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Modulation of the cholinergic system by synthetic derivatives of caffeine

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Cholinergic deficit is regarded as an important factor in Alzheimer's disease. Two molecular targets for its treatment are the acetylcholinesterase (AChE) and the nicotinic receptor (nAChR). We previously demonstrated that caffeine acts on nAChRs as a weak agonist and it is known that it inhibits AChE. Here, we synthetized more potent bifunctional caffeine derivatives or analogs. A theophylline fragment was connected with a pyrrole fragment through homologation from 3 to 7 carbon atoms to form the compounds C_3 to C_7 (C_n). We found that all C_n inhibited the AChE, having C_7 the strongest effect. To explore if the analogs influence the nAChR conformational state, the nAChR conformational-sensitive probe crystal violet (CrV) and nAChR-rich membranes from *T. californica* were used. The analogs produced changes in the K_D values of CrV, being C_5 and C_6 the most potent. To understand the molecular mechanism underlying these conformational changes, we recorded single-channel events from the muscle nAChR. We observed that all the compounds activated muscle nAChR at low concentrations and the activation was as isolated openings even at the highest Cn concentrations. Thus, our results demonstrate that the new compounds behave as dual modulators by acting as AChE inhibitors and as wick nAChR agonists. To gain insights about the molecular interaction of these compounds with both receptors we performed *in-silico* studies. Our results bring new information about the mechanism of modulation of pharmacologic targets for the design of new therapies for the intervention in neurological diseases.