

# Preemptive Analgesic Effect of Intrathecal Applications of Neuroactive Steroids in a Rodent Model of Post-Surgical Pain: Evidence for the Role of T-Type Calcium Channels

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## Abstract:

Preemptive management of post-incisional pain remains challenging. Here, we examined the role of preemptive use of neuroactive steroids with activity on low-voltage activated T-type Ca<sup>2+</sup> channels (T-channels) and  $\gamma$ -aminobutyric acid A (GABA<sub>A</sub>) receptors in the development and maintenance of post-incisional pain. We use neuroactive steroids with distinct effects on GABA<sub>A</sub> receptors and/or T-channels: Alphaxalone (combined GABAergic agent and T-channel inhibitor), ECN (T-channel inhibitor), CDNC24 (GABAergic agent), and compared them with an established analgesic, morphine (an opioid agonist without known effect on either T-channels or GABA receptors). Adult female rats sustained the skin and muscle incision on the plantar surface of the right paw. We injected the agents of choice intrathecally either before or after the development of post-incisional pain. The pain development was monitored by studying mechanical hypersensitivity. Alphaxalone and ECN, but not morphine, are effective in alleviating mechanical hyperalgesia when administered preemptively whereas morphine provides dose-dependent pain relief only when administered once the pain had developed. CDNC24 on the other hand did not offer any analgesic benefit. Neuroactive steroids that inhibit T-currents—Alphaxalone and ECN—unlike morphine, are effective preemptive analgesics that may offer a promising therapeutic approach to the treatment of post-incisional pain, especially mechanical hypersensitivity.

**Keywords:** incision pain; mechanical hypersensitivity; GABAergic; morphine; voltage-gated calcium channels; adult female rats