Minireview

The Inositol 1,4,5-Trisphosphate Receptor – Transcriptional Regulation and Modulation by Phosphorylation

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Abstract. Inositol 1,4,5-trisphosphate receptors (IP_3Rs) are intracellular membrane calcium channels essential for the release of calcium from intracellular stores. They form pathways for Ca^{2+} release that amplifies signals transmitted *via* plasma membrane receptors and so mediate a large array of calcium-regulated signal transduction events, from control of gene expression, through regulation of cell proliferation and other functions, to cell death. Molecular properties, expression and regulation of IP_3Rs have been recently reviewed by others and thus these aspects will be mentioned only briefly in this article. This minireview will focus on the transcriptional regulation of IP_3Rs and their modulation by phosphorylation.

Key words: Inositol 1,4,5-trisphosphate receptor — Transcriptional regulation — Phosphorylation

The inositol 1,4,5-trisphosphate receptors (IP_3Rs) are intracellular membrane calcium channels essential for calcium release from intracellular stores. They mediate the calcium-mobilising effect of a wide range of hormones, cytokines and neurotransmitters. Activation of these receptors results in intracellular calcium signals that display impressive fidelity, frequently manifested through a complex array of temporal and spatial characteristics (Yule 2001). Molecular cloning has identified three isoforms of IP_3Rs, IP_3R type 1, 2 and 3 (IP_3R-1, -2 and -3). All three isoforms are 60–70 % homologous and vary in their tissue distribution and hugely in their levels of expression (Berridge 1993; Taylor et al. 1999). The IP_3R consists of homotetramers or heterotetramers of IP_3R isoform subunits with approximately 2,700 amino acids *per* subunit, having approximate molecular mass of 300 kDa. Each subunit contains three functionally distinct regions: the transmembrane ion channel pore domain at the C-terminal end, the IP_3-binding domain at the N-terminal region and the modulatory (transduction) domain between them (Patel et al. 1999; Thrower et al. 2001; Bosanac et al. 2002). The transmembrane domain

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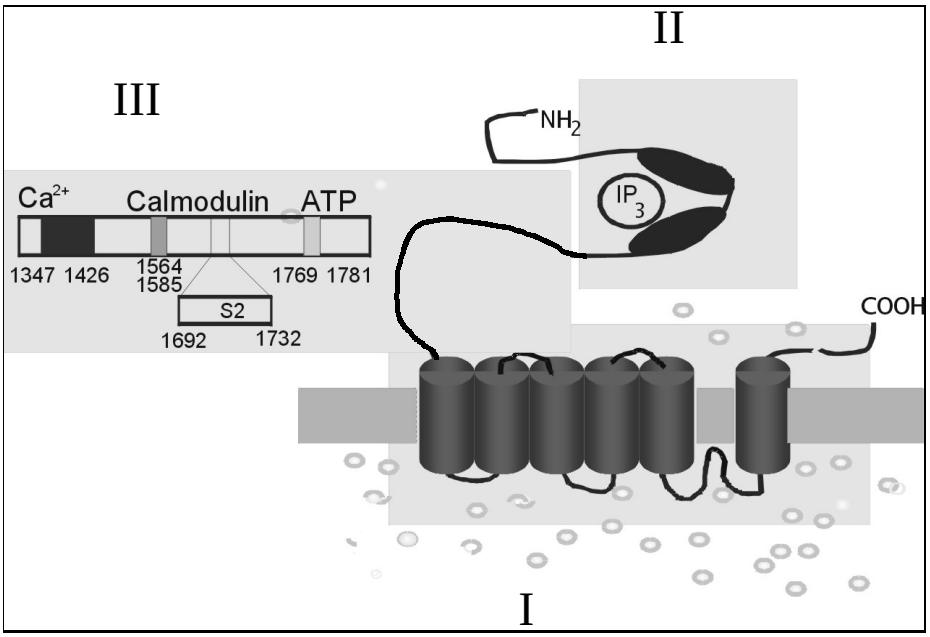

Figure 1. Structure of the IP_3 receptor. IP_3R contains three functionally distinct regions: I, transmembrane ion channel pore domain at the C-terminal end; II, IP_3-binding domain at the N-terminal region; and III, modulatory domain between them. Modulatory domain contains binding sites for calcium, ATP and calmodulin, but also alternatively spliced S2 region.

contains 6 transmembrane segments, with a pore forming region between segments 5 and 6 (Figure 1). Majority of the calcium binding sites occurs in the modulatory domain, where also the putative binding sites for calmodulin and adenosine triphosphate (ATP) are localised.

