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Mechanisms of Non-Steroid Anti-Inflammatory Drugs Action on Acid-Sensing Ion Channels of Hippocampal Interneurons

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The inhibitiory action of non-steroid anti-inflammatory drugs (diclofenac, ibuprofen, aspirin and salicylic acid) was investigated on acid-sensing ion channels (ASIC) in isolated hippocampal interneurons and on recombinant homo- and heteromeric ASICs expressed in CHO cells. Diclofenac and ibuprofen inhibited proton-induced currents in a range of concentrations from 100 μM to 3 mM (IC_{50} were 622 ± 34 μM and 3.42 ± 0.50 mM respectively). The non-competitive inhibition was fast and fully reversible for both drugs. Aspirin and salicylic acid were ineffective up to 500 μM. Diclofenac and ibuprofen decreased the amplitude of proton-evoked currents and slowed the rate of currents decay with a good correlation between these two effects ($r = 0.99$, $p < 0.05$ for both drugs). Simultaneous application of acid solution (pH = 5.5) and diclofenac was required for its inhibitory action. Unlike amiloride, nonselective inhibitor of ENaC/Deg family of sodium channels, the action of diclofenac was voltage-independent. No competition was found between diclofenac and amiloride. Analysis of the action of diclofenac and ibuprofen on activation and desensitization of ASICs showed that diclofenac but not ibuprofen shifted the steady-state desensitization curve to more alkaline pH values. The reason for this shift was slowing down the recovery from desensitization of ASICs. Thus, diclofenac may serve as a neuroprotective agent during pathological conditions associated with acidification of extracellular environment.

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