Spetea *et al.*: *Intrinsic Activity*, 2023; **11**(Suppl.1):A1.6
doi:10.25006/IA.11.S1-A1.6
published online: 22 September 2023

INTRINSIC ACTIVITY

27th Scientific Symposium of the Austrian Pharmacological Society

Vienna, 29–30 September 2023

MEETING ABSTRACT

A1.6

Selective activation of the κ-opioid receptor as an effective strategy for treatment of chronic pain

Mariana SPETEA[1,*], Aina-Leonor OLIVÉ-MARTI[1], Alexandra PEER[1], Edin MURATSPAHIĆ[2], Christian W. GRUBER[2], Helmut SCHMIDHAMMER[1]

[1]*Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Austria;* [2]*Institute of Pharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, Austria*

Background: Adequate treatment of chronic pain remains an unmet clinical need at the beginning of the third millennium. Chronic pain is still poorly managed because of the lack of efficacious therapies, high side-effect burden or abuse liability of the present pharmacotherapies. Drugs targeting the μ-opioid receptor (MOR) are very effective analgesics. With continued use, opioid safety is dramatically reduced because of the side effects of physical dependence and addiction, promoting development of opioid-use disorders and overdose deaths. The κ-opioid receptor (KOR) has a central role in modulating neurotransmission in central and peripheral neuronal circuits that subserve pain and other behavioral responses. Among alternative treatment strategies, the KOR is viewed as a promising strategy for pain therapeutics without the deleterious adverse effects of the MOR. In this study, we report and compare the antinociceptive effects of structurally distinct and selective KOR agonists in a mouse model of chronic inflammatory pain. The investigated KOR agonists include the prototypical KOR ligand U50,488, the clinically used antipruritic drugs nalfurafine and difelikephalin, the two diphenethylamines HS665 and HS666, and the peptide–small molecule conjugate DNCP-β-NalA(1).

Methods: Chronic inflammatory pain was induced in mice by injection of complete Freund's adjuvant (CFA) to the dorsal side of the right hindpaw. Nociceptive behavior was assessed 72 hours post-CFA by measuring paw withdrawal latencies to thermal stimulation using the Hargreaves test. Locomotor activity was determined using the rotarod and open-field tests. The elevated plus maze (EPM) test was used for anxiety-like behaviors. The experimental drugs were administered subcutaneously.

Results: Behavioral studies showed that all KOR agonists effectively inhibited pain responses of mice with CFA-induced inflammatory hyperalgesia. Subcutaneous drug administration produced a significant increase in paw withdrawal latencies to thermal stimulation in a time- and dose-dependent manner. However, characteristic differences were observed in the time course of the antinociceptive effects. Nalfurafine and DNCP-β-NalA(1) had a rapid but short duration (up to one hour) of the antinociceptive effect, whereas a long duration of action (4–7 hours) was measured for the other KOR agonists. We also show that the attenuation in pain-related behavior was antagonized by the selective KOR antagonist nor-binaltorphimine, demonstrating a KOR-dependent mechanism of action. In the rotarod test, no sedation or motor incoordination was caused by HS665, HS666 or DNCP-β-NalA(1), whereas locomotor dysfunction was produced by U50,488. No significant effects on spontaneous locomotor activity were observed after acute and chronic administration in mice with HS665 and HS666. In the EPM test, HS665 and HS666 did induce anxiety-like behavior in mice.

Discussion: We show that selective activation of the KOR by different structural classes of KOR agonists, peptide and small molecules, effectively attenuates thermal sensitivity in mice with CFA-induced chronic inflammatory pain, with a favorable benefit / side effect ratio regarding CNS-mediated KOR side effects. Thus, targeting the KOR represents a promising strategy for an improved and safer treatment of chronic pain states.

Acknowledgements: The study was supported by the Austrian Science Fund FWF (grants no. I4697 and P32109).

Keywords: κ-opioid receptors – chronic pain – antinociception – sedation – anxiety

*Corresponding author e-mail: *mariana.spetea@uibk.ac.at*