chronic SCI is cardiovascular disease (Popa et al., 2010; Furlan & Fehlings, 2008). In addition, individuals can experience changes in blood pressure, heart rate, blood flow, hypotension, bradycardia, deep vein thrombosis, and are at long-term risk for coronary heart disease and atherosclerosis (see Furlan & Fehlings, 2008; Popa et al., 2010; Grigorean et al., 2009 for review). Frequently, patients with a cervical or high thoracic (above T6) injury will also experience autonomic dysreflexia, which is characterized by an increase in blood pressure in response to stimulation (noxious or not) below the level of injury, often bowel or bladder distension (see Weaver et al., 2002; Weaver et al., 2006; Rabchevsky, 2006). This sudden increase in blood pressure, while often within normal limits for healthy individuals, can be life-threatening (Furlan & Fehlings, 2008) in individuals with a SCI.

Similarly, in a population susceptible to bladder infections, pressure ulcers, pneumonia, gastrointestinal infections, and frequent hospitalizations, immune suppression is dangerous. In fact, infections are the leading cause of death in individuals with cervical or high thoracic injuries (DeVivo et al., 1989). In the SCI population, immune (non-microglial / astrocyte responses) suppression results from dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Morphine may further reduce the systemic immune response by decreasing lymphocyte levels (Weed et al., 2006). Clinically the effects of morphine on immunosuppression are also quite clear (see Odunayo et al., 2010; Eisenstein et al., 2006; Mellon & Bayer, 1998) as an opioid-induced immune suppression is thought to play a role in the increased incidence of bacterial infections in heroin addicts (Zhang et al., 2008). Experimentally, increased bacterial infection is also evident in the liver, spleen, kidneys, heart, and lungs of mice receiving morphine (Zhang et al., 2008). Imposing opioid-induced immune suppression on to a population vulnerable to infections should be considered before beginning treatment with an opioid.

Feng et al. (2005) also conducted studies examining the effects of morphine dependence and withdrawal on immune function. Alarmingly, they found a single injection of lipopolysaccharide (LPS), an endotoxin found in the outer membrane of gram-negative bacteria, 24-hours following the removal of a morphine pellet (in place 96 hours) is 100% lethal within 50 hours of administration (Feng et al., 2005). This was not seen with morphine withdrawal followed by saline injection, or with the LPS alone group. LPS is known to exert effects through TLR4, leading to the release of pro-inflammatory cytokines (for review see Hutchinson et al., 2011). Of the many cytokines activated, the increase in mortality appears to be related to increases in TNF-α, as treatment with an anti-TNFα antibody at the time of LPS administration and again 3 hours later decreased mortality (Feng et al., 2005). This is significant as any withdrawal from opioid treatment for pain following SCI, in the presence of a bacterial infection, can leave the individual at higher risk for sepsis and, possibly, death.

Even in the absence of withdrawal, morphine administration can increase mortality. Headrick and associates (1995) reported increased mortality with administration of the opioid active dynorphin (1–17), but not with the opioid-inactive dynorphin (2–17). A single dose of morphine 24-hours following a thoracic contusion injury has also been linked to increased mortality in rats when given at the time of noxious electrical stimulation (Hook et al., 2007, 2009). Nearly 50% of subjects treated with morphine and electrical stimulation died, while none treated with saline did. Moreover, morphine-dependent mortality was seen when the drug was no longer pharmacologically active, suggesting an indirect effect of treatment. A follow-up study showed increased mortality with a single intrathecal dose of morphine given in the acute phase of SCI and in the absence of nociceptive stimulation (Hook et al., 2009). While not statistically significant, this result is still startling. In humans,

nociceptive stimulation (e.g. from tissue damage and peripheral injuries) commonly occurs at the same time as SCI (Sekhon & Fehlings, 2001).

In addition to immune suppression and mortality, addiction is a significant concern when using drugs of abuse to treat pain after SCI. Previous studies addressing the addictive properties of morphine in the context of pain treatment suggest animals experiencing neuropathic (Ozaki et al., 2002) or arthritic (Lyness et al., 1989) pain are less likely to become addicted to morphine. Our recent studies, however, examining the addictive potential of morphine following a contusion SCI suggest otherwise. Initially, we demonstrated that animals with a moderate contusion injury show an *increased* preference for a morphine-paired context relative to sham and intact controls in the acute phase of SCI, suggesting an increased addictive potential for morphine (Woller et al., 2012). This increased preference is, however, not solely indicative of addictive potential. Further examination of the addictive potential of morphine, using a self-administration paradigm yielded dose-dependent effects (Woller et al., 2012). During self-administration sessions, conducted on days 1–7 post injury, rats had access to either a low, moderate, or high concentration of morphine. At a moderate concentration, contused rats self-administered significantly less morphine than sham or intact animals. When given access to a high concentration, however, injured rats quickly administered the entire amount available to them (30 mg), a behavior indicative of addiction. This dose, administered in approximately 4 hours, far exceeds that required for analgesia (Hook et al. 2007; 2009). Together these data concur with those collected in spinal nerve ligation studies, suggesting that the efficacy of muopioid receptor agonists for maintaining self-administration shifts to the right after spinal injury. However, escalating doses of morphine, with the potential development of analgesic tolerance, may increase the potential for addiction after SCI.

