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Nucleotides excite sensory neurons via two P2Y receptors and a dual signaling cascade

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Background

Sensory neurons innervating the skin provide information about physical contact between organisms and the environment including stimuli that lead to pain sensation. Metabotropic P2Y receptors have been suggested to be important in the signaling of sensory neurons, but their effects and signaling mechanism remained controversial.

Methods

Patch-clamp recordings were performed in primary cultures of dorsal root ganglion (DRG) neurons from neonatal rats, P2Y receptor ligands and signaling interceptors were applied.

Results

ADP (EC₅₀: 7.5 μM), ATP (EC₅₀: 0.5 μM), UTP (EC₅₀: 0.8 μM), and thio-UTP (EC₅₀: 0.4 μM) increased the number of action potentials fired in response to current injection; UDP failed to affect action potential firing. The effect of ADP was attenuated by a P2Y₁ antagonist. This enhancement of excitability was abolished by flupirtine (30 μM), a K_V7 channel opener, and slightly, but insignificantly attenuated by iodoresiniferatoxin (0.3 μM). Under voltage clamp, the same nucleotides inhibited currents through K_V7 channels in a concentration-dependent manner with similar EC₅₀ values. The P2Y₁-specific agonist MRS2365 also caused an inhibition of K_V7 channels (EC₅₀ value of 8.68 nM), and the P2Y₁ antagonist MRS2179 attenuated the inhibition by ADP. Treatment of sensory neurons with the phospholipase C inhibitor U73122, with the Ca²⁺-ATPase inhibitor thapsigargin, or the Ca²⁺ chelator BAPTA-AM abolished the inhibition of K_V7 channels by ADP. Moreover, ADP and ATP increased amplitudes of currents through TRPV1 receptors evoked by capsaicin.

Conclusions

Activation of P2Y₁ and P2Y₂ receptors increases the excitability of sensory neurons via a dual mechanism: an inhibition of K_V7 channels via phospholipase C and increases in intracellular Ca²⁺, and a sensitization of TRPV1 receptors, with the former mechanism being the decisive one.

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