Anti-nociceptive effects of the selective CB$_2$ agonist MT178 in inflammatory and chronic rodent pain models

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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.