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Ligand-gated ion channels: From 3D structure to transmembrane signaling

Neurotransmitter-gated ion channels of the Cys-loop receptor family mediate fast neurotransmission throughout the nervous system. The molecular processes of neurotransmitter binding, subsequent opening of the ion channel and ion permeation remain poorly understood. Here we review the progress in the field and present our own recent results of high-resolution X-ray crystallography, single particle imaging, and molecular modeling studies of a mammalian Cys-loop receptor, the mouse serotonin 5-HT_3 receptor. We revealed at atomic detail how neurotransmitter binding on the extracellular domain of the 5-HT_3 receptor induces sequential conformational transitions in the receptor opening a transmembrane ion channel: Agonist binding first induced distinct conformational fluctuations of particular side chains in the highly conserved ligand binding cage, followed by tilting-twisting movements of the extracellular domain which coupled to the transmembrane TM2 helices to open the hydrophobic gate and forming a continuous transmembrane water pathway. The structural transitions in the receptor's transmembrane part finally coupled to the intracellular region opening passages for ion release. The details of structural transitions of the 5-HT_3 receptor deliver important insights for understanding the activation mechanism of mammalian Cys-loop receptors.

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