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BRAIN RESEARCH

Research Report

Behavioral characterization and effect of clinical drugs in a rat model of pain following spinal cord compression

*Aldric Hama**, *Jacqueline Sagen*

University of Miami, Miller School of Medicine, The Miami Project to Cure Paralysis, 1095 NW 14th Terrace (R-48), Miami, FL 33136, USA

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ABSTRACT

Chronic pain symptoms, including spontaneous unevoked pain and evoked cutaneous hypersensitivity, appear following spinal cord injury (SCI). A reliable preclinical model is needed to develop effective analgesic treatments for these symptoms. A previously described rat model of SCI pain was modified and behaviorally characterized and used to test clinically available drugs. A segment of the mid-thoracic spinal cord was compressed for 60 s with a micro-vascular clip. The sensitivity of the hind paws to noxious heat (Hargreaves test), innocuous tactile (von Frey filaments), and cooling (acetone) stimuli were determined once per week beginning 1 week following spinal compression. Spinal cord compression led to long lasting hypersensitivity to stimuli, lasting for at least 12 weeks post-surgery. Systemic baclofen, gabapentin, tramadol, and morphine dose-dependently attenuated tactile hypersensitivity. No effect on tactile hypersensitivity was observed with amitriptyline, carbamazepine, rofecoxib, and diazepam. Baclofen and morphine also dose-dependently ameliorated heat hypersensitivity. In contrast, no effect on heat hypersensitivity was observed with amitriptyline, carbamazepine, diazepam and gabapentin. The current data suggest that the model can potentially differentiate those drugs with analgesic efficacy from those that do not have efficacy in SCI pain. Thus, the model may be useful for rapid screening and clinical translation of promising SCI pain therapies.

1. Introduction

Despite advances in understanding the mechanism of acute pain, neuropathic pain resulting from spinal cord injury (SCI) remains difficult to treat. Following SCI, a majority of patients suffer from long-lasting pain, many of whom characterize the pain as either moderate or severe (Eide, 1998; Nicholson, 2004). A mix of pain resulting from nerve or spinal cord trauma and musculoskeletal pain may exist within the SCI pain patient, presenting in dermatomes either above or at the level of injury (Finnerup and Jensen, 2004). Below-level SCI pain is thought to be of central origin, attributed to lesioning or dysfunction of both white and grey matter (Finnerup et al., 2003, 2007). Patients with below-level unevoked pain describe it as 'burning' or 'shooting'. Abnormal responses to cutaneous stimulation with either a noxious or innocuous stimulus may also be found in the painful area (Eide et al., 1996; Finnerup et al., 2007). The intensity and persistence of below-level pain are such that they diminish participation in rehabilitation programs and degrade quality of life.

In parallel with improved heath care for SCI patients, there have been numerous preclinical advances in understanding

* *Corresponding author*. Fax: +1 305 243 3923.
E-mail address: ahama@med.miami.edu (A. Hama).

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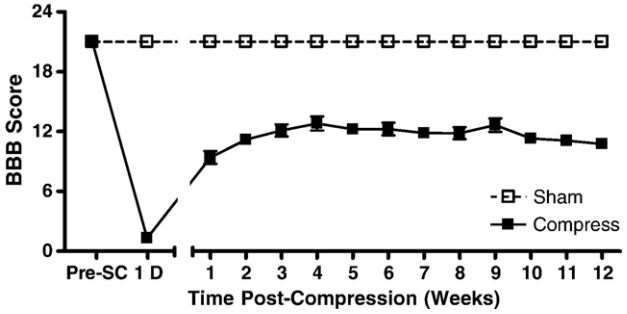

Fig. 1 – Effect of spinal cord compression injury on locomotor function. Time (in weeks) following spinal compression is shown on the horizontal axis and Basso, Beattie, and Bresnahan (BBB) locomotor rating is shown on the vertical axis. Rats were tested prior to spinal compression ("Pre-SC"), 1 day (1 D) after surgery and then weekly following compression for 12 weeks. Data are mean ± S.E.M. Compress, *n* = 20 rats. Sham, *n* = 8.

