The Effect of Chronic Mechanical Allodynia on Anxiety in the Chronic Constrictive Nerve Injury Pain Model in Rats

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Introduction

Clinically, chronic pain and affective disorders often occur as co-morbidities. We studied the development of anxiety in a model of chronic constrictive injury (CCI) to the sciatic nerve in Sprague-Dawley rats. The results presented here illustrate that the CCI model of chronic neuropathic pain alters the anxiety phenotype in Sprague-Dawley rats and this model may be useful for assessing the development of concurrent affective disorders over time.

Methods

Animals

- Female Sprague-Dawley rats (175-200g)

Sciatic Nerve Ligation (Chronic Constrictive Nerve Injury)

- Loose ligatures with 4.0 Chromic gut absorbable sutures tied around left sciatic nerve [Bennett and Xie. Pain 33(1) 1998]

von Frey Test for Mechanical Allodynia

- 2-3 weeks following sciatic nerve ligation
- von Frey filaments (0.4, 0.7, 1.2, 2.0, 3.6, 5.5, 8.5, 15g)
- If response is negative, next ascending filament is used
- If response is positive, next descending filament is used
- 50% Paw Withdrawal Threshold (PWT) calculated based on the pattern of positive and negative responses (e.g. 'xoxoxo') in vicinity of the threshold [Dixon 1980; Chaplan 1994]

Cold Plate

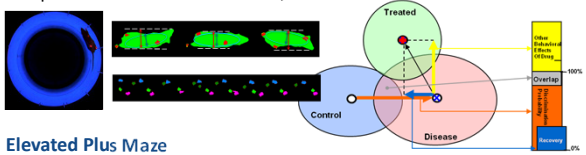
- Following an acclimation period, animals are placed on the cold plate apparatus (UGO Basile) with a temperature of 4°C
- Response latency indicated by a paw lift, paw lick, or paw shake

RotaRod

- On the first day, animals are trained to balance and walk on the rotarod apparatus which is rotating at a constant speed
- One the second day, animals are tested on the rotarod with an accelerating speed. The latency to fall from the rotarod is an indicator of motor function.

NeuroCube® System for Gait Analysis

- Animals were tested in the NeuroCube® System for 5 min
- Computer vision analyzed gait geometry and dynamics
- Algorithms de-correlate gait features and cloud plots show the separation between control, injured, and treated animals in an optimal discrimination feature space.



Elevated Plus Maze

- The EPM assesses anxiety. The maze (Hamilton Kinder) consists of two closed arms and two open arms forming a cross.
- Animals were placed in the center of the maze and the computerized system monitors their movement during a 5 min test

Results

von Frey Mechanical Allodynia

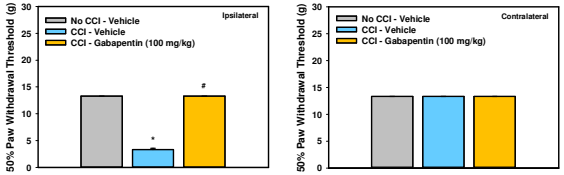


Figure 1. Sciatic nerve ligation produces mechanical allodynia in ipsilateral hindpaw. At 2-3 weeks following sciatic nerve ligation in the chronic constrictive nerve injury model (CCI), animals develop mechanical allodynia in the ipsilateral hindpaw as indicated by a lower paw withdrawal threshold to von Frey filaments. This allodynia is acutely reduced by gabapentin treatment (100 mg/kg). Data are presented as mean ± SEM. *p<0.001 vs. No CCI. #p<0.001 vs. CCI-Vehicle.

Cold Plate Hyperalgesia

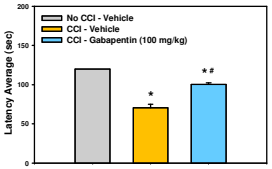


Figure 2. Sciatic nerve ligation produces cold hyperalgesia in ipsilateral hindpaw. Animals with chronic constrictive nerve injury (CCI) to the sciatic nerve show reduced latency to paw lift in the cold plate test.

CCI animals treated with gabapentin (100 mg/kg) show an increased latency to paw lift indicative of analgesia. The latency in the gabapentin group, however, was still lower than uninjured controls. Data are presented as mean ± SEM. *p<0.001 vs. No CCI. #p<0.001 vs. CCI-Vehicle.

RotaRod Motor Function

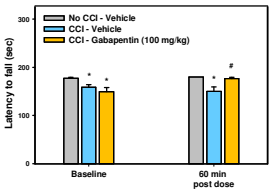


Figure 3. Sciatic nerve ligation causes motor impairments in the RotaRod test. CCI animals exhibit motor deficits as indicated by significantly reduced latency to fall from the rotarod during baseline testing.

Treatment of CCI animals with gabapentin (100 mg/kg) significantly delays the latency to fall from the rotarod to levels similar to uninjured controls. Data are presented as mean ± SEM. *p<0.05 vs. No CCI. #p<0.05 vs. CCI-Vehicle.

NeuroCube® Gait Analysis

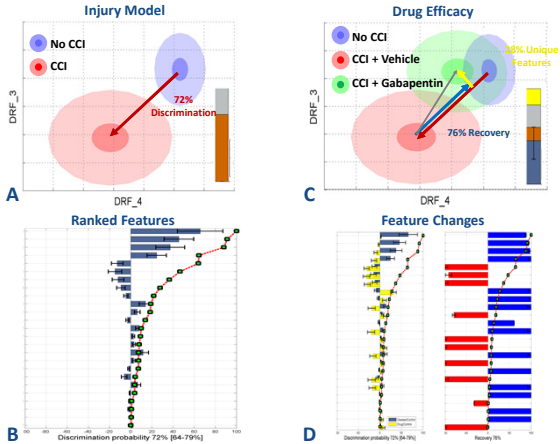


Figure 4. Sciatic nerve ligation produces gait deficits in NeuroCube®. Animals with sciatic nerve ligation show 72% feature discrimination in gait features compared to uninjured controls (A). Ranked feature analysis reveals increases in swing and stride durations along with reductions in stand durations are among the highest discriminating features (B). Treatment with gabapentin produces 76% recovery (blue in C) in gait features (C and D). NeuroCube® also detected 28% changes which are new and different from controls (yellow in C denotes other effects).

Elevated Plus Maze

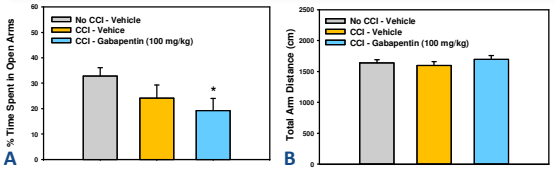


Figure 5. Animals with sciatic nerve ligation exhibit evidence of anxiety. Following chronic constrictive sciatic nerve injury, animals showed some reduction in the time spent in the open arms of the elevated plus maze which is indicative of an anxiety phenotype. Administration of gabapentin (100 mg/kg) analgesia to reduce neuropathic pain further decreased the time spent in the open arms (A). All animals exhibited similar total distance travelled indicating that no treatment caused sedation during the trial. Data are presented as mean ± SEM. *p<0.05 vs. No CCI.

Summary

The chronic constrictive injury model of the sciatic nerve produces robust pathology in sensory allodynia and motor deficits. Data here suggests this model may be useful for assessing the development of affective co-morbidities such as anxiety over time.