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Research Report

Pregabalin attenuates place escape/avoidance behavior in a rat model of spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) pain in humans is difficult to treat, and the lack of valid methods to measure behavior comparable to the complex human pain experience preclinically represents an important obstacle to finding better treatments for this type of central pain. The place escape/avoidance paradigm (PEAP) relies on the active choice of an animal between its natural preference for a dark environment or pain relief, and it has been suggested to measure the affective-motivational component of pain. We have modified the method to a T10 spinal cord contusion model (SCC) of at-level central neuropathic pain in Sprague–Dawley rats. In order to demonstrate sensitivity to change in escape/avoidance behavior and thus the applicability of the PEAP method to predict drug efficacy, we investigated the effect of pregabalin (30 mg/kg) treatment in a randomized design. SCC animals displayed increased escape/avoidance behavior postinjury, indicating at-level mechanical hypersensitivity. Second, we found no correlation between state anxiety levels in SCC animals (elevated plus maze) and PEAP behavior, suggesting that the PEAP measurement is not biased by differences in anxiety levels. Third, we demonstrated a decrease in escape/avoidance behavior in response to treatment with the analgesic drug pregabalin. Thus, the PEAP may be applicable as a surrogate correlate of human pain. In conclusion, the primary finding in this study was a sensitivity to change in escape/avoidance behavior induced by pharmacological modulation with analgesics, supporting the use of the PEAP as a central outcome measure in preclinical SCI pain research.

1. Introduction

Spinal cord injury (SCI) pain in humans is difficult to treat (Murphy and Reid, 2001; Norrbrink and Lundeberg, 2005; Siddall et al., 2003; Widerstrom-Noga and Turk, 2003). At the same time, the lack of valid methods to measure behavior comparable to the complex human pain experience preclinically represents a major obstacle to finding better treatments for this type of central pain (Blackburn-Munro, 2004; Rice et al., 2008; Vierck et al., 2008). Furthermore, measuring simple withdrawal reflexes after SCI cannot be recommended due to development of the spastic syndrome (Baastrup et al., 2010). The place escape/avoidance paradigm (PEAP) is a behavioral test in which the animal is confronted with the choice between a dark environment (natural preference), combined with repeated stimulation of an area suspected to be painful, and an aversive bright environment with escape of such stimulation. The PEAP thus requires cortical processing and

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Abbreviations: SCI, spinal cord injury; SCC, spinal cord contusion; EPM, elevated plus maze; PEAP, place escape/avoidance paradigm

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has been suggested to measure the affective-motivational component of pain possibly mediated by the anterior cingulate cortex (LaBuda and Fuchs, 2000a, 2007; LaGraize et al., 2004, 2006). The method has been used in rodent models of inflammatory (Boyce-Rustay et al., 2009; Uhelski and Fuchs, 2009; Wilson et al., 2007) and peripheral neuropathic pain (LaBuda and Fuchs, 2000b; Pedersen and Blackburn-Munro, 2006) and has been shown to be sensitive to treatment with clinically relevant analgesics. In a series of pilot studies, we have modified the method (regarding reference site, initial habituation, stimulation intensity, etc.) to a spinal cord contusion model (SCC) of central neuropathic pain. The model results in a bilateral injury and altered sensitivity to mechanical stimulation of the paws and hindquarter and presence of injury-induced at-level pain-like behavior (Baastrup et al., 2010). In order to demonstrate sensitivity to change in escape/avoidance behavior in animals with a spinal cord contusion (SCC) and thus assess the applicability of the PEAP method to detect drug efficacy, we investigated the effect of a single treatment of pregabalin (30 mg/kg), the current first-line therapy for clinical SCI pain (Baastrup and Finnerup, 2008; Finnerup et al., 2010; Siddall et al., 2006; Vranken et al., 2008).

It has previously been suggested that the ability to learn an escape and avoidance task may be influenced by the animal's state of anxiety and that more anxious animals demonstrate increased avoidance and fear-like responses (Ho et al., 2002). Anxiety is a frequent comorbidity in different pain conditions including SCI (Haythornthwaite and Benrud-Larson, 2000; Narita et al., 2006; Nicholson and Verma, 2004; Roeska et al., 2008; Wallace et al., 2008), making it an important possible confounder.

The purpose of the present study was to evaluate the effect of pregabalin on PEAP behavior following SCI.

