Abstract:

Intoxication with local anesthetics may induce cardiac arrhythmias by interaction with ion channels. Ropivacaine has been introduced into clinical anesthesia as a safer alternative to bupivacaine, which is associated with a relatively high risk of cardiac arrhythmias. Diverging safety profiles may result from differences in the mode of interaction with cardiac Na(+) channels. We conducted this study to test this hypothesis and to provide experimental basis for the ongoing discussion regarding the cardiotoxic profiles of these local anesthetics. The influence of bupivacaine and ropivacaine on the electrophysiological properties of Na(+) channels was investigated in human embryonic kidney-293 cells stably transfected with SCN5A channels cloned from the human heart using the patch-clamp technique in the outside-out configuration. Open-channel block of SCN5A channels was concentration dependent, with bupivacaine being approximately 4.5-fold more potent than ropivacaine (IC50 = 69.5 ± 8.2 ?M vs IC50 = 322.2 ± 29.9 ?M). Both drugs influenced the voltage dependency of channel activation and steady-state inactivation by shifting the membrane potential of half-maximal activation/inactivation toward somewhat more negative membrane potentials. In their inactivated state, SCN5A channels were slightly more sensitive toward bupivacaine than toward ropivacaine (IC50 = 2.18 ± 0.16 ?M vs IC50 = 2.73...
± 0.27 μM). Blockade of inactivated channels developed in a concentration-dependent manner, with comparable time constants for both drugs, whereas recovery from block was approximately 2-fold faster for ropivacaine than for bupivacaine. Human cardiac Na(+) channels show state-dependent inhibition by ropivacaine, and the mode of interaction is comparable to that of bupivacaine. Therefore, modest differences in cardiotoxicity between these local anesthetic drugs are compatible with subtle differences in their interaction with human cardiac Na(+) channels.