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MEETING ABSTRACT

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K_V7 and TRPV1 channels: neuronal targets for the analgesic action of paracetamol

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Background: Paracetamol/acetaminophen (APAP) is a commonly used analgesic whose site and mechanism of action remain controversial. 5–15% of APAP is converted into a reactive intermediate, NAPQI (*N*-acetyl-*p*-benzoquinone imine), by cytochrome P450 enzymes. Neuronal subtypes of voltage-gated potassium channels (K_V7 family) give rise to the characteristic M current, which plays an important role in regulating neuronal excitability and has translational significance in pain management. Similarly, TRP channels, specifically TRPV1 and TRPA1 play critical roles in processing nociceptive input. Therefore, effects of APAP and its metabolites were investigated on these ion channels in dorsal root ganglia (DRG) and spinal dorsal horn (SDH) cultures prepared from rats.
Methods: Electrophysiological recordings were made using the perforated patch-clamp technique.
Results: Currents through K_V7 channels in SDH- and TRPV1-positive DRG neurons showed an irreversible enhancement up to 250% and 120% of control with 3 µM NAPQI, respectively. TRPV1 currents in DRG neurons were irreversibly enhanced up to 200% of control with 3 µM NAPQI. Application of 1 µM NAPQI for 10 minutes resulted in an initial period of depolarization followed by significant hyperpolarization of the membrane potential in 70% of DRG neurons while the others showed a persistent hyperpolarization irrespective of their TRP status. There was a concomitant decrease in the excitability of DRG neurons. DRG neurons showed a depolarization of the membrane potential on application of 30 µM linopirdine, an antagonist of K_V7 channels, which was adjusted for; on further co-application with 1 µM NAPQI for 10 minutes, the membrane potential steadily depolarized with no significant change in excitability. Another APAP metabolite, AM404 (10 µM) did not affect the magnitude of the K_V7 current but caused a significant depolarization of the membrane potential in DRG neurons without affecting excitability. Persistent hyperpolarization of the membrane potential and a significant decrease in excitability in response to 1 µM NAPQI for 10 minutes was seen in SDH neurons. 100 µM APAP applied alone did not affect any of these parameters.
Discussion: These results suggest that the analgesic action of APAP may involve an enhancement of K_V7 and TRPV1 currents by NAPQI as an active metabolite.
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