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CELLULAR AND MOLECULAR NEUROBIOLOGY

Human 5-HT3 receptors: Structural and functional features.

Albano Mazzarini Dimarco^{1,2}, Cecilia Bouzat^{1,2}, Jeremías Corradi^{1,2}

1 Instituto de Investigaciones Bioquímicas de Bahía Blanca - INIBIBB

2 Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur

Presenting author:

Albano Mazzarini Dimarco, amazzarini@inibibb-conicet.gob.ar

The 5-HT3 receptor is a ligand-gated ion channel that converts the binding of serotonin (5-HT) into a transient cation current which mediates fast excitatory responses in peripheral and central nervous systems. Five human subunits (A-E) have been identified to date. The A subunit can assemble to form homomeric receptors (5-HT3A), or combine with B-E subunits to form heteromeric receptors (5-HT3AB-E). To determine subunit composition and stoichiometry of heteromeric receptors we constructed a high-conductance A subunit (AHC), which allowed us to detect single-channel events, and expressed the AHC with C, D or E subunits. From macroscopic currents we observed an increase in the 5-HT EC50 values for all subunit combinations with respect to that of 5-HT3AHC. Expression of the AHC to form 5-HT3AHC receptors showed opening events of homogeneous amplitudes. However, when AHC was expressed in combination with one of the C-E subunits, events with different amplitudes were detected, thus confirming the expression of heteromeric receptors. In-silico studies provided insights into the contribution of the different subunits to the binding site conformation. Thus, our results confirm that C-E subunits can combine with the A subunit to form heteromeric receptors, and bring structural and functional details about the different human 5-HT3 receptors that can be expressed.