The TRPM8 antagonist RGM8-51 displays analgesic activity in different pain models

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TRPM8 channels are overexpressed in sensory neurons after nerve injury or inflammation, resulting in enhanced sensitivity (allodynia and hyperalgesia) to physical stimulation, and have been implicated in migraine, but the interest of TRPM8 antagonists is still a matter of controversy (1,2). The aim of our work was to evaluate the analgesic activity of a TRPM8 antagonist, RGM8-51, in different pain models, looking for similarities and differences with other antagonists. To this end, we used the mouse oxaliplatin-induced peripheral neuropathy, the chronic constriction injury of the rat sciatic nerve (CCI) and mouse NTG-induced migraine-like models. Compound RGM8-51 reduces the cold allodynia induced by oxaliplatin, from 15 to 60 min after administration (0.1-1 µg, i.pl.), decreases the nocifensive responses to cold, heat and mechanical stimuli in the CCI model (10 µg, i.pl., 30 mg/Kg, i.p.), and relief chronic pain associated to migraine in mouse, in a sex-dependent manner (10 or 30 mg/Kg, i.v.). The β–lactam derivative RGM8-51 not only has analgesic activity in all assayed animal models, but also seems to have a different mode of interaction with the TRPM8 channel than other antagonists, as suggested by docking studies.

References

1. Pérez de Vega, M.J., Gómez-Monterrey, I., Ferrer-Montiel, A. González-Muñiz, R. Transient Receptor Potential Melastatin 8 Channel (TRPM8) Modulation: Cool Entryway for Treating Pain and Cancer, *J. Med. Chem.*, ***2016,*** *59*, 10006−10029.
2. Izquierdo, C.; Martín-Martínez, M.; Gómez Monterrey, I. González-Muñiz, R. TRPM8 Channels: Advances in Structural Studies and Pharmacological Modulation. *Int. J. Mol. Sci.* **2021**, 22, 8502.

Key words: TRPM8, antagonist, analgesia, neuropathic pain, migraine
Acknowledgments: Supported by the Spanish MINECO (RTI-2018-097189-B-C2), CM (IND2017/BMD-7673) and CSIC (PIE201980E030).
Disclosures: The authors declare no competing financial interests.