Anti-nociceptive effects of the selective CB_2 agonist MT178 in inflammatory and chronic rodent pain models

K. Varani[1], F. Vincenzi[1], M. Targa[1], C. Corciulo[1], S. Gessi[1], S. Merighi[1], G. Saponaro[2],M.A. Tabrizi[2], P.G. Baraldi[2], P.A. Borea[1]

[1] Dept of Medical Sciences, Section of Pharmacology, University of Ferrara, Ferrara, Italy;
[2] Dept of Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy

Neurotransmission and neuroinflammation are modulated by the endocannabinoid signaling system based on the CB_1 and CB_2 cannabinoid receptors [1]. The stimulation of CB_2 receptors modified the cytokine milieu contributing to the accumulation of anti-inflammatory mediators [2]. Therefore, CB_2 agonists could represent attractive therapeutic target affecting a myriad of immune responses from inflammation to neuroprotection [3]. Cannabinoid CB_2 receptor activation by selective agonists has been shown to produce analgesic effects in preclinical models of inflammatory, neuropathic and bone cancer pain. In this study the effect of a novel CB_2 agonist (MT178, N-adamantyl- 3-ethyl- 3,7-dihydro- 7-oxo- 10-(pyrrolidin-1-yl)- 2H- [1,4]oxazino [2,3,4-ij]quinoline-6-carboxamide) was evaluated in different animal models of pain. First of all, in vitro competition binding experiments performed on rat, mouse or human CB receptors revealed a high affinity and selectivity of MT178. Moreover, MT178 showed a high CB_2 selectivity making it suitable as anti-nociceptive drug without CNS side effects. The novel CB_2 compound behaves as a potent full agonist as indicated by cyclic AMP experiments performed in human CB_2 receptors expressed in CHO cells [4]. The analgesic properties of the novel CB_2 agonist were evaluated in various *in vivo* experiments such as writhing and formalin assays showing a good efficacy comparable with that produced by the non-selective CB agonist WIN 55,212-2. Furthermore, the effect of MT178 was reversed by the selective CB_2 antagonist AM 630 but not by the selective CB_1 antagonist AM 251 supporting a CB_2-mediated mechanism of action. A dose-dependent anti-allodynic effect of the novel CB_2 compound in the streptozotocin (STZ)-induced diabetic neuropathy was found. In a bone cancer pain model and in the acid-induced muscle pain (AIMP) model, MT178 was able to significantly reduce mechanical hyperalgesia in a dose-related manner. Notably, MT178 failed to provoke locomotor disturbance and catalepsy, which were observed following the administration of WIN 55,212-2. CB_2 receptor mechanism of action was investigated in dorsal root ganglia (DRG) where MT178 mediated a reduction of [^{3}H]-D-aspartate release. MT178 was also able to inhibit capsaicin-induced substance P release and NF-kB activation.
These results demonstrate that systemic administration of MT178 produced a robust analgesia in different pain models via CB_2 receptors providing an interesting approach to analgesic therapy in inflammatory and chronic pain without CB_1-mediated central side effects.

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