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Inhibition effects of P2X receptor antagonists on ecto-nucleotidases responsible for tuning pain to analgesia in the nociceptive pathway

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Purinergic signaling is involved in pain generation and modulation in the nociceptive sensory nervous system. Adenosine triphosphate (ATP) induces pain via activation of ionotropic P2X receptors, while adenosine mediates anti-nociception via activation of metabotropic P1 receptors. ATP and adenosine signaling are modulated by functional activity of ecto-nucleotidases, which are the dominant enzymes responsible for extracellular ATP degradation and adenosine generation. Our previous work had demonstrated expression of ecto-nucleotidase NTPDase3 and CD73 in the trigeminal ganglia nociceptive neurons. In addition, we detected functional ecto-ATPase and ecto-AMPase activity within the trigeminal nociceptive pathway. These results indicate that NTPDase3 and/or CD73 may provide alternative targets for drug development for controlling dental orofacial pain. In this work, we tested if purinergic receptor blockers affect ecto-nucleotidase activities detected in trigeminal nociceptive nerves. Using enzymatic histochemistry, we found that an NTPDase3 inhibitor (PSB-06126) reduced ATP degradation in trigeminal ganglion neurons and their brainstem projections. We also found that a CD73 inhibitor (adenosine 5'-(α,β-methylene) diphosphate) reduced adenosine generation in trigeminal ganglion neurons and their brainstem projections. Furthermore, we confirmed that both PSB-06126 and adenosine 5'-(α,β-methylene) diphosphate reduced ATP degradation and adenosine generation, respectively, in the outermost layer of the trigeminal sub-nucleus caudalis in the brain stem, which corresponds to the spinal cord dorsal horn nociceptive region. Effects of P2X receptor blockers (A740003, A804598, NF110) on ecto-nucleotidase activities within the trigeminal nociceptive pathway were also detected. Our results provide evidence to support the existence of ecto-nucleotidase NTPDase3 and CD73 activities within the trigeminal nociceptive pathway. Our results also highlight the potential role of agents that affect the purinergic signaling in pain signal generation and modulation by manipulation of ecto-nucleotidase activities within the trigeminal nociceptive pathway.

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