The refined biomimetic NeuroDigm GEL™ model of neuropathic pain in a mature rat

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Abstract

Background: Many humans suffering with chronic neuropathic pain have no objective evidence of an etiological lesion or disease. Frequently their persistent pain occurs after the healing of a soft tissue injury. Based on clinical observations over time, our hypothesis was that after an injury in mammals the process of tissue repair could cause chronic neural pain. Our objectives were to create the delayed onset of neuropathic pain in rats with minimal nerve trauma using a physiologic hydrogel, and characterize the rats' responses to known analgesics and a targeted biologic.

Methods: In mature male Sprague Dawley rats (age 9.5 months) a percutaneous implant of tissue-derived hydrogel was placed in the musculofascial tunnel of the distal tibial nerve*. Subcutaneous morphine (3 mg/kg), celecoxib (10 mg/kg), gabapentin (25 mg/kg) and duloxetine (10 mg/kg) were each screened in the model three times each over 5 months after pain behaviors developed. Sham and control groups were used in all screenings. A pilot study followed in which recombinant human erythropoietin (200 units) was injected by the GEL™ neural procedure site.

Results: The GEL group gradually developed mechanical hypersensitivity lasting months. Morphine, initially effective, had less analgesia over time. Celecoxib produced no analgesia, while gabapentin and duloxetine at low doses demonstrated profound analgesia at all times tested. The injected erythropoietin markedly decreased bilateral pain behavior that had been present for over 4 months, $p \leq 0.001$. Histology of the GEL group tibial nerve revealed a site of focal neural remodeling, with neural regeneration, as found in nerve biopsies of patients with neuropathic pain.

Conclusion: The refined NeuroDigm GEL model induces a neural response resulting in robust neuropathic pain behavior. The analgesic responses in this model reflect known responses of humans with neuropathic pain. The targeted recombinant human erythropoietin at the ectopic neural lesion appears to alleviate the persistent pain behavior in the GEL™ model rodents.

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