?4?2 nicotinic receptors with high and low acetylcholine sensitivity: Pharmacology, stoichiometry, and sensitivity to long-term exposure to nicotine

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?4 and ?2 nicotinic acetylcholine receptor (nAChR) subunits expressed heterologously assemble into receptors with high (HS) and low (LS) sensitivity to acetylcholine (ACh); their relative proportions depend on the ?4 to ?2 ratio. In this study, injection of oocytes with 1:10 ?4/?2 subunit cDNA ratios favored expression of HS ?4?2 nAChRs, as evidenced by monophasic ACh concentration-response curves, whereas injections with 10:1 cDNA ratios favored expression of LS ?4?2 receptors. The stoichiometry was inferred from the shifts in the ACh EC 50 values caused by Leu to Thr mutations at position 9? of the second transmembrane domain of ?4 and ?2. The 1:10 injection ratio produced the (?4)2(?2)3 stoichiometry, whereas 10:1 injections produced the (?4)3(?2)2 stoichiometry. The agonists epibatidine, 3-[2(S)-azetidinylmethoxy]pyridine (A-85380), 5-ethoxy-metanicotine (TC-2559), cytisine, and 3-Br-cytisine and the antagonists dihydro-?-erythroidine and d-tubocurarine were more potent at HS recep