Enhancing Effects of Salicylate on Quinidine-Induced Block of Human Wild Type and LQT3 Related Mutant Cardiac Na⁺ Channels

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Background: To study the enhancing action of salicylate on local anesthetics, we investigated salicylate effects on quinidine-induced block of human cardiac and skeletal muscle Na⁺ channels. Methods: Human cardiac wild-type (hH1), LQT3-related mutant (ΔKPQ), and skeletal muscle (hSkM1) Na⁺ channels α-subunits were expressed in COS7 cells and were examined by the whole-cell patch clamp technique. Results: Salicylate enhanced the quinidine-induced tonic block and UDB of both wild-type hH1 and hSkM1 currents at a holding potential (HP) of -100 mV but not at a HP of -140 mV. Salicylate decreased the IC₅₀ value for the quinidine-induced tonic block of hH1 without changes in Hill coefficient at a HP of -100 mV. Salicylate further produced a shift of the steady-state inactivation curve of hH1 toward hyperpolarizing direction in the presence of quinidine. Based on the modulated receptor theory, it is probable that salicylate decreases the dissociation constant for quinidine binding to inactivated state channels. Salicylate significantly enhanced the quinidine-induced tonic block and UDB of the peak and steady-state ΔKPQ channel current. Conclusions: Salicylate enhances quinidine-induced tonic block and UDB of Na⁺ channels via increasing the affinity of quinidine to inactivated state Na⁺ channels α-subunits.

Keywords: LQT3, salicylate, quinidine