Impromptu

Colloquia in Physiology & Vascular Biology

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Physiology, Schwarzspanierstrasse 17, 1090 Vienna, **"gr. HS. Physiology"**.
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Inhibition of acid-sensing ion channels by diminazene and APETx2 evoke partial and highly variable antihyperalgesia in a rat model of inflammatory pain

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Abstract:

Acid-sensing ion channels (ASICs) are primary acid sensors in mammals, with the ASIC1b and ASIC3 subtypes being involved in peripheral nociception. The antiprotozoal drug diminazene is a moderately potent ASIC inhibitor but its analgesic activity has not been assessed. We determined the ASIC subtype selectivity of diminazene and the mechanism by which it inhibits ASICs using voltage-clamp electrophysiology of *Xenopus* oocytes expressing ASICs 1–3. Its peripheral analgesic activity was then assessed relative to APETx2, an ASIC3 inhibitor, and morphine, in a Freund's Complete Adjuvant-induced rat model of inflammatory pain.Diminazene inhibited homomeric rat ASICs with IC_{50} values of ~200–800 nM, via an open channel and subtype-dependent mechanism. In rats with FCA-induced inflammatory pain in one hindpaw, diminazene and APETx2 evoked more potent peripheral antihyperalgesia than morphine, but the effect was partial for APETx2. We show that APETx2 potentiates rat ASIC1b at concentrations 30–100-fold higher than its ASIC3 inhibitory concentration, which may have implications for its use in *in vivo* experiments. Diminazene and APETx2 are moderately potent ASIC inhibitors and they both evoke peripheral antihyperalgesia in a rat model of chronic inflammatory pain. APETx2 has complex ASIC pharmacology, which must be considered when it is used as a supposedly selective ASIC3 inhibitor *in vivo*. Our use of outbred rats revealed responders and non-responders when ASIC inhibition was used to alleviate inflammatory pain, which is aligned with the concept of number-needed-to-treat in human clinical studies.