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Local interactions between anandamide, an endocannabinoid, and ibuprofen, a nonsteroidal anti-inflammatory drug, in acute and inflammatory pain

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Abstract

Anandamide, an endocannabinoid, is degraded by the enzyme fatty acid amide hydrolase which can be inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs). The present work was designed to study the peripheral interactions between anandamide and ibuprofen (a non-specific cyclooxygenase inhibitor) in the rat formalin test. We first determined the ED50 for anandamide (0.018 microg +/- 0.009), ibuprofen (0.18 microg +/- 0.09), and their combination (0.006 microg +/- 0.002). Drugs were given 15 min before a 2.5% formalin injection into the dorsal surface of the right hind paw. Results were analyzed using isobolographic analysis. The antinociceptive interaction between anandamide and ibuprofen was synergistic. To further investigate the mechanisms by which the combination of anandamide with ibuprofen produced their antinociceptive effects, we used specific antagonists for the cannabinoid CB1 (AM251; 80 microg) and CB2 (AM630; 25 microg) receptors. We demonstrated that the antinociceptive effects of ibuprofen were not antagonized by either AM251 or AM630 and that those of anandamide were antagonized by AM251 but not by AM630. The synergistic antinociceptive effects of the combination of anandamide with ibuprofen were completely antagonized by AM251 but only partially inhibited by AM630. In conclusion, locally (hind paw) injected anandamide, ibuprofen or combination thereof decreased pain behavior in the formalin test. The combination of anandamide with ibuprofen produced synergistic antinociceptive effects involving both cannabinoid CB1 and CB2 receptors. Comprehension of the mechanisms involved needs further investigation.

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