The three-dimensional structure of the IP_3R-1 was reported at a 2.4 nm resolution (Jiang et al. 2002). The structure of IP_3R-1 was strikingly different from that of the ryanodine receptor calcium release channel. The IP_3R assumes the shape of an uneven dumbbell with one end significantly larger than the other. The larger bulky end with four arms protruding laterally by about 5 nm was suggested to constitute the cytoplasmic side of the protein. The IP_3R is about 17 nm high and the lateral dimension is about 15.5 nm. The smaller end, the lateral dimension of which is about 10 nm, probably forms the membrane-spanning domain with the central pore. Recently, the crystal structure of the IP_3-binding core of IP_3R-1 in complex with IP_3 (residues 226–576) at a 0.22 nm resolution has been presented (Bosanac et al. 2002). The cleft formed between an N-terminal β-trefoil domain (residues 224–436) and a C-terminal α-helical domain containing an 'armadillo repeat'-like fold (residues 437–604) exposes a cluster of arginine and lysine residues that coor-

dinate the three-phosphoryl groups of IP_3. Residues E425, D426, E428, D442 and D444 have been shown to be essential for the coordination of Ca^{2+} (Sienaert et al. 2002). These residues within the IP_3-binding domain are a part of the two putative Ca^{2+}-binding sites. This leads to a tempting speculation on the Ca^{2+}-IP_3 coupling mechanism required for channel activation. Binding of Ca^{2+} to the IP_3R-1 induced marked structural changes in the tetrameric receptor, indicating that Ca^{2+} ions regulate IP_3R gating activity through the rearrangement of functional domains (Hamada et al. 2002).

IP_3R interacts physically with many proteins (for a review see Bultynck et al. 1999). All IP_3R subtypes interact with talin, a focal contact cytoskeletal protein, vinculin and α-actin (Sugiyama et al. 2000). A direct interaction between IP_3Rs and myosin II regulates local organisation of IP_3 signalling in *C. elegans* (Walker et al. 2002). Interaction with the store-operated channel/Ca^{2+}-release calcium channel (CRAC), with HIV-1 pathogenicity factor, or with homer proteins in the longitudinal sarcoplasmic reticulum of skeletal muscle fibres were observed (Lewis 2001; Manninen and Saksela 2002; Salanova et al. 2002). Yoo et al. (2000, 2001) showed complex formation between IP_3Rs and chromogranins A and B in the native state in the secretory granules of bovine adrenal medullary chromaffin cells.

The IP_3R-1 is predominantly expressed in the central nervous system, particularly in the cerebellum. The IP_3R-2 is present in many tissues; high levels are found in the spinal cord and glial cells. The IP_3R-3 is found in the kidney, brain, gastrointestinal tract and pancreatic islets (Furuichi et al 1990; Miyakama et al. 1999). IP_3Rs are most abundantly expressed in intracellular membranes of the organelles, e.g. in the endoplasmic reticulum, the nuclear envelope, the Golgi apparatus, and possibly in secretory vesicles (for review see Taylor et al. 1999; Nakanishi et al. 1996). IP_3Rs are also expressed in the plasma membrane of some cells (Putney 1997; Lischka et al. 1999; Tanimura et al. 2000). Recently it was found that IP_3Rs are functionally involved in the store-operated calcium influx, mitochondrial calcium homeostasis, and excitation-contraction coupling in the atrium (Kiselyov et al. 1998; Hajnoczky et al. 2000; Lipp et al. 2000; Gilabert et al. 2001).

Chronic stimulation of receptors linked to the formation of IP_3 led, over a period of several hours, to a massive decrease in the number of IP_3Rs, a decrease in sensitivity of the intracellular Ca^{2+} stores to IP_3, and also a decrease in the frequency of Ca^{2+} puffs (Wojcikiewicz and Nahorski 1991; Wojcikiewicz et al. 1992; Tovey et al. 2001). Such adaptive decreases in IP_3 sensitivity have now been observed in many cell types. The large conformational changes that follow IP_3 binding to its receptors seem to be the essential trigger for IP_3R degradation (Zhu et al. 1999). Poly-ubiquitination, covalent attachment of the short protein, ubiquitin, to lysine residues of a target protein of IP_3R, followed by degradation in proteasomes (the ubiquitin/proteasome pathway) was suggested in the process of degradation (Hershko and Ciechanover 1998; Oberdorf et al. 1999). Phosphorylation of Ser-1588 and 1755 did not inhibit IP_3R poly-ubiquitination (Wojcikiewicz et al. 2003).

