The Role of Na\textsuperscript{+} Channel Activities in Nociception and Neuropathic Pain: Insights from Pharmacological Studies

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A frequently used method for preventing pain is the blockade of impulses in peripheral nociceptors, usually by discrete exposure of the nerve to local anesthetics or other agents that block voltage-gated Na\textsuperscript{+} channels. In such procedures relatively high concentrations of drug are used, e.g. 1 - 2 \% lidocaine (40-80 mM), about 100 times greater than the concentrations required to block normal impulses in isolated nerves equilibrated with these drugs. By contrast, the same agents may be administered intravenously to relieve neuropathic pain but at much lower plasma concentrations, e.g. 2 - 5 \mu g/ml lidocaine (5 - 10 \mu M), yet these plasma concentrations have no effect on normal action potentials, even in isolated nerve.

Two hypotheses have been proposed to explain this difference between required drug concentrations. First, the Na\textsuperscript{+} channels that are probably the primary targets for such agents may be altered during the neuronal changes that accompany chronic, neuropathic pain, such that newly expressed channels, uniquely responsible for pathological impulse patterns, are susceptible to unusually low drug concentrations. Second, a change in the distribution of the normal Na\textsuperscript{+} channels, e.g. lowered overall density, altered spatial distribution, or of other channels, e.g. K\textsuperscript{+} or Ca\textsuperscript{2+} channels, can change the nature of action potentials in injured neurons so that the resulting impulse patterns have a great sensitivity to these drugs, even with the same primary drug targets.