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Coexisting mechanical hypersensitivity and anxiety in a rat model of spinal cord injury and the effect of pregabalin, morphine, and midazolam treatment

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ABSTRACT

Background and purpose: Spinal cord injury (SCI) has detrimental consequences that include chronic neuropathic pain, which is seen in 40-50% of patients, and symptoms of anxiety and depression, which affect 13-45% of SCI patients. The coexistence of pain, anxiety, and depression is known from other neuropathic pain conditions, but the relationship between these symptoms is not clear and has not been investigated in a preclinical model of SCI so far.

The aim of this study was to investigate anxiety-like behavior and at-level mechanical hypersensitivity following experimental spinal cord contusion (SCC) in female Sprague-Dawley rats, and the effects of analgesic and anxiolytic drugs.

Methods: Mechanical sensitivity and elevated plus maze (EPM) behavior were measured pre- and postinjury in SCC and sham animals. Pregabalin 30 mg/kg, morphine 3 mg/kg, midazolam 0.5 mg/kg, and 0.9% NaCl were evaluated in a randomly allocated, blinded balanced design.

Results: SCC animals developed persistent at-level mechanical hypersensitivity and decreased open arm activity in the EPM, which indicates an anxiety-like state. Pregabalin, a dual-acting analgesic and anxiolytic drug reduced both hypersensitivity and anxiety-like behavior, while the analgesic drug morphine only reduced hypersensitivity. The anxiolytic drug midazolam in the dose used had no effect on either parameter.

Conclusions: SCC animals developed long lasting coexisting at-level mechanical hypersensitivity and anxiety-like behavior, but there was no evidence to support a causal relationship between pain and anxiety following SCI.

Implications: The findings that at-level mechanical hypersensitivity and anxiety-like behavior develops concomitantly in the spinal cord contusion models and that both symptoms is persistent provide basis for further investigation of the mechanisms and connection behind these two clinically relevant symptoms after injury to the central nervous system.

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1. Introduction

A spinal cord injury (SCI) may have many detrimental consequences including chronic neuropathic pain [1], which is seen in 40–50% of patients [2–4], and symptoms like anxiety and depression, which affect 13–45% of SCI patients [5–9]. Other serious problems include pareses, spasticity and spasms, decreased bladder and bowel function, and autonomic dysfunction. The coexistence of pain, anxiety and depression is known from other neuropathic pain conditions [10–15], but the underlying mechanisms are not clear, although a common pathophysiological mechanism seems unlikely [16–18].

The intensity of pain in SCI has been associated with increased levels of anxiety [19], and Nicholson et al. found a significant difference in pain severity when comparing those with and without possible clinical levels of anxiety and depression [8]. However, the relation between pain and anxiety is complex, and anxiety levels in SCI have also been shown to relate to, e.g., gastrointestinal symptoms [20], autonomic dysfunction [21], severe complications, and level of autonomy [6], and to be more affected by other consequences of SCI than pain [22].

Given the unclear relationship between symptoms of anxiety and pain in SCI, there is a need for additional research, and preclinical studies may represent a novel approach. Preclinical pain research has frequently utilized simple measurements such as paw withdrawal or other reflexive behaviour as the only outcome measure, representing, at best, only the sensory component of the pain

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Abbreviations: SCI, spinal cord injury; SCC, spinal cord contusion; EPM, elevated plus maze.

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Table 1
Distance travelled in the open field and time spent in the EPM by animals with a 12.5 mm SCC at bone segment T10. Data is presented as average distance (cm) ± S.E.M.

	Total distance (cm) open field		Open arms (cm) elevated plus maze	
	SCC	Sham	SCC	Sham
Preinjury	4009 ± 91	3942 ± 151	76.58 ± 9.74	74.73 ± 8.03
4 weeks	2277 ± 177*	2478 ± 213*	35.72 ± 11.83*	34.58 ± 8.10*
6 weeks	–	–	13.58 ± 5.16*	58.95 ± 8.49
12 weeks	854 ± 58*	969 ± 93	10.01 ± 3.66*	39.73 ± 8.28*
NaCl	2187 ± 179	2249 ± 261	8.35 ± 4.11	74.41 ± 16.93
Pregabalin	2139 ± 164	2597 ± 269	17.20 ± 8.42#	59.27 ± 16.64
Morphine	2249 ± 249	2765 ± 182	2.63 ± 1.87	56.46 ± 20.11
Midazolam	1895 ± 212	1712 ± 272##	10.10 ± 3.97	68.45 ± 11.28

The total distances for both SCC and sham animals were not different at any time point (Injury group: $p = 0.564$; mixed model) or between treatments (Injury group: $p = 0.290$, mixed model). There was a significant effect of time ($p < 0.001$, mixed model) and treatment ($p = 0.008$, mixed model).

* $p < 0.05$ compared with preinjury measurement.

\# $p < 0.05$ compared with NaCl.

