Pharmacological and molecular modeling studies on 6-desoxo-N-methylmorphinans as potent agonists interacting with the µ-opioid receptor

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Background: Pain remains one of the main challenges in human medicine at the beginning of the third millennium, with ca. 20–30% of people worldwide suffering from chronic pain. Opioid analgesics are the cornerstone drugs for the treatment of moderate to severe pain, but their clinical use is hampered by numerous adverse effects. Pharmacological actions of opioids are primarily mediated through activation of the µ-opioid (MOP) receptor. One long-standing focus in drug discovery has been the search for opioids exhibiting a favorable dissociation between analgesia and side effects. Morphinans are the most common and highly effective analgesics. Oxycodeone, a clinically relevant analgesic, represents a valuable scaffold for the design of MOP ligands, with examples including the 14-OMO, 14-O-benzyl (14-OBO)- and 14-methyl-substituted derivatives, and the 5-methyl-substituted analogue, 14-methoxycodeine (14-MM). Position 6 on the morphinan skeleton was shown to play a key role on opioid activity in vitro and in vivo. In this study, the consequence of 6-carbonyl (6-CO) group deletion in targeted N-methylmorphinans on ligand–MOP receptor interaction, signaling and antinociceptive activity was evaluated.

Methods: In vitro radioligand binding and [35S]GTPγS functional assays were performed with membranes from Chinese hamster ovary (CHO) cells stably expressing the human opioid receptors. Antinociceptive activities were determined using the hot-plate test in mice after subcutaneous administration. For molecular docking to the murine MOP receptor crystal structure, ligands were prepared using the LigandScout (version 3.1), and docking was performed using the GOLD (version 5.1) software.

Results: Binding studies indicated that the 6-desoxy-N-methylmorphinans display affinities in the subnanomolar range at the human MOP receptor, and are MOP receptor-selective. The loss of the 6-CO group was not favorable when comparing oxycodone and 14-MM to their 6-desoxy counterparts, while a significant increase in MOP binding was observed for 6-desoxo-14-OBO. The 6-desoxo derivatives activate G proteins with high potency as full MOP agonists, with 6-desoxo-14-OMO, 6-desoxo-14-OBO and 6-desoxo-14-MM retaining or displaying an improved agonism than the parent compound, exception being 6-desoxoxycodeine. In vivo, they were effective against acute thermal nociception in mice, with comparable potency to lead molecules. Docking of the 6-desoxy-N-methylmorphinans to the crystal structure of activated MOP receptor revealed important molecular interactions, which these MOP agonists share and distinguish them.

Discussion: The absence of a 6-CO group in targeted N-methylmorphinans strongly impacts binding to the MOP receptor and post-receptor signaling, with all presented derivatives evolving as potent MOP agonists. The current results expand the understanding of the impact of the 6-CO-to-6-CH₂ alteration in N-methylmorphinans on ligand–MOP receptor interaction and molecular mode of action, and may aid in identification of new opioid analgesics with improved pharmacological profiles.

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