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Bimodal action of protons on ATP currents of rat PC12 cells

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Abstract

The mode of action of extracellular protons on ATP-gated P2X2 receptors remains controversial as either enhancement or depression of ATP-mediated currents has been reported. By investigating, at different pH, the electrophysiological effect of ATP on P2X2 receptors and complementing it with receptor modelling, the present study suggests a unified mechanism for both potentiation and inactivation of ATP receptors by protons. Our experiments on patch-clamped PC12 cells showed that, on the same cell, mild acidification potentiated currents induced by low ATP concentrations (<0.1 mM) and attenuated responses to high ATP concentrations (>1 mM) with emergence of current fading and rebound. To clarify the nature of the ATP/H+ interaction, we used the Ding and Sachs's "loop" receptor model which best describes the behavior of such receptors with two open states linked via one inactivated state. No effects by protons could be ascribed to H+-mediated open channel block. However, by assuming that protons facilitated binding of ATP to resting as well as open receptors, the model could closely replicate H+-induced potentiation of currents evoked by low ATP doses plus fading and rebound induced by high ATP doses. The latter phenomenon was due to receptor transition to the inactive state. The present data suggest that the high concentration of protons released with ATP (and catecholamines) from secretory vesicles may allow a dual action of H+ on P2X2 receptors. This condition might also occur on P2X2 receptors of central neurons exposed to low pH during ischemia.

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Keywords

Fading and rebound, Modelling, pH, Potentiation, Purinergic