\## $p = 0.056$ compared with NaCl-treated sham animals.

experience [23,24]. In contrast, multiple different endpoints are recommended in clinical trials on pain conditions, including measurements of anxiety, depression, sleep disturbances, and quality of life [25]. Recently, focus on the importance of these comorbidities as well as on the need to include measurements of the affective-motivational component of pain has increased in preclinical research. Methodology has been updated with novel pain assays developed to measure the affective component of pain (e.g., the place escape/avoidance paradigm and operant escape) [26–29], and endpoints that measure symptoms such as anxiety are included (e.g., the elevated plus maze or the open field) [30,31], thereby attempting to bridge the gap between preclinical and clinical research.

Previous studies that have combined measurements of mechanical hypersensitivity and anxiety-like behaviour in models of neuropathic pain, e.g., partial nerve ligation [32,33], sciatic nerve ligation in mice [34] and rats [35], varicella zoster-associated pain [35], and HIV-associated neuropathic pain [36], have found significantly increased anxiety-like behaviour 0–4 weeks after injury. Moreover, analgesics reversed both mechanical hypersensitivity and anxiety, which supports the hypothesis that anxiety may be a consequence of persistent pain in these models. Other studies using the spinal nerve ligation model [37] and a mouse model of sciatic nerve ligation [38] did, however, not find significant signs of anxiety. No preclinical studies have so far investigated the relation between hypersensitivity and anxiety in a model of SCI or in an extended period including the later more chronic stage.

We have previously characterized the central pain syndrome following spinal cord contusion (SCC) in rodents. This clinically relevant model [39,40] resulted in persistent and robust evoked at-level mechanical hypersensitivity [23,29,41].

The aim of the study was to investigate whether anxiety-like behaviour could be observed following SCC, and if the anxiety-like behaviour would be present concomitantly with evoked at-level mechanical hypersensitivity. Furthermore, we compared the antihypersensitivity and analgesic and anxiolytic properties of a classical anxiolytic drug (midazolam), an analgesic drug (morphine), and a mixed anxiolytic and analgesic drug (pregabalin).

2. Results

2.1. General observations

A total of 42 animals were included in the study. The average time to a locomotor score ≥4 was 12 days for SCC animals and 1 day for sham animals. Sporadic mild spontaneous spasms were initially observed in SCC animals, but the mobility, evaluated by the total distance travelled in the open field, was similar for both SCC and sham animals at all times tested (injury group: $p = 0.564$, time: $p < 0.001$; mixed model) (Table 1). There were no significant differences in general health (e.g., weight and fur coat) or behaviour between the injury groups, nor were any signs of distress observed (e.g., self-inflicted abrasions, spontaneous or handling-evoked vocalization).

2.2. Development of mechanical hypersensitivity

The animals were tested for mechanical sensitivity preinjury and 4, 6, and 12 weeks postinjury. Preinjury, no difference between the injury groups was observed ($p = 0.131$, Student's t-test) (Fig. 1a). Following injury, SCC animals ($n = 20$) had significantly lower at-level mechanical sensitivity thresholds than sham animals ($n = 21$) ($p < 0.001$, mixed model excluding preinjury). At-level mechanical sensitivity thresholds of SCC animals were, in contrast to the sham animals ($p = 0.156$, mixed model), significantly decreased postinjury compared with preinjury ($p < 0.001$, mixed model) remaining low throughout the test period. The thresholds were on average decreased by 71% (8.51–2.46 g) in the SCC animals as compared with preinjury, and at 6 and 12 weeks postinjury, SCC animals had a 65% lower threshold than sham animals. One SCC animal did not develop any mechanical hypersensitivity and was thus excluded from the drug study.

2.3. Development of anxiety

Anxiety levels were determined by the time spent in the open arms of the EPM. Preinjury, there was no difference between the injury groups ($p = 0.884$, Student's t-test) (Fig. 1b). An overall effect of injury group was observed ($p = 0.036$, mixed model excluding preinjury), and both SCC and sham animals experienced an initial decrease in time spent in open arms 2 weeks postinjury ($p < 0.001$, SCC and $p = 0.003$, sham; mixed model contrast), with a further decrease in SCC animals at 6 weeks ($p = 0.017$, mixed model contrast) lasting throughout the test period. The decrease amounted on average to 85% at 6 and 12 weeks compared with preinjury. In sham animals, in contrast, there was no difference at 6 weeks compared with preinjury ($p = 0.101$, mixed model contrast), nor were the levels at 6 and 12 weeks significantly different ($p = 0.067$, mixed model contrast). SCC animals spent less time (76% on average) in the open arms compared with sham animals at both 6 and 12 weeks postinjury ($p < 0.001$ and $p = 0.003$ respectively, Student's t-test). Repeating the mixed model analysis including the total distance travelled in the EPM as a covariate did not affect the above conclusions.

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