

## Nociception, Neuropathic and Inflammatory Pain

Pain, being one of the most uncomfortable sensations we experience, is a critical component of our body's defense system. It is a mechanism that allows us to remove ourselves from dangerous situations as we move away from noxious stimuli, prevents further damage as we escape stimuli that causes pain after an initial insult, and promotes the healing process as we take great care to protect an injured body part. Pain is divided into two main categories: acute and chronic pain.

Acute or nociceptive pain is part of a rapid warning relay instructing the motor neurons of the central nervous system to minimize detected physical harm. It is mediated by nociceptors, on A- $\delta$  and C fibers. These nociceptors are free nerve endings that terminate just below the skin, in tendons, joints, and in body organs. They serve to detect cutaneous pain, somatic pain and visceral pain. Nociception can be associated with nerve damage caused by trauma, diseases such as diabetes, shingles, irritable bowel syndrome, late-stage cancer or the toxic effects of chemotherapy. It typically responds well to treatment with opioids and NSAIDs.

Chronic pain, however, serves no biologic function as it is not a symptom of a disease process but is a disease process itself. There are two types of chronic pain: inflammatory nociceptive pain and neuropathic pain. Inflammatory nociceptive pain is associated with tissue damage and the resulting inflammatory process. It is adaptive in that it elicits physiologic responses that promote healing.

Neuropathic pain is produced by damage to the neurons in the peripheral and central nervous systems and involves sensitization of these systems. In peripheral sensitization, there is an increase in the stimulation of peripheral nociceptors that amplifies pain signals to the central nervous system. In central sensitization, neurons that originate in the dorsal horn of the spinal cord become hyperstimulated, increasing pain signals to the brain and thereby increasing pain sensation. It is most commonly associated with chronic allodynia and hyperalgesia.

One of the challenges for researchers and clinicians alike is that chronic pain may involve a mix of both inflammatory and neuropathic components. In inflammatory nociceptive pain, inflammation may cause damage to the neurons and produce neuropathic pain. Likewise, neuronal injury may cause an inflammatory reaction (neurogenic inflammation) that contributes to inflammatory pain.

### Animal Models for Nociception:

**Tail Flick:** this model is typically used to measure the response to noxious and visceral stimuli. It utilizes thermal and mechanical stimuli and measures the latency time until the animal responds.

**Visceral Pain:** this model is used for screening the effectiveness of analgesic agents. It utilizes noxious chemical irritation of the peritoneum and measures the pain response.

**Post-operative pain.** These models are utilized for screening the pathophysiology of hyperalgesia and can be performed in the rat or pig via incision or surgical procedure respectively. Pain is measured by evaluating the physiological changes in the animals pre- and post-procedure. Three major observations are part of the pain scoring system:

- Animal solitary performance (walking and vocalization)
- Animal social behavior
- Time an animal was able to stay on a sling

### Animal Models for Neuropathic Pain:

**Chronic constriction injury neuropathic pain in rats.** This model involves inflammation around the nerve giving it both a neuropathic and inflammatory component. It can be used as a secondary phase if compounds show effectiveness in both a nociceptive and inflammatory model.

The model is based on chronic constriction of the sciatic nerve, known as the Bennett and Xie model. Sprague Dawley male rats (250 gr.) are anesthetized with a combination of sodium pentobarbitone sodium and xylazine HCl. Under anesthesia the right sciatic nerve is explored at a location above the femoral joint. Four loose knots are applied to the sciatic nerve. The wound is then closed. Animals are treated once with antibiotic. Two weeks later, the rats are tested for their pain threshold using thermal and mechanical tests and the Vonfrey filament test. Animals that demonstrated reduced threshold in the operated leg are included in the study. Twenty-four hours later animals are divided into different treatment and dose groups. Their pain threshold is re-measured and then they are treated with TI.

**Taxol induced neuropathic pain.** This model involves the nerve endings and does not contain an inflammatory component. Rats are injected with taxol on days 1, 3, 5, 7, and 9 and changes in pain threshold are measured.

### Inflammatory Pain

**Carrageenan induced inflammatory pain**

Inflammatory pain is induced by SC intraplantar injection of 1  $\mu$ l of 2% carrageenan in saline solution into the hind paw of dry ice sedated rats (Sprague Dawley male 200 g). Only one paw was injected with carrageenan while the other paw remains intact as control. Before carrageenan injection and 180 minutes after the injection, pain threshold is evaluated in both hind paw using thermal and mechanical stimuli.