(P12) Multi-cavity structure of the inositol 1,4,5-trisphosphate receptor with L-shaped ligand-binding domains

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Inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R) is an intracellular Ca^{2+} release channel that is gated by co-agonists, Ca^{2+} and IP_3. Ca^{2+} released through the channel triggers numerous physiological processes, including fertilization, cell proliferation, development, muscle contraction, secretion, and neural plasticity. The structure of the IP_3R has been divided into five functional domains: the N-terminal coupling domain, the IP_3-binding domain, the internal coupling domain, the transmembrane domain, and the C-terminal gatekeeper domain. We clarified a 2.2-angstrom crystal structure of the IP_3-binding domain, residues 224 to 604, of mouse type 1 IP_3R in complex with IP_3. The asymmetric, boomerang-like structure consists of an N-terminal β-trefoil domain and a C-terminal α-helical domain containing an 'armadillo repeat'-like fold. The cleft formed by the two domains exposes a cluster of arginine and lysine residues that coordinate the three phosphoryl groups of IP_3. Putative Ca^{2+}-binding sites are identified in two separate locations within the IP_3-binding core. We also analyzed the three-dimensional structure of the IP_3-free form of the homotetrameric receptor. The analysis was based on single particle technique using an originally developed electron microscope equipped with a helium cooled specimen stage (cryo-electron microscopy) and an automatic particle picking system. The structure is composed of a spherical cytoplasmic domain and a square-shaped lumenal domain. It is similar in the voltage-sensitive Na^+-channel, although the cytoplasmic domain of IP_3R is roughly ten times bigger than that of Na^+-channel. Multiple internal cavities connect the transmembrane domain to the large cytoplasmic domain containing prominent four L-shaped densities, in which we fit the crystal structure of the IP_3-binding domain. To obtain a better fit into the density map of the unliganded IP_3R, the crystal structure had to be modified, consequently the two calcium-binding sites in the IP_3-binding domain come into close vicinity. These changes indicate a possible mechanism for the regulation of Ca^{2+} release by the two co-agonists, Ca^{2+} and IP_3.

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