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Role of IP_3 receptor signaling in cell functions and diseases

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A B S T R A C T

IP_3 receptor (IP_3R) was found to release Ca^{2+} from non-mitochondrial store but the exact localization and the mode of action of IP_3 remained a mystery. IP_3R was identified to be P_{400} protein, a protein, which was missing in the cerebellum of ataxic mutant mice lacking Ca^{2+} spikes in Pukinje cells. IP_3R was an IP_3 binding protein and was a Ca^{2+} channel localized on the endoplasmic reticulum. Full-length cDNA of IP_3R type 1 was initially cloned and later two other isoforms of IP_3R (IP_3R type 2 and type 3) were cloned in vertebrates. Interestingly, the phosphorylation sites, splicing sites, associated molecules, IP_3 binding affinity and 5′ promoter sequences of each isoform were different. Thus each isoform of IP_3 receptor plays a role as a signaling hub offering a unique platform for matching various functional molecules that determines different trajectories of cell signaling. Because of this distinct role of each isoform of IP_3R, the dysregulation of IP_3 receptor causes various kinds of diseases in human and rodents such as ataxia, vulnerability to neuronal degeneration, heart disease, exocrine secretion deficit, taste perception deficit. Moreover, IP_3 was found not only to release Ca^{2+}, but also to release IRBIT (*I*P_3 *r*eceptor *b*inding protein released with *i*nositol *t*risphosphate) essential for the regulation of acid-base balance, RNA synthesis and ribonucleotide reductase.

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The beginnings

When cells receive signals through receptors on the plasma membrane, the information is transmitted to various types of signaling cascades inside the cells leading cells to respond. Among the various intracellular signaling pathways, IP_3 signaling and diacylglycerol (DAG)-protein kinase C (PKC) pathways are fundamental to cell physiology. Upon activation of upstream receptors, two messenger molecules, IP_3 and DAG are hydrolyzed from phosphatidylinositol 4,5-bisphosphate (PIP2). This bifurcating signaling pathway is of fundamental importance in regulating a wide range of cellular processes (Fig. 1). DAG activates PKC to phosphorylate various proteins, leading to various cellular responses. As for the other messenger molecule IP_3, an important breakthrough occurred when it was demonstrated that IP_3 releases Ca^{2+} from non-mitochondrial internal stores (Streb et al., 1983) and that this Ca^{2+} released from internal store seemed to play various roles. It was puzzling why IP_3, a molecule with such simple structure, could exert such diverse functions.

Search for the target molecule of IP_3

Why does IP_3 exert such a variety of phenomena? The source of variety could be the function of Ca^{2+} or IP_3R. There are many papers on the function of Ca^{2+} up to now (Carafoli and Klee, 1999; Mikoshiba, 2007b, 2012; Pochet, 2000; Maruyama, 1995) (Islam, 2012). Therefore, I here focus on the mechanism how IP_3 signal is converted to multiple signals. To understand the function of IP_3, one way is to analyze the enzymes that synthesizes or degrade IP_3. Another way is to study the property of the target molecule of IP_3, IP_3 receptor, and investigate its biochemical, molecular and physiological properties. For this purpose they tried to identify IP_3R protein. There were various approaches to understand the property of IP_3R. One approach is to purify IP_3 binding protein and to subsequently determine of the amino acid sequence. Another approach is to clone the cDNA that encodes the full-length IP_3R, which also tells us the amino acid sequence of the IP_3R. The most important thing was to purify and characterize the IP_3R from the aspects of biochemistry and physiology.

Purification of the IP_3 receptor

Many researchers were attempting to purify the protein from various tissues (Spat et al., 1986) (Prentki et al., 1984; Sudhof et al., 1991; Supattapone et al., 1988) (Maeda et al., 1988): The IP_3 binding

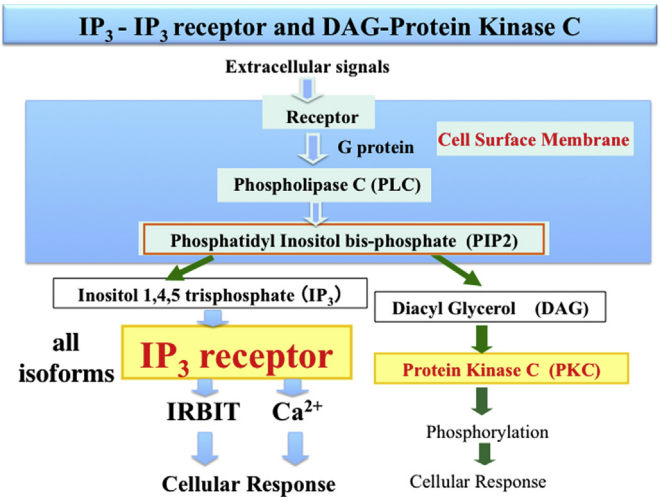

Fig. 1. IP_3– IP_3 receptor and Diacylglycerol (DAG)-Protein Kinase C (PKC) signaling system. IP_3 binds to IP_3 receptor and releases Ca^{2+} from intracellular stores and also releases IRBIT from the IP_3 binding core of IP_3 receptor. DAG activates PKC and PKC regulates various molecules by phosphorylation.