La Plata - 2018

XLVII Reunión Anual de la Sociedad Argentina de Biofísica

Libro de Resúmenes

5 al 7 de Diciembre 2018

Facultad de Ciencias Médicas de La Plata - UNLP

Molecular Pharmacology of a Serotonin-gated Chloride Channel

Rodriguez Araujo N[a], Corradi J[a], Bouzat C[a]
a - Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB-CONICET)

Serotonin-gated ion channels (5-HT_3) belong to the family of Cys-loop receptors, which are pentameric proteins that mediate fast synaptic transmission. In mammals, 5-HT_3 receptors are non-selective cation channels that can be found as homomers (5-HT_3A) or heteromers when combined with 5HT3B-E subunits. The free-leaving nematode *Caenorhabditis elegans* is a model for the study of the nervous system and human diseases, and for antiparasitic drug discovery. *C. elegans* contains a homomeric serotonin-gated Cys-loop receptor, MOD-1, that is permeable to chloride. We here expressed MOD-1 in mammalian cells and explored the properties of activation and modulation of MOD-1 by whole cell recordings. Dose-response curves showed an EC_{50} for 5-HT of ~1 mM, which is in the same range as that of human 5-HT_3A receptors. The analysis showed that currents do not show rectification, desensitize slowly and recover from desensitization with a time constant of about 1 s. To characterize the pharmacology of MOD-1, we tested compounds that have been shown to modulate 5-HT_3 and other Cys-loop receptors. The antiparasitic drug ivermectin (IVM), which acts as an activator or modulator of different receptors, neither activated nor potentiated MOD-1. However, pre-exposure to IVM (10-50 mM) decreased 5-HT induced currents, indicating that it acts as an inhibitor of MOD-1. The 5-HT_3 receptor potentiator, 5-hydroxyindol, did not affect MOD-1 function, whereas thymol, which is an activator and/or modulator of 5-HT_3 receptors, could only modulate MOD-1 activity. These results contribute to the understanding of the molecular pharmacology of MOD-1 as a potential drug target for anthelmintic therapy.