IS THE CHRONIC CONSTRICTION INJURY MODEL IN THE MOUSE AN ADEQUATE SCREENING MODEL FOR ANALGESIC ACTIVITY?

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INTRODUCTION
Different models of neuropathies have been established in the rat whose behavior after nociceptive stimulations is extensively described in the literature. However, similar murine models may be useful for proof-of-concept studies with transgenic animals or during the early stages of drug development. The objective of this study was to establish a Chronic Constriction Injury (CCI) model in mice and to validate it pharmacologically.

MATERIAL & METHODS

- **Surgery:** Male NMRI mice (Janvier Labs) were used. Three ligatures spaced 1 mm apart were loosely tied around the sciatic nerve. The wound was then sutured and the mice were allowed to recover.
- **Testing phase:** At least one week after the surgery, mice were submitted to a pre-test by tactile stimulation (electronic von Frey measurement) of the hind paws and assigned to treatment groups matched on the basis of their withdrawal response. The mice were subsequently evaluated using 2 additional pain endpoints: thermal and tactile hyperalgesia. Analgesic effects of morphine (Coopération Pharmaceutique Française, i.p.) and tramadol (Sigma-Aldrich, p.o.) were investigated in two separate experiments on Day 7 and Day 14, respectively.
- **Pain endpoints:**
  - **Tactile allodynia evaluation: electronic von Frey test:** The animal was placed under an inverted acrylic plastic box on a grid floor and left free to habituate for at least 30 minutes. The tip of an electronic von Frey probe was then applied with increasing force to the hindpaw. The force required to induce paw-withdrawal was automatically recorded. This procedure was carried out 3 times and the mean force per paw was calculated.
  - **Thermal hyperalgesia evaluation: plantar test:** A mobile infrared radiant source was focused under the hindpaw. The paw-withdrawal latency was automatically recorded. In order to prevent tissue damage the heat source was automatically turned off after 45 seconds.
  - **Tactile hyperalgesia evaluation: pinchmeter test:** The device consisted of a pair of large blunt forceps, equipped with 2 strain gauges connected to a modified electronic dynamometer. The tips of the forceps were placed around the hindpaw. The force applied was incremented manually (maximum of 800 g) until the paw withdrawal response. The maximum force applied was automatically recorded and displayed by the dynamometer. This procedure was carried out 3 times and the mean force per paw was calculated.
- **Statistics:** The data are represented as mean ± SEM of the response. The differences between the test with the baseline data are expressed as delta. Statistical analysis of drug effects were performed by comparing treated test for post hoc comparisons.

RESULTS

- **Tactile allodynia evaluation: electronic von Frey test**
  - Morphine (8 and 12 mg/kg i.p.) displayed an analgesic effect whereas tramadol was nearly inactive up to 128 mg/kg p.o.
  - Morphine (4 mg/kg i.p.) displayed an analgesic effect whereas tramadol was nearly inactive up to 128 mg/kg i.p.
- **Thermal hyperalgesia evaluation: plantar test**
  - Morphine (8 and 12 mg/kg i.p.) and tramadol (128 mg/kg p.o.) displayed an analgesic effect. Nevertheless, the hyper-reactivity of mice complicated the measurement of paw-withdrawal latency.
  - Morphine (64 and 128 mg/kg p.o.) displayed an analgesic effect whereas tramadol (128 mg/kg p.o.) was nearly inactive.
- **Tactile hyperalgesia evaluation: pinchmeter test**
  - Morphine (12 mg/kg i.p.) and tramadol (64 and 128 mg/kg p.o.) displayed an analgesic effect.

CONCLUSION

These results suggest that CCI surgery in the mouse clearly induces neuropathic pain and that tactile allodynia and hyperalgesia can be used as endpoints in this model. The CCI model in the mouse is therefore appropriate for screening for analgesic activity, prior to follow-up testing in the rat, including additional endpoints such as thermal allodynia and hyperalgesia.