Nicotinic acetylcholine receptors (nAChR) as targets of quinuclidine-based anticholinesterase drugs

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We screened the potential of quinuclidine-based compounds to interact with nicotinic acetylcholine receptors (nAChRs), important ligand-gated ion channels. The quinuclidine compounds were designed as inhibitors of the acetylcholinesterase (AChE; essential in neurotransmission) in the synapses. We hypothesized that compounds developed to bind to AChE could also act on nAChRs due to the shared substrate, the neurotransmitter acetylcholine (ACh). The interaction with the nAChRs was studied on SH-SY5Y cells as a well-accepted model, following changes in the intracellular Ca^{2+} release upon nAChRs stimulation by agonists ACh or nicotine. As results indicate, 24 out of 38 compounds inhibited nAChR signaling with both agonists. The highest IC_{50} of 0.02 μM was observed for the compound with a C14 alkyl chain attached to the quinuclidine core. This compound was also a potent inhibitor of AChE which affirms the hypothesis of its multitarget action. Also, we developed two QSAR regression models for the estimation of quinuclidine nAChR inhibition potential in the presence of ACh or nicotine. The models included only two descriptors, with MLOGP2 (octanol-water partition coefficient) present in both models, and the second descriptor being either nCs (number of total secondary C(sp3) atoms) in the case of nicotine or nH (number of hydrogen atoms) in the case of acetylcholine. Both models showed very good statistics r = 0.968, S.E. = 0.27 and S.E.cv = 0.30 (N = 29) and r = 0.968, S.E. = 0.32 and S.E.cv = 0.36 (N = 31) for pIC_{50} (nicotine) and pIC_{30} (ACh), respectively. Overall, the results indicated the potential of tested compounds to be further studied as nAChR modulators and the possibility of predicting their action using generated models.

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