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Differential functional properties between homoeric and heteromeric 5-HT3 receptors

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The serotonin type 3 receptor (5-HT3) is a ligand-gated ion channel that converts the binding of serotonin (5-HT) into a transient cation current and mediates fast excitatory responses in peripheral and central nervous systems. Five human subunits (A-E) have been identified to date, of which only the A subunit can form homomeric receptors (5-HT3A). We performed single-channel and macroscopic current recordings from cells expressing different subunit combinations to determine how the accessory subunits (B-E) contribute to the receptor functional properties. The incorporation of the B subunit increased about 5-fold the EC50 value of 5-HT responses with respect to 5-HT3A receptors. At the single-channel level, 5HT3A receptors cannot be studied due to their reduced conductance. Thus, we also used a high-conductance A subunit (AHC) that forms channels of about 4.5 pA, with openings grouped in long activation episodes of 287 ± 123 ms (-70 mV). The heteromeric 5-HT3AB channel showed reduced amplitude (about 2.0 pA) and briefer activation episodes with respect to the homomeric receptor (47.1 ± 4.4 ms). The pattern of channel activation did not show a clear 5-HT concentration dependence for 5HT3A and 5HT3AB receptors. Also, both receptors were activated and potentiated by the allosteric agonist carvacrol. Expression of AHC with C, D or E subunits showed opening events of different amplitudes, indicating that A can assemble with one of these accessory subunits. However, the frequency of opening was very low, suggesting that more complex subunit arrangements may occur. Molecular docking studies provided insights into how the different accessory subunits may contribute to the binding site. This study provides information required for identifying functional heteromeric receptors in native cells and for understanding their distinct roles and opens doors for the development of specific ligands.

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