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14-Methoxy-metopon: a highly potent μ opioid agonist on rat vas deferens

Kornél P Király[1], Pál Riba[1], Tamás Friedmann[1], Mahmoud Al-Khrasani[1], Helmut Schmidhammer[2] and Susanna Fürst[1]

[1]*Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary*

[2]*Department of Pharmaceutical Chemistry, Institute of Pharmacy, University of Innsbruck, Austria*

E-Mail: furzsu@pharma.sote.hu

Morphine, the opioid analgesic most abundantly used for severe acute and chronic pain, is associated with several adverse effects such as respiratory depression, tolerance and dependence. The intensive search to find new opioids possessing a better pharmacological profile has resulted in 14-O-methyloxymorphone (14-O-MOX) and 14-methoxy-metopon (MET), a highly μ-selective and very potent opioid agonist. Our aim was to test the compounds in the rat vas deferens (RVD) bioassay system in order to further analyze their μ receptor efficacy and elucidate the structure-activity relationship between the compounds and oxymorphone (OX), their parent molecule. RVD was prepared, mounted and stimulated as described by Ronai et al. [1]. Opioid actions were measured by determining the inhibitory effects on the electrically evoked twitches. Antagonist activity was determined by the single-dose method. MET exerted full agonist activity in RVD, unlike OX and 14-O-MOX which were only partial agonists. Naltrexone, the reference μ receptor antagonist, antagonized the inhibitory actions on the electrically evoked twitches of the test compounds with a similar potency than in mouse vas deferens indicating the presence of μ opioid receptors in RVD. We found that MET is a highly efficacious μ receptor agonist and that the 5-methyl substitution may be responsible for the full agonist activity. We could not prove the distinction between rat vas deferens and other μ receptor-containing organs.

References

1. Rónai AZ, Berzétei IP and Kurgyis J. **Opioid effects in developing rat vas deferens.** *Cell Mol Neurobiol* 1981, **1:**335–342.