Ray *et al.: Intrinsic Activity*, 2015; **3**(Suppl. 2):A2.5
http://www.intrinsicactivity.org/2015/3/S2/A2.5
published online: 9 September 2015

21st Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the British Pharmacological Society and the Pharmacological Societies of Croatia, Serbia and Slovenia

Graz, 16–18 September 2015

MEETING ABSTRACT

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K_V7 channels: potential targets for antinociceptive action of paracetamol

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Background: Paracetamol (acetaminophen; APAP) is a widely used analgesic and is well understood in the context of its benefits and side effects. Multiple pathways have been proposed to explain the mechanism underlying its analgesic action, yet a clear explanation remains elusive. The postulated mechanisms include inhibition of cyclooxygenase enzymes, effects on the descending serotonergic inhibitory pathways, and interactions with opioidergic systems and nitric oxide pathways. Paracetamol is mainly eliminated by glucuronidation and sulfation, while some of it is converted into a reactive intermediate, NAPQI (*N*-acetyl-*p*-benzoquinone imine) by cytochrome P450 enzymes. The M current is characteristic of the neuronal subtypes of voltage-gated potassium channels (K_V7 family). Inhibition of M currents is linked to enhanced neuronal excitability while their augmentation causes neuronal silencing, with established translational use in pain management and epilepsy. Moreover, oxidative modification of K_V7 channels has been shown to enhance M currents with a triplet of cysteines in the channel S2–S3 linker as the mediator of oxidative sensitivity. The project aims at understanding whether NAPQI is involved in the antinociceptive action of paracetamol.

Methods: tsA201 cells were transfected using the Turbofect kit (Fermentas). DRG neurons were dissected from 10 day old rats and cultured at 37 °C/5% CO_2 for 2 days. Electrophysiological recordings were made using the perforated patch-clamp technique. NAPQI was perfused for 3 minutes at each concentration followed by washout for 5 minutes.

Results: Our preliminary data show a progressive enhancement of M current in heterologously expressed $K_V7.2$ homomers starting at 0.3 µM NAPQI with a threefold rise at 10 µM, which is maintained during a control washout for 5 minutes. The $K_V7.2/7.3$ heteromers and capsaicin-positive DRG neurons showed a similar profile with a maximal response at 0.3 µM and 1 µM NAPQI, respectively, and a sustained decrease in the amplitude of current during washout.

Discussion: These results indicate that the mechanism of action of paracetamol could be explained by the enhancement of M current and consequently a decrease in excitability of DRG neurons by its metabolite NAPQI.

Acknowledgements: This project is funded by the doctoral program “Cell Communication in Health and Disease” (CCHD; co-financed by FWF and the Medical University of Vienna; W1205).

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