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Meeting abstract

5-Benzyl substituted 14-methoxymetopon, a high affinity μ opioid receptor agonist with potent antinociceptive activity in mice

Mariana Spetea, Catalina-Roxana Bohotin and Helmut Schmidhammer*

Address: Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences, University of Innsbruck, 6020 Innsbruck, Austria

Email: Helmut Schmidhammer* - helmut.schmidhammer@uibk.ac.at

* Corresponding author

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Pain constitutes a major public-health problem with an impact on both the individual and the society that is still inadequately treated. All clinically used opioid analgesics for severe acute and chronic pain, e.g. morphine, fentanyl and oxycodone, are agonists activating central μ opioid receptors. Their clinical use is associated with a number of adverse actions, such as respiratory depression, sedation, nausea, constipation, tolerance and addiction. One of the major aims of medicinal chemistry and opioid pharmacology is to develop opioids with high affinity and/or selectivity for the μ opioid receptor, exhibiting a favorable dissociation between analgesia and the occurrence of side effects. 14-Methoxymetopon, designed by our group, was described as a highly potent and selective μ opioid agonist with an unusual pharmacological and functional profile, being genuinely safer than the "gold standard pain-killer" morphine. With the aim to identify and develop scientifically proven opioid drugs with a reliable target-oriented pharmacological profile, established efficacy and favorable safety index, a new analogue of 14-methoxymetopon, containing a benzyl substituent at position 5, was investigated for its *in vitro* biological and *in vivo* pharmacological activities. Binding affinities and selectivities to opioid receptors were determined in rodent brain membranes using competition binding assays. Analgesic activity after subcutaneous (s.c.) administration was assessed in mice using tail-flick and hot-plate tests. The rotarod test was used to evaluate the drug effect on motor coordination. *In vitro* binding studies indicated that the 5-benzyl analogue of 14-methoxymetopon displayed high affinity and selectivity at the μ opioid receptor. It showed a significant increase in affinity (20-fold) at the μ receptor as compared to that of morphine. The 5-benzyl derivative produced dose-dependent analgesic effects in the tail-flick and hot-plate tests after s.c. administration to mice. The antinociceptive dose necessary to elicit a 50% effect (ED_{50}) was 43 μg/kg in the tail-flick test and 53 μg/kg in the hot-plate test. Compared to 14-methoxymetopon, the new analogue showed comparable antinociceptive potency, while it was about 50-fold more active than morphine. No significant impairment of the motor performance was induced by the novel opioid. These findings show that introduction of a 5-benzyl substituent into 14-methoxymetopon did not significantly affect the *in vitro* and *in vivo* pharmacological properties compared to the parent compound. The interesting pharmacological profiles of this class of morphinans will serve as a basis for our continuing exploration of potent opioid analgesics for the pharmacotherapy of pain.