Opioid administration has effects throughout the body following SCI, including attenuation of locomotor function, facilitation of pain development, suppression of immune activation, and the potential for addiction. Even without the negative effects related to pain and locomotor function, opioid-induced susceptibility to infection and HPA dysfunction are serious in individuals with a spinal cord injury. Additionally, any withdrawal from opioids, as may occur throughout the night in an individual using an opioid for the treatment of SCI-related pain, can be dangerous, as it has been linked, experimentally, to increased mortality. Caution is clearly warranted when opioids are used to treat pain after SCI.

Concluding Remarks

Opioids have long been a standard in the treatment of pain following SCI. In this review, however, we argue that opioid administration can interact with SCI pathology by exacerbating excitotoxicity and glial activation to negatively impact locomotor recovery, pain, and general health. In the absence of descending inhibition, the spinal cord may be particularly vulnerable to increased levels of glutamate, resulting in NMDA-mediated excitotoxicity initiated by classic and non-classic opioid receptor activation, and resulting in detrimental effects. Nonetheless, for patients faced with a lifetime of intractable pain, opioids as effective analgesics cannot simply be removed as a treatment. For this reason, research is needed to develop guidelines for the safe use of these agents following injury.

Indeed, dose-dependent effects on recovery of locomotor function have been seen with morphine administration via either an intrathecal or intravenous route. Hook et al. (2009) found that a single 90μg, but not 30μg, intrathecal administration of morphine attenuates recovery of locomotor function. Similarly, Woller et al. (2012) have shown that administration of high amounts (50–100 mg/kg/day for 7 days) of intravenous morphine, a more clinically relevant route of administration, also results in the attenuation of locomotor

function and decreased weight, while the administration of lower amounts (<50 mg/kg/day) only results in weight loss. Considering patients are often given 120 mg/kg morphine (Chu et al., 2006) for the treatment of pain initially, with doses escalating as needed for pain relief, this result is concerning. Together, this data suggests high doses of morphine administered either intrathecally or intravenously in the acute phase can have adverse consequences on recovery of locomotor function following experimental SCI. Doses given clinically in this phase of injury should be carefully monitored.

Equally important is the time at which opioid administration begins. The acutely injured spinal cord environment differs from that of the chronic phase. As discussed in this review, opioid administration in the acute phase can exacerbate the pathology (e.g. increase excitotoxicity, increase glial activation) of SCI. In the chronic phase of injury, however, many of the inflammatory and endogenous opioid responses have subsided. Administration of opioids in the chronic phase of injury, then, may not be as detrimental and may not lead to an attenuation of recovery of locomotor function. Indeed, preliminary data suggests intrathecal or intravenous morphine administered in the chronic phase (Days 14 + post injury) of injury, when locomotor recovery has reached a plateau, does not impact locomotor function (Woller et al. in preparation). Animals, given 90μg intrathecal morphine 14-days following SCI do not show an attenuation of recovery even two weeks following administration. These results suggest morphine administration may be most detrimental to recovery of locomotor function when administered soon after injury.

Apart from monitoring dose, route, and phase of injury in which morphine is administered, research is needed to examine potential drug combinations that can improve the analgesic efficacy of morphine while preventing the negative (e.g. decreased locomotor function, development of tolerance) consequences. Studies have shown that administration of an NMDA antagonist is an effective treatment for attenuation of both neuropathic pain and recovery of locomotor function. This treatment, however, is associated with unwanted side effects such as hallucination, dysphoria, and locomotor deficits, making it unsuitable for clinical use. In addition, while an NMDA antagonist has been successful in promoting recovery of function in animal models (Lonjon et al., 2010), the success in clinical trials is yet to be determined (Kwon et al., 2010). Thus, it is important to look at alternative therapies. For instance, Kim et al. (2012) found that treatment with an NR2B subunit specific antagonist produces fewer unwanted side effects and reverses mechanical allodynia when administered two weeks following a contusion injury. In addition, a number of studies have shown that treatment with an antagonist for the NR2B subunit blocks morphine-induced reward (Ma et al., 2011; Narita et al., 2000; Ma et al., 2006). For instance, Ma et al. (2006a) showed that treatment with Ifenprodil, an antagonist specific for the NR2B subunit of the NMDA receptor, decreased a morphine-induced conditioned place preference. The same treatment did not decrease a place preference for natural reinforcers (e.g. food consumption or social interaction). Thus, coadministration of an NR2B subunit antagonist with morphine could be a potential treatment for pain following SCI and could lower the abuse potential of morphine.

