La Plata - 2018

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Facultad de Ciencias Médicas de La Plata - UNLP

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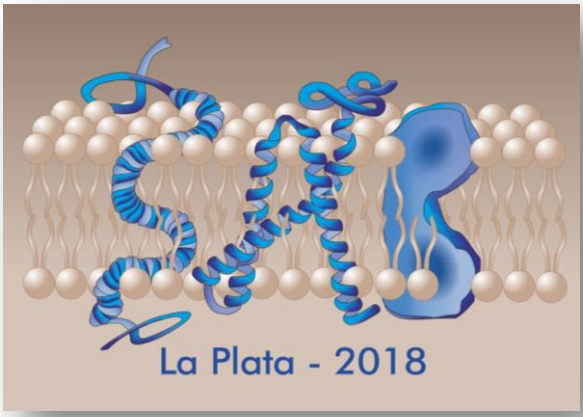

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Mechanism of 5-HT_3 receptor activation and modulation by allosteric drugs

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Serotonin type 3 receptors (5-HT_3) are cation-selective channels that belong to the Cys-loop receptor family. They are involved in fast excitatory transmission in central and peripheral nervous systems and are implicated in gastrointestinal and neurological functions. Five different subunits (A-E) have been identified in humans, and the A subunit is the only one capable of forming functional homomeric receptors (5-HT_3A). These receptors are activated by agonist binding to orthosteric sites located at the interfaces between two adjacent subunits at the extracellular region. Carvacrol and thymol have been classified as positive allosteric modulators that also act as allosteric agonists (ago-PAMs). To characterize their mechanism of activation and modulation we used the high-conductance form of the 5-HT_3A receptor that allows detection of single-channel openings from patch-clamp recordings. We observed that both ligands activate the receptor, eliciting openings in quick succession grouped in clusters of high open probability. Mean closed, open and cluster durations remained constant at all agonist concentrations tested. When each ago-PAM was evaluated in the presence of tryptamine (an orthosteric agonist), we observed events with mean open durations similar to those observed in the presence of tryptamine alone, but cluster duration was clearly prolonged probably due to decreased desensitization. These results suggest that the mechanism of activation is governed by the orthosteric agonist while the allosteric drug is only acting as a potentiator. Altogether, our results describe the mechanism underlying human 5-HT_3A receptor activation and modulation by two allosteric agonists and provide relevant information for the design of more efficacious and specific drugs.