



Peripheral antinociceptive effects of MC4 receptor antagonists in a rat model of neuropathic pain – a biochemical and behavioral study

Katarzyna Starowicz¹, Shaaban A. Mousa⁴, Ilona Obara¹, Agnieszka Chocyk², Ryszard Przewłocki³, Krzysztof Wędzony², Halina Machelska⁴, Barbara Przewłocka¹

¹Department of Pain Pharmacology, ²Department of Pharmacology, ³Department of Molecular Neuropharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

⁴Klinik für Anaesthesiologie und Operative Intensivmedizin, Charité-Universitätsmedizin, Campus Benjamin Franklin, Hindenburgdamm 30, D-12207 Berlin, Germany

Correspondence: Barbara Przewłocka, e-mail: przebar@if-pan.krakow.pl

Abstract:

Recent studies have suggested that melanocortins contribute to the generation and/or maintenance of pathological pain. Experimental evidence indicates a primary role for melanocortin 4 (MC4) receptors in pathological pain. In a previous study, we described the presence of MC4 receptor transcripts in the dorsal root ganglia (DRG). This finding prompted us to investigate the peripheral antinociceptive effects of MC4 receptor antagonists. In addition, we assess the expression of MC4 receptors in the spinal cord and the DRG of rats subjected to neuropathic pain induced by chronic constriction injury (CCI) of the sciatic nerve. Injection of the MC4 receptor antagonists Asp3-Lys8- Ac-Nle-Asp-His-D-Nal(2')-Arg-Trp-Lys-NH₂ (SHU9119) and Mpr1-Cys8-Mpr-Glu-His-(D-Nal)-Arg-Trp-Gly-Cys-Pro-Pro-Lys-Asp-NH₂ (JKC-363) into the ipsilateral paw resulted in a significant and dose-dependent alleviation of mechanical allodynia (assayed by the von Frey test) and thermal hyperalgesia (assayed by the Hargreaves test). Compared to naive control animals, immunohistochemistry revealed a 40% and 22% increase in MC4 receptor-immunoreactivity (IR) in the dorsal horn of the spinal cord ipsilateral to the injury at 3 and 14 days after CCI, respectively. Similarly, in the ipsilateral L4-L5 DRG, a 21.1% enhancement in MC4 receptor-IR was seen 3 days after CCI, as well as a 40.5% increase 14 days after CCI. Together, painful neuropathy resulted in the up-regulation of MC4 receptors in the spinal and peripheral nociceptive pathways. This up-regulation of MC4 receptors promotes the pronociceptive action of their endogenous ligands. Therefore, a block of the MC4 receptors results in the antagonism of neuropathic pain and such treatment could be beneficial therapeutically for individuals with chronic neuropathic pain.

Key words:

pain, neuropathy, melanocortin 4 receptor, chronic constriction injury, immunohistochemistry, SHU9119, JKC-363

Abbreviations: CCI – chronic constriction injury, DRG – dorsal root ganglion, *ipI* – intraplantar, IR – immunoreactivity, MC4 receptor – melanocortin 4 receptor, ROD – relative optical density

Introduction

Neuropathic pain can develop because of traumatic or metabolic injury of the peripheral nervous system. One of the major limitations in neuropathic pain therapy is a reduced analgesic potency and a reduced efficacy of morphine. In this regard, a possible involvement of proopiomelanocortin (POMC)-derived melanocortins and the melanocortin 4 (MC4) receptor has attracted attention recently. The melanocortin and the opioid systems appear to act in opposition to one another. As a result, melanocortins are considered endogenous functional antagonists of opioids [4, 24]. Interactions between melanocortins and opioids in morphine-induced locomotor activity and antinociception have been assessed in mice [6]. Furthermore, an antagonistic interaction between the MC4 receptor agonist, melanotan I([Nle⁴, D-Phe⁷] -MSH (NDP- -MSH)), and morphine has been reported, as well as an additive interaction between MC4 receptor antagonist and morphine [12]. These data confirm the authors own observation of the potentiation of morphine analgesia by melanocortin receptor antagonist in rats tolerant to morphine [21]. Moreover, the impact of supraspinal MC4 receptors modulation on the development of tolerance and dependence on morphine's antinociceptive effect has also been reported in rats [12]. Recent reports have demonstrated effective antinociception after blockade of spinal MC4 receptors with MC4 receptor antagonists in a model of neuropathic pain [22, 27]. In agreement with the above study, a recent paper by Gao et al. [7] used an oligonucleotide microarray to identify the MC4 receptor as a new target in rats for nociceptive study, along with the glutamatergic receptors, a ghrelin precursor, and neurotrophin 1. A potentiation of morphine analgesia by the MC4 receptor antagonist, Asp3-Lys8-Ac-Nle-Asp-His-D-Nal(2')-Arg-Trp-Lys-NH₂ (SHU9119), was observed in a neuropathic pain model [21, 27]. These findings suggest the hypothesis of a higher activity of the melanocortin system in neuropathic pain. A study by Beltramo et al. [1] demonstrated an up-regulation of POMC and MC4 receptor expression in the spinal cord. This increase in POMC and MC4 re-

ceptor expression paralleled the presence of neuropathic pain symptoms, such as tactile allodynia and thermal hyperalgesia. Furthermore, we previously demonstrated the expression of MC4 receptor mRNA in the dorsal root ganglia (DRG) in the sciatic nerve of injured rats [20]. These data suggest the contribution of presynaptic MC4 receptors on primary afferents to the modulation of neuropathic pain. This alternative mechanism allows for antinociception after the application of small, systemically inactive doses of MC4 receptor ligands directly into the injured peripheral tissue. Antinociception has been shown for other receptor ligands [11, 17, 25, 29] and for the local (in contrast to peripheral) injection of a variety of receptor ligands with limited access to the central nervous system, both of which minimize adverse central actions [5, 16]. The mechanism of antinociception involves the peripheral MC4 receptors, which are synthesized in the cell bodies of the primary afferent sensory neurons located in the DRG, and their respective ligands, which are present on peripheral afferent axons of sensory neurons. In order to test the involvement of peripherally located MC4 receptors in the nociceptive transmission of chronic pain, we investigated the effects of selective MC4 receptor antagonists on mechanical allodynia and thermal hyperalgesia in chronic constriction injury (CCI) neuropathy. The selective MC4 receptor antagonists were administered intraplantarly (*ipI*) to the ipsilateral hind paw. The level of mRNA expression does not always parallel the level of protein expression. Therefore, to elucidate the significance of changes in MC4 receptor expression at the protein level, we used immunohistochemistry to examine the MC4 receptor immunoreactivity (IR) in the lumbar spinal cord and L4 and L5 DRG of the rats with neuropathic pain induced by CCI of the sciatic nerve.

Materials and Methods

Animals

Experiments were performed in male Wistar rats (License Breeding House, Rembertów, Poland) weighing between 220–250 g at the time of surgery. Animals were housed individually in cages lined with sawdust. Standard laboratory rodent chow and water were

Download English Version:

<https://daneshyari.com/en/article/2012363>

Download Persian Version:

<https://daneshyari.com/article/2012363>

[Daneshyari.com](https://daneshyari.com)