Three-dimensional rearrangements within IP_3 receptor by Ca^{2+}

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Allosteric binding of Ca^{2+} to IP_3 receptor (IP_3R) is essential to control the IP_3-gated release of Ca^{2+} passing through a channel domain within IP_3R. The requirement of dual messengers, IP_3 and Ca^{2+}, for channel regulation of IP_3R is considered to be pivotal for the crosstalk and coordinated dynamics of intracellular signalling. Here, we present biochemical and electron microscopic evidence of Ca^{2+}-sensitive structural changes in the three-dimensional (3D) structure of type 1 IP_3R. (J. Biol. Chem. 277 21115-21118 2002, J. Biol. Chem (in revision) 2003). Low concentrations of Ca^{2+} and high concentrations of Sr^{2+} and Ba^{2+} were shown to be effective for the limited proteolysis, but Mg^{2+} had no effect on the proteolysis at any concentrations tested. The electron microscopy and the limited proteolysis consistently demonstrated that the effective concentration of Ca^{2+} for conformational changes was less than 10^{-7} M, that this low concentration of Ca^{2+} only acted as a co-activator, and that IP_3 scarcely affected the conformational states. The structure without Ca^{2+}, as reconstructed by 3D electron microscopy, had a "mushroom-like" appearance consisting of a large square-shaped head and a small channel domain linked by four thin bridges. The projection image of the "head-to-head" assembly comprising two particles confirmed the side view of the 3D structure without Ca^{2+}. The "windmill-like" form with Ca^{2+} also contains the four bridges connecting from the IP3-binding domain towards the channel domain. These data suggest that the Ca^{2+}-specific conformational change structurally regulates the IP_3-triggered channel opening.

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