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# Stable, synthetic analogs of diadenosine tetraphosphate inhibit rat and human P2X3 receptors and inflammatory pain

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## Abstract

© 2016, © The Author(s) 2016.Background: A growing body of evidence suggests that ATP-gated P2X3 receptors (P2X3Rs) are implicated in chronic pain. We address the possibility that stable, synthetic analogs of diadenosine tetraphosphate (Ap4A) might induce antinociceptive effects by inhibiting P2X3Rs in peripheral sensory neurons. Results: The effects of two stable, synthetic Ap4A analogs (AppNHppA and AppCH2ppA) are studied firstly in vitro on HEK293 cells expressing recombinant rat P2XRs (P2X2Rs, P2X3Rs, P2X4Rs, and P2X7Rs) and then using native rat brain cells (cultured trigeminal, nodose, or dorsal root ganglion neurons). Thereafter, the action of these stable, synthetic Ap4A analogs on inflammatory pain and thermal hyperalgesia is studied through the measurement of antinociceptive effects in formalin and Hargreaves plantar tests in rats in vivo. In vitro inhibition of rat P2X3Rs (not P2X2Rs, P2X4Rs nor P2X7Rs) is shown to take place mediated by high-affinity desensitization (at low concentrations; IC50 values 100–250 nM) giving way to only weak partial agonism at much higher concentrations (EC50 values ≥ 10 μM). Similar inhibitory activity is observed with human recombinant P2X3Rs. The inhibitory effects of AppNHppA on nodose, dorsal root, and trigeminal neuron whole cell currents suggest that stable, synthetic Ap4A analogs inhibit homomeric P2X3Rs in preference to heteromeric P2X2/3Rs. Both Ap4A analogs mediate clear inhibition of pain responses in both in vivo inflammation models. Conclusions: Stable, synthetic Ap4A analogs (AppNHppA and AppCH2ppA) being weak partial agonist provoke potent high-affinity desensitization-mediated inhibition of homomeric P2X3Rs at low concentrations. Therefore, both analogs demonstrate clear potential as potent analgesic agents for use in the management of chronic pain associated with heightened P2X3R activation.

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## Keywords

dorsal root ganglion, high-affinity desensitization, inflammatory pain, P2X3 receptors, stable synthetic diadenosine tetraphosphate analogs