553.1/AA10 Murine Models of Neuropathic Pain

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BACKGROUND: Chronic pain, especially neuropathic pain, in humans is often not adequately treated by currently available therapeutics. Animal models provide pivotal systems for preclinical study of pain. However, most studies on neuropathic pain have been carried out in rat models. Recent years has seen the dramatic expansion in the use of transgenic models for the study of physiological and pathophysiological functions, in particular in mice. However, functional studies such as *in vivo* electrophysiology can prove more problematic in small rodents.

AIMS: To investigate the feasibility of mouse models of neuropathic pain.

METHODS: Behavioural (von Frey hair) and electrophysiological (*in vitro* and *in vivo*) studies were undertaken in adult male mice (BL6 CB F1, 25-35g) of common models of neuropathic pain, including chronic constriction injury (CCI)[1], spinal nerve ligation (SNL/Chung model)[2] and streptozocin-induced diabetic neuropathy[3]. The effects of classic analgesics such as amitriptyline, morphine, gabapentin and pethedine, were then subsequently tested in these models.

Results: symptoms and signs of neuropathic pain detected in mice were similar as observed in the rat models.

Conclusion: We conclude that mouse models of neuropathic pain, similar to those pioneered in rats, would be useful tools for the genetic, physiological and pharmacological study of neuropathic pain.

References:

1. Bennett, G.J. and Xie, Y.-K.. (1988) Pain, 33, 87.
2. Kim, S.H. and Chung, J.M. (1992) Pain, 50, 355.
3. Courteis, C, et al. (1993) Pain, 53, 81.

CCI model

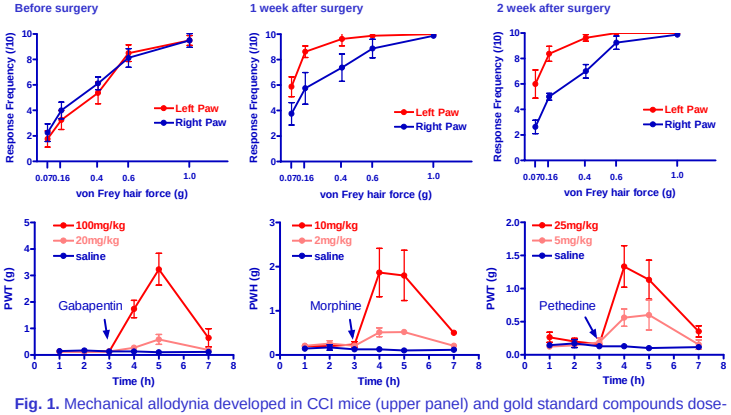


Fig. 1. Mechanical allodynia developed in CCI mice (upper panel) and gold standard compounds dose-dependently reversed significantly mechanical allodynia in CCI mouse model (lower panel) compared to vehicle control. One way ANOVA test was used to compared compound effects at the same time points with vehicle control group.

SNL (Chung) model

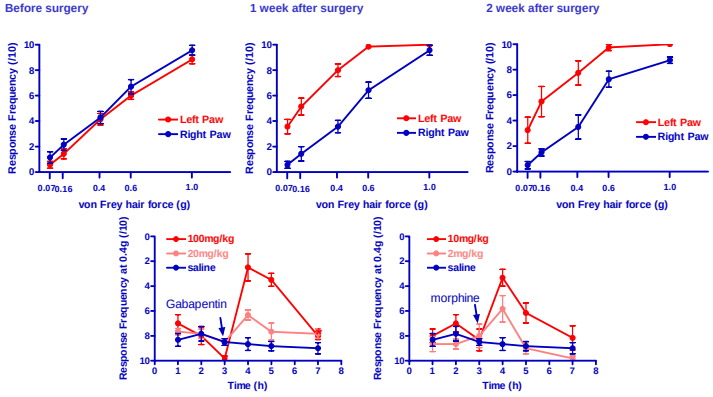


Fig. 2. Mechanical allodynia developed in Chung model mice (upper panel) and dose-dependent and significant (one-way ANOVA test) reversion of gold standard compounds compared to vehicle control.