Another potential treatment for pain involves the reversal of synaptic LTP. Central sensitization and LTP share many common mechanisms, and are thought to be a synaptic mechanism of memory (Colingridge, 1987; Ji et al., 2003). Similarly, the induction of LTP is a model for some forms of hyperalgesia and neuropathic pain (Sandkühler, 2009; Costigan et al., 2009). A recent study suggests that LTP can be reversed by a brief, high dose of the opioid agonist remifentanil (Drdla-Schutting et al., 2012). In this study, hyperalgesia in rats was induced by an injection of capsaicin into the hindpaw. Capsaicin injection resulted in signs of mechanical hyperalgesia that were partially reversed by a 1-hour, high-dose (30 μg/kg^{-1}, followed by 450 μg/kg^{-1}/hr^{-1}, i.v.) remifentanil infusion

(Drdla-Schutting et al., 2012). This effect was maintained even after the short-acting opioid agonist had cleared the system. Administration of a second dose completely reversed the hyperalgesia (Drdla-Schutting et al., 2012). Normally, continuous opioid treatment is needed for effective pain relief, often resulting in the development of tolerance, and the need for escalating doses. Here, two doses of a short-acting opioid completely reversed mechanical hyperalgesia. The behavioral evidence of this reversal provides an exciting potential therapy for pain, and should be investigated on a longer time scale and in other models of pain, such as neuropathic pain resulting from SCI.

In addition, activation of the TLR4 is responsible for many of the negative effects of morphine administration. It has been demonstrated that the blockade of TLR4 increases opioid efficacy (Hutchinson et al., 2007; Johnston et al., 2004), and blocks other negative effects of opioids such as respiratory depression (Hutchinson et al., 2008a; Hutchinson et al., 2008b; Hutchinson et al., 2008c). Yet as discussed previously, while blocking TLR4 can decrease pain and increase opioid efficacy, it can contribute negatively to recovery of locomotor function after SCI. Potentially, if the blockade of TLR4 activity was via selective inhibition of microglia (e.g. via minocycline), it may prove an effective treatment strategy. The timing of administration of a TLR4 antagonist may also be critical: administration of an antagonist may be beneficial in conjunction with morphine in the chronic, but not acute, phase of injury. Whether antagonizing TLR4 with (+)-naloxone can be used repeatedly with morphine for the treatment of pain (and prevention of addiction) has yet to be determined. As combination drug therapies are being used for the treatment of chronic pain with some success (for review, see Mao et al., 2011), these possibilities need to be explored.

Given the numerous negative consequences associated with opioid administration in the spinally injured population, clinical opioid use must be further evaluated and refined. However, the use of opioids is not only relevant to SCI pain. In fact, the definition of neuropathic pain has recently been changed and now only includes pain resulting from “lesions or disease of the somatosensory system” (Jensen et al., 2011). Thus, central pain resulting from stroke, or even TBI, falls under the same treatment guidelines as those for pain resulting from SCI. While the pathology differs from that of SCI, there may be similar concerns related to opioid use in other central models of pain or disease that need to be considered before initiation of an opioid treatment regimen.

Acknowledgments

The authors would like to thank James Grau, Sandra Garraway, Miriam Aceves, Sioui Maldonado Bouchard, and Mary Katherine Funk for their comments on a previous version of this paper.

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Highlights

- Opioid administration may synergistically contribute to the pathology of spinal cord injury
- Opioids increase the development of pain and decrease locomotor function after SCI
- Clinical opioid use must be evaluated and refined

Table 1

This table summarizes both the beneficial and adverse consequences of opioid administration in the Acute (D1–7) and Chronic (D7+) phases of spinal cord injury. In both phases, opioid administration results in pain relief. However, this pain relief is accompanied by numerous consequences.

Consequence of SCI or Opioid Administration	**Mechanisms Common to SCI and Opioid Administration**	
Decreased locomotor function	Excitotoxic cell death	Increased extracellular glutamate
		Increased NMDAR activation
		Increased dynorphin levels
	Increased glial activation	Release glutamate, ATP, CGRP, pro-inflammatory cytokines, ROS, NO
	Apoptosis	Initiated via activation of caspase-3, increased Bax and decreased Bcl-2 Causes release of pro-inflammatory cytokines
Pain development	Central sensitization	Increased NMDAR activation
		Increased extracellular glutamate
	OIH	Increased NMDAR activation
		Increased glutamate availability
		Increased spinal dynorphin
	Increased glial activation	Release glutamate, ATP, CGRP, pro-inflammatory cytokines, ROS, NO, activation of MAPK pathways, TLR's
Increased risk of infection	Immune suppression, HPA dysregulation	Decreased lymphocyte levels
Mortality	Increased glial activation	Increased pro-inflammatory cytokines