Molecular determinants for competitive inhibition of ?4?2 nicotinic acetylcholine receptors

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The Erythrina alkaloids erysodine and dihydro-?-erythroidine (DH?E) are potent and selective competitive inhibitors of ?4?2 nicotinic acetylcholine receptors (nAChRs), but little is known about the molecular determinants of the sensitivity of this receptor subtype to inhibition by this class of antagonists. We addressed this issue by examining the effects of DH?E and a range of aromatic Erythrina alkaloids on [3H]cytisine binding and receptor function in conjunction with homology models of the ?4?2 nAChR, mutagenesis, and functional assays. The lactone group of DH?E and a hydroxyl group at position C-16 in aromatic Erythrina alkaloids were identified as major determinants of potency, which was decreased when the conserved residue Tyr126 in loop A of the ?4 subunit was substituted by alanine. Sensitivity to inhibition was also decreased by substituting the conserved aromatic residues ?4Trp182 (loop B), ?4Tyr230 (loop C), and ?2Trp82 (loop D) and the nonconserved ?2Thr84; however, only