Streptozocin-induced diabetic neuropathy

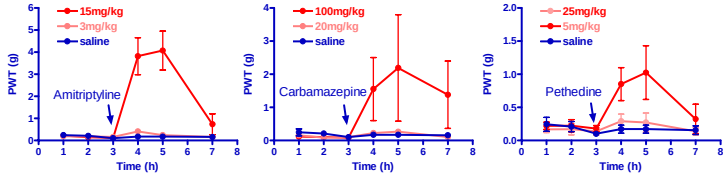


Fig. 3. Dose-response relation of gold standard compounds in significantly reversing mechanical allodynia in Streptozocin-induced diabetic mouse model (One way ANOVA test).

Ectopic Discharge: Effect of lignocaine

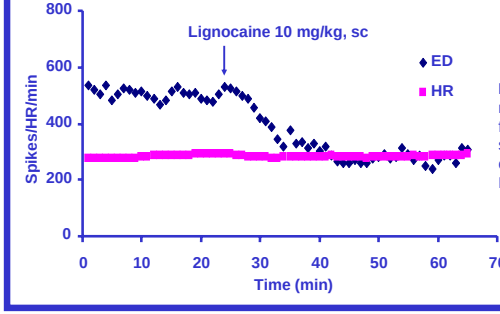


Fig. 4. Ectopic discharge (ED), recorded *in vivo* from a sural nerve fibre of a CCI mouse, was significantly inhibited by sub-cutaneous injection of lignocaine. HR: heart rate.

Somatic AP recording of mouse DRG *in vivo*

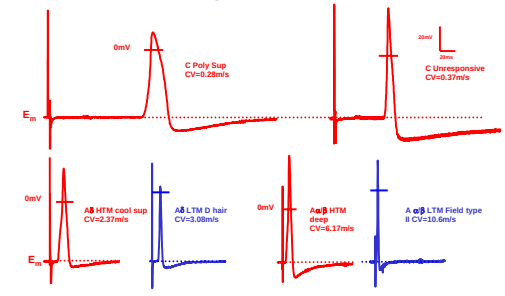


Fig. 5 Example of action potentials (APs) recorded from physiologically identified DRG neurons of C57Bl6 mouse. Sup: superficial; HTM: high-threshold mechanoreceptor; LTM: low-threshold mechanoreceptor; CV: conduction velocity.

Electrotonic coupling in mouse olfactory bulb neurons

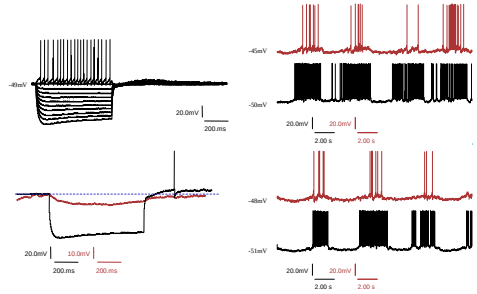


Fig. 6 Paired recording of olfactory neurons from mouse slice showing current transferring between two electrotonically coupled cells.

Mouse prefrontal cortex slice recording

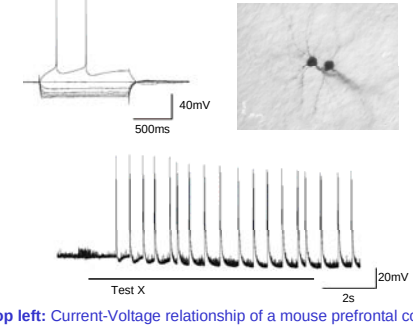


Fig. 7 Top left: Current-Voltage relationship of a mouse prefrontal cortex neuron in mouse brain slice by current clamp recording. **Top right:** Biocytin staining to show cell morphology recorded. **Bottom:** Current clamp recording from the above cell to show response to a compound test.