

NOVEL DRUGS THAT TARGET NICOTINIC RECEPTOR SUBTYPES

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Besides the obvious connection between nicotinic receptors (nAChRs) and smoking addiction, nAChRs have also been linked to several diseases (*e.g.*, depression, epilepsy, schizophrenia, Alzheimer's and Parkinson's disease). The development of novel agents that differentiate between nAChRs subtypes may lead to new treatment strategies for these diseases. Our laboratory is designing new nAChR subtype-selective drugs that are structurally related to methyllycaconitine (MLA), the most potent nonpeptide nAChR antagonist known with selectivity for $\alpha 7$ nAChRs. In addition, MLA has moderate affinity (K_i value, 1.3 μM) for $\alpha 3\beta 4^*$ nAChRs, as documented through binding studies, and inhibits bovine adrenal catecholamine secretion (IC_{50} value, 2.6 μM) mediated through activation of $\alpha 3\beta 4^*$ nAChRs. In these studies functional and binding experiments were performed and the specificity and potency of these MLA derivatives on $\alpha 3\beta 4^*$, $\alpha 4\beta 2$, and $\alpha 7$ nAChRs receptors were determined. We have now defined structural determinants that affect potency and selectivity at specific nAChR subtypes. These data document the utility of our MLA derivatives to study nAChR subtypes and support our hypothesis that more specific nicotinic drugs can be developed that target nAChR-related pathologies.

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