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Submission ID **216** – **Poster**
Membrane Transporters and Channels

DUAL EFFECT OF THE ACETYLCHOLINESTERASE INHIBITOR CAFFEINE ON THE MUSCLE NICOTINIC ACETYLCHOLINE RECEPTOR

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Cholinergic deficit is regarded as an important factor responsible for Alzheimer's disease symptoms. One of the molecular targets for the treatment of this disease is acetylcholinesterase (AChE), an enzyme that hydrolyzes acetylcholine at the synaptic cleft. It has been shown that some AChE inhibitors also act at nicotinic receptors (nAChR) potentiating their therapeutic effect. We found that metabolic extracts of Camellia sinensis (red tea) exhibit a strong anticholinesterase activity. By chromatography and NMR spectroscopy we found that caffeine was the active compound exerting such effect. We next explored if caffeine has a direct effect on the nAChR. Using the AChR conformational-sensitive probe crystal violet (CrV), an AChR open channel blocker, and AChR-rich membranes from Torpedo californica, we observed that increasing concentrations of caffeine (10-300 μM) decreased the KD of CrV in the resting state without changes in the KD in the desensitized

state. In the presence of α-bungarotoxin, a specific AChR competitive antagonist, a dual effect was evident: low concentrations of caffeine did not produce any effect in the KD of CrV in the resting state, whereas higher concentrations produce a great increase of this value compatible with a competition with CrV for its site on the channel pore. To confirm this, we performed single channel recordings in Bosc cells expressing the adult muscle nAChR in the presence of 30 μM ACh and increasing concentrations of caffeine (150-20000 μM). We found that the mean open duration decreases, and the relative area of the briefer closed component and the cluster duration increase as a function of caffeine concentration. All these observations are compatible with an open channel blocker. Thus, our results suggest a dual effect of caffeine on the muscle AChR: at low concentrations, in the absence of agonist, induces an AChR conformational change, whereas at high concentrations caffeine acts as an AChR open channel blocker.