View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Kazan Federal University Digital Repository

The Journal of pharmacology and experimental therapeutics, 2017, vol.361, N3, pages 472-481

Selective Calcium-Dependent Inhibition of ATP-Gated P2X3 Receptors by Bisphosphonate-Induced Endogenous ATP Analog AppppI

Ishchenko Y., Shakirzyanova A., Giniatullina R., Skorinkin A., Bart G., Turhanen P., Määttä J., Mönkkönen J., Giniatullin R.

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

Copyright © 2017 by The American Society for Pharmacology and Experimental Therapeutics. Pain is the most unbearable symptom accompanying primary bone cancers and bone metastases. Bone resorptive disorders are often associated with hypercalcemia, contributing to the pathologic process. Nitrogen-containing bisphosphonates (NBPs) are efficiently used to treat bone cancers and metastases. Apart from their toxic effect on cancer cells, NBPs also provide analgesia via poorly understood mechanisms. We previously showed that NBPs, by inhibiting the mevalonate pathway, induced formation of novel ATP analogs such as AppppI [1-adenosin-5'-yl ester 3-(3-methylbut-3-enyl) triphosphoric acid diester], which can potentially be involved in NBP analgesia. In this study, we used the patch-clamp technique to explore the action of AppppI on native ATP-gated P2X receptors in rat sensory neurons and rat and human P2X3, P2X2, and P2X7 receptors expressed in human embryonic kidney cells. We found that although AppppI has weak agonist activity, it is a potent inhibitor of P2X3 receptors operating in the nanomolar range. The inhibitory action of AppppI was completely blocked in hypercalcemia-like conditions and was stronger in human than in rat P2X3 receptors. In contrast, P2X2 and P2X7 receptors were insensitive to AppppI, suggesting a high selectivity of AppppI for the P2X3 receptor subtype. NBP, metabolite isopentenyl pyrophosphate, and endogenous AMP did not exert any inhibitory action, indicating that only intact AppppI has inhibitory activity. Ca2+-dependent inhibition was stronger in trigeminal neurons preferentially expressing desensitizing P2X3 subunits than in nodose ganglia neurons, which also express nondesensitizing P2X2 subunits. Altogether, we characterized previously unknown purinergic mechanisms of NBP-induced metabolites and suggest AppppI as the endogenous pain inhibitor contributing to cancer treatment with NBPs.

http://dx.doi.org/10.1124/jpet.116.238840