The risk that the results obtained with the PEAP test may be confounded by state anxiety was investigated by measuring the anxiety level of the animals prior to PEAP testing using the elevated plus maze (EPM) (Pellow et al., 1985).

2. Results

The average time to a locomotor score ≥4 was 12 days for SCC animals and 1 day for sham animals. Locomotor recovery was monitored throughout the study and remained stable. Sporadic mild spontaneous spasms were initially observed in SCC animals. There were no significant differences in general health (e.g., weight and fur coat condition) or behavior between injury groups, nor were any signs of distress observed (e.g., self-inflicted abrasions, spontaneous or handling-evoked vocalization). There was no difference in the total distance travelled in the openfield between the SCC and sham animals (no drug application), which could have indicated difference in general locomotion and thus the ability of the two groups to perform comparably in the EPM and the PEAP.

2.1. *Mechanical hypersensitivity and anxiety*

All 14 SCC animals developed at-level mechanical hypersensitivity following injury (>25% decrease in at-level mechanical sensitivity threshold compared with the preinjury level) measured by a 76% average decrease in at-level mechanical sensitivity threshold (Fig. 1A), which was significantly different compared with preinjury ($p<0.001$, Wilcoxon signed-rank sum test) and with sham animals postinjury ($p<0.001$, Mann–Whitney rank sum test). No animals were thus excluded from the study. Furthermore, SCC animals spent significantly less time in the open arms of the EPM

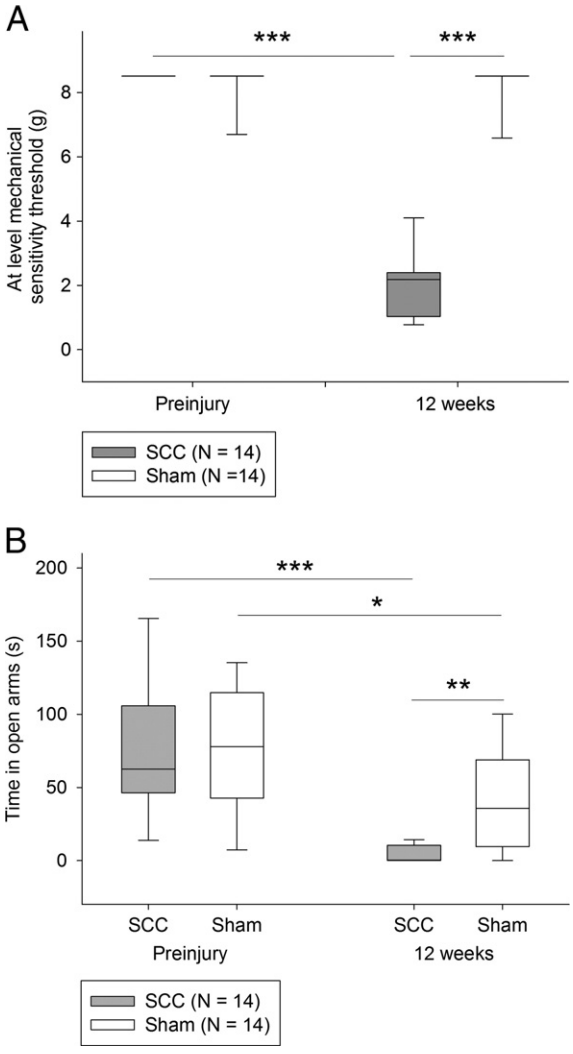

Fig. 1 – At-level mechanical sensitivity. Development of at-level mechanical hypersensitivity (A) and anxiety (B) after a T10 12.5 mm SCC injury in female Sprague–Dawley rats. Boxes represent medians with 25th and 75th percentiles; error bars 5th and 95th percentiles. *$p<0.05$, **$p<0.005$, ***$p<0.001$. (A) At-level mechanical sensitivity thresholds are decreased in the SCC group postinjury compared with sham animals ($p<0.001$, Mann–Whitney rank sum test) and preinjury ($p<0.001$, Wilcoxon signed-rank sum test). (B) The time spent in the open arms of the EPM is decreased in both SCC and sham animals following an injury compared with preinjury ($p<0.001$, SCC and $p=0.013$, Sham; Wilcoxon signed-rank sum test). Postinjury, the time in open arms was lower for SCC animals than for sham animals ($p=0.002$, Mann–Whitney rank sum test).