IP_3R subtypes differ markedly in their response to endogenous as well as exogenous modulators. Details of the effect of the endogenous modulators, i.e. IP_3,

Ca^{2+}, ATP, phosphorylation, on IP_3Rs were recently reviewed (Taylor 1998; Patel et al. 1999; Iino 2000; Thrower et al. 2001) and we will focus only on some of them.

It is generally accepted that IP_3R is activated only in the presence of IP_3. However, the recently discovered family of calmodulin (CaM)-like neuronal Ca^{2+} sensor proteins called Ca^{2+}-binding proteins (CaBPs/caldendrin) were reported to activate IP_3R in the absence of IP_3 (Yang et al. 2002). Moreover, chromogranin A, which forms a complex with IP_3R, drastically increased IP_3R channel activity in the secretory granules of bovine adrenal medullary chromaffin cells (Thrower et al. 2002).

Single channel properties of IP_3Rs were obtained mostly in bilayer lipid membranes, where Ca^{2+} was used as an ion carrier. Cytosolic Ca^{2+}, binding directly to IP_3R, exerts a bell-shaped dependence on the IP_3R-1. Low concentrations of calcium (200–300 nmol/l) increase channel activity in the presence of IP_3, while high Ca^{2+} concentrations inhibit it (Iino 1990; Bezprozvanny et al. 1991). It was reported that the Ca^{2+} dependence of single IP_3R-2 is not bell-shaped and that IP_3R-3 is not inhibited at high Ca^{2+} concentrations (Hagar et al. 1998). However, the inhibitory effect of calcium on all types of IP_3R is still controversial, since it was not observed in other studies (Swatton et al. 1999; Missiaen et al. 1998 ; Mak et al. 2000).

In presence of the IP_3, ATP increases activity of IP_3Rs (Bezprozvanny and Ehrlich 1993) by binding to two high affinity sites on the IP_3R-1 or to one binding site on the IP_3R-3 (Maes et al. 2000). At higher concentrations (0.5 mmol/l) it inhibits IP_3R, what can be prevented by raising the IP_3 concentration, indicating possible competitive binding of ATP to the IP_3-binding domain. On the other side, different modulation of single channel properties of IP_3Rs by IP_3, Ca^{2+} and ATP was observed in patch clamp studies of IP_3R channels in the outer membrane of isolated cell nuclei (Mak et al. 2000, 2001; Boehning et al. 2001). This controversy among the results obtained in the lipid bilayer and in patch clamp experiments is not yet resolved.

Despite the fact that different calmodulin-binding sites have been characterised in the IP_3R, their function remains elusive (for review see Nadif Kasri et al. 2002). CaM inhibited IP_3 induced Ca^{2+}-release (IICR), regulated IP_3R sensitivity to Ca^{2+}, and inhibited IP_3R-1 in planar lipid bilayer (Michikawa et al. 1999). However, in some reports the interaction of CaM with the high-affinity Ca^{2+}-CaM-binding site in the modulatory domain of the IP_3R-1 did not play a direct role in biphasic modulation of IP_3R-1 by cytosolic Ca^{2+} or in IP_3R-1 inhibition by CaM (Nosyreva et al. 2002).

A variety of pharmacological compounds modulates IP_3R function (for review see Michelangeli et al. 1995). The most of them function as non-specific modulators. Only a few compounds activate IP_3R directly. Recently, new exogenous compounds adenophostin A and B from fungal products were found to be full IP_3R agonists. They activated IP_3R in the absence of IP_3 and were approximately 100-fold more potent than IP_3 (Takahashi et al. 1994). Several pharmacologically active drugs inhibit IP_3Rs non-specifically. The most common is the non-specific competitive

inhibitor heparin. The compound KN-93, a Ca^{2+} calmodulin-dependent protein kinase II (Ca^{2+}/CaMKII) inhibitor, directly inhibited IP_3R-1, and the compounds 2-aminoethoxydiphenyl borate (2APB) and curcumin inhibited IICR from cerebellar microsomes (Maruyama et al. 1997; Dyer et al. 2002; Smyth et al. 2002). Uchiyama et al. (2002) developed a recombinant hyperaffinity IP_3 absorbent (IP_3 sponge), which has approximately 1000-fold higher affinity for the IP_3 than the parental IP_3R-1. Trapping IP_3 with the IP_3 sponge inhibited IICR in cells or microsomes. The IP_3 sponge is a specific and significant tool for studying IP_3-calcium signalling.

