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Review

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.

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Introduction

Neuropathic pain, resulting from injury, significantly impacts quality of life in people living with spinal cord injury (SCI) (Cairns et al., 1996; Celik et al., 2012; Harden and Cohen, 2003; Wetering et al., 2010). 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 will discontinue opioid treatment (Moore and 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; 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 (Gwak and Hulsebosch, 2011a, 2011b; Gwak et al., 2012; Hulsebosch, 2008).

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 and Ho, 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 min after injury, remain elevated for an hour, and return to normal over a period of 1.5 h (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 (Matos et al., 2012; Tsai 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., 1981, 1988; Gómez-Pinilla et al., 1989; Mills et al., 2000, 2001; Wrathall et al., 1994, 1996, 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 (Artola and Singer, 1987; Woolf and Thompson, 1991). 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, 2007, 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