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Nucleotide homeostasis and purinergic nociceptive signaling in rat meninges in migraine-like conditions

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Abstract

© 2016, Springer Science+Business Media Dordrecht.Extracellular ATP is suspected to contribute to migraine pain but regulatory mechanisms controlling pro-nociceptive purinergic mechanisms in the meninges remain unknown. We studied the peculiarities of metabolic and signaling pathways of ATP and its downstream metabolites in rat meninges and in cultured trigeminal cells exposed to the migraine mediator calcitonin gene-related peptide (CGRP). Under resting conditions, meningeal ATP and ADP remained at low nanomolar levels, whereas extracellular AMP and adenosine concentrations were one-two orders higher. CGRP increased ATP and ADP levels in meninges and trigeminal cultures and reduced adenosine concentration in trigeminal cells. Degradation rates for exogenous nucleotides remained similar in control and CGRP-treated meninges, indicating that CGRP triggers nucleotide release without affecting nucleotide-inactivating pathways. Lead nitrate-based enzyme histochemistry of whole mount meninges revealed the presence of high ATPase, ADPase, and AMPase activities, primarily localized in the medial meningeal artery. ATP and ADP induced large intracellular Ca2+ transients both in neurons and in glial cells whereas AMP and adenosine were ineffective. In trigeminal glia, ATP partially operated via P2X7 receptors. ATP, but not other nucleotides, activated nociceptive spikes in meningeal trigeminal nerve fibers providing a rationale for high degradation rate of pro-nociceptive ATP. Pro-nociceptive effect of ATP in meningeal nerves was reproduced by α,β-meATP operating via P2X3 receptors. Collectively, extracellular ATP, which level is controlled by CGRP, can persistently activate trigeminal nerves in meninges which considered as the origin site of migraine headache. These data are consistent with the purinergic hypothesis of migraine pain and suggest new targets against trigeminal pain.

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Keywords

Adenosine, ADP, AMP, ATP, CGRP, Meninges, Migraine, NTPDase, Pain, Trigeminal neurons