the mechanism of spinal cord repair and in developing potential therapies (Kastin and Pan, 2005; Kulbatski et al., 2005). While the breadth of the treatments ranges from molecular to cellular-based strategies, the primary objective of all of these is the re-establishment of normal connections by either regeneration of damaged spinal axons or encouraging spared axons to sprout and re-innervate toward the appropriate target (Deumens et al., 2005). However, creating new neural connections, particularly in the spinal dorsal horn, underlies persistent abnormal pain perception (Woolf et al., 1992). Sprouting has been reported in cervical dorsal horn following implantation of stem cells at a thoracic level SCI (Hofstetter et al., 2005). In these rats, increased fore paw sensitivity to cutaneous stimulation was reported. Thus, in conjunction with functional recovery, there may be sprouting-associated persistent pain as an unintended side-effect of the various spinal cord regenerative treatments, analogous to the uncontrollable dyskinesias observed following transplantation of fetal cells into Parkinson's patients (Ma et al., 2002). It is crucial that efficacious treatments for SCI pain be developed in advance of the initiation of clinical trials that aim to restore spinal cord functionality, such that patients are able to complete the entire treatment and rehabilitation course.

There are limited pharmacological options for chronic SCI pain. One issue is the lack of a validated model of SCI pain that could provide clinicians with a rational basis for initiating clinical trials of promising novel therapeutics. There are rat models of SCI that display clinical symptoms, including spontaneous pain-related behavior, but the predictive validity of these models is not clear (Chiou-Tan et al., 1996; Xu et al., 1992). Recently, pain-related symptoms were reported in a rat model of SCI pain induced by a brief compression of the spinal cord (Bruce et al., 2002; Oatway et al., 2004). The current study further characterizes the symptoms over time and evaluates the efficacy of clinically relevant analgesic drugs. An advantage of this model over previously described below-level SCI pain models is that the compression evokes several pathological processes including ischemia, incomplete axonal loss, and cell death. Also, the severity of the injury does not preclude testing of the hind paws at relatively early stages, which may be a critical window for most successful rehabilitation outcomes (Bunge et al., 1993; Kakulas, 1987). Thus, the spinal compression model offers an opportunity to evaluate the effects of clinically relevant drugs that have yet to be tried in below-level SCI pain, and, eventually, novel therapeutics.

2. Results

2.1. *BBB scores*

Prior to spinal cord compression, the BBB locomotor rating for rats was 21, indicating coordinated fore and hind paw movement, consistent toe clearance from the walking surface and trunk stability (Fig. 1) (Basso et al., 1995). One day after compression surgery, the BBB rating was 1.3 ± 0.6, which indicated hind limb flaccid paralysis with slight movement of the hip and/or knee. One week after compression surgery, rats showed markedly improved locomotor function, where BBB ratings increased to 9.4 ± 0.6, which indicated plantar placement of the paw with weight support or stepping with the dorsal but not plantar surface of the hind paw. At 2 weeks post-compression, BBB ratings increased to 11.2 ± 0.4, indicating frequent hind paw weight support and hind paw plantar stepping. No further improvement of locomotor function was observed following compression surgery, the mean BBB rating not increasing beyond 12 (frequent to consistent weight-supported plantar stepping and occasional hind and fore paw coordination) for the 12 week observation period.

By contrast, rats following a sham surgery did not show decreased locomotor function at any time (Fig. 1).

2.2. *Heat*

Although not specifically quantified, many of the rats after spinal compression displayed licking of the hind paw and prolonged hind paw flinching following stimulation, particularly following application of heat. Some rats displayed unilateral and other rats displayed bilateral mechanical

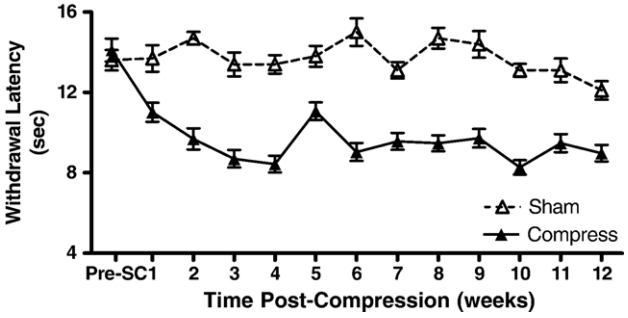

Fig. 2 – Effect of spinal cord compression on hind paw sensitivity to noxious heat over time. Time (in weeks) following spinal compression is shown on the horizontal axis and withdrawal latency (in seconds) is displayed on the vertical axis. Rats were tested prior to spinal compression ("Pre-SC") and weekly following compression for 12 weeks. Data are mean ± S.E.M. of the combined left and right hind paw latencies. Compress, *n* = 20 rats. Sham, *n* = 8.