ROLE OF GW842166X, A CB2 RECEPTOR AGONIST, IN SEVERAL RAT MODELS OF NEUROPATHIC AND INFLAMMATORY PAIN

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Chronic pain states, such as those caused by nerve injury (neuropathic) and inflammation are associated with abnormal sensory sensations, which include allodynia and hyperalgesia. These chronic states appear to be resistant to traditional analgesics. There is now considerable evidence that a number of cannabinoid receptor agonists reduce allodynia and hyperalgesia associated with neuropathic and inflammatory models of chronic pain. However, cannabinoid CB1 receptor activation produces a spectrum of psychotropic side effects. For this reason, recent chronic pain studies have focused on selective CB2 receptor agonists which avoid centrally mediated CB1 receptor side effects.
In this work, we use GW842166X, a CB2 selective receptor agonist reported to be active in reducing inflammation and neuropathy after repeated treatment, to study the role of CB2 agonists in the modulation of pain. Specifically, we investigated whether the compound shows its effectiveness in reducing pain also after one single acute dose. For this reason, the compound has been tested in the inflammatory model of the chronic arthritis induced by Freund's adjuvant (CFA) and in two different models of neuropathic pain: the chronic constriction injury (CCI) and the L5-L6 spinal nerve ligation model (SNL). GW842166X (10, 30 mg/kg, ip) is antinociceptive in both models of neuropathic pain. In fact, it significantly reduces the cold allodynia evaluated in CCI rats with the cold plate test, and reverts the mechanical allodynia measured in SNL rats with the von Frey hair test, showing a comparable effect to the reference compound gabapentin (50 mg/kg, po). Moreover, a single dose of GW842166X (10, 30 mg/kg, ip), significantly attenuates the thermal hyperalgesia and the mechanical allodynia evaluated in CFA rats, 48 hrs after the injection of 50 µg of Freund's adjuvant in the right hind paw. In this case, the analgesic activity of the CB2 agonist is even better compared to the standard NSAID compound, naproxen (10, 30 mg/kg, po). In addiction, we perform an antagonism study, demonstrating that the antiallodynic effect of the compound is mediated by CB2 receptors, since the selective CB2 receptor antagonist, SR144528 (3 mg/kg, ip), reverts GW842166X activity in the SNL model. In the current study, we show a further characterization of the analgesic properties of GW842166X and in particular, we hightlight the role of the CB2 receptor system in the modulation of chronic pain state, supporting the indication of the clinical utility of CB2 receptor selective agonists, which avoid the classical side effects mediated by CB1 receptors.