Gene transcription and modulation of IP_3R gene expression

Transcription of the IP_3Rs is directed from their promoters. A promoter of the IP_3R-1 gene was assigned between −528 to +169 relative to the transcription start site (Furutama et al. 1996). The IP_3R-1 gene has a typical RNA polymerase II-type promoter with a unique transcription initiation point and a consensus TATA-box in the promoter. The nucleotide sequence of the 5' region of the human IP_3R-1 gene exposed potential transcription regulatory sites (Figure 2). These potential transcription regulatory sites include the steroid hormone response element (HRE), CAATT enhancer-binding protein element (C/EBP), retinoic acid responsive element (RARE), AP-1 and AP-2 sites, NF-κB sites and SRE (Kirkwood et al. 1997). Although C/EBP was found in several regions of hippocampus, in cerebellar Purkinje cells and in part of the cortex in the adult brain of mice, it cannot be responsible exclusively for the predominate expression of the IP_3R-1 gene in CNS, because C/EBP binding site is outside of the region (from −528 to +169) capable of inducing normal expression patterns in transgenic mice (Furutama et al. 1996).

In both the human and mouse promoter, putative binding sites for transcription factors sensitive to retinoic acid were found. The activity of the isolated human IP_3R-1 promoter is decreased by approximately 30 % after treatment with 0.5 μmol/l retinoic acid for 48 hours. This decrease in human IP_3R-1 promoter activity is likely to be mediated through the AP-2 binding site (Deelman et al. 1998). Also, endogenous IP_3R-1 mRNA is downregulated in A7r5 cells after treatment with 0.5 μmol/l retinoic acid for 48 hours, indicating that the endogenous rat IP_3R-1 promoter is also sensitive to retinoic acid (Deelman et al. 1998).

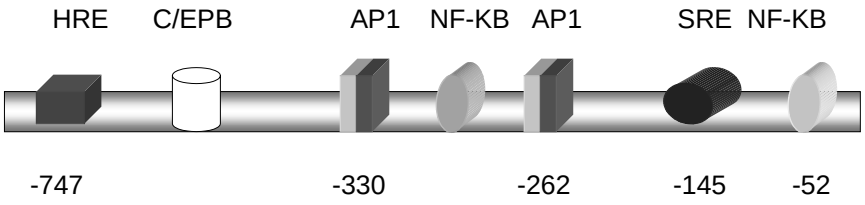

Figure 2. Potential transcription regulatory sites of the human IP_3R-1 gene.

Comparison of the promoter structures of the three genes of IP_3R-1, -2 and -3 revealed that the promoter structures of the ubiquitous IP_3R-2 and -3 genes were obviously distinct from that of the neural IP_3R-1 (Tamura et al. 2001). The IP_3R-1 promoter contains a TATA element and a single transcription start site, while the type 2 and 3 receptor genes, have no consensus TATA element and possess multiple transcription start points (seven for IP_3R-2 and four for IP_3R-3; Morikawa et al. 1997; Tamura et al. 2001). Seven transcription start points for the IP_3R-2 gene are located around 300 bp upstream from the first ATG codon and for the IP_3R-3 gene there are four transcription start points between positions −325 and −285. Additionally, from comparison with IP_3R-1, these two genes are relatively rich in G/C nucleotides in their promoter regions (i.e. IP_3R-1, 62 %; IP_3R-2, 73 %; IP_3R-3, 83 %) (Tamura et al. 2001). Moreover, a number of CpG-islands (clusters of CG or GC) were observed in the control region of IP_3R-2 and -3 genes. These features of a promoter are characteristic of the so-called housekeeping genes that exhibit ubiquitous expression patterns (Tamura et al., 2001).

The gene encoding the type 1 isoform is subject to alternative splicing and gives rise to three splice variants that have been denoted as S1, S2 and S3. The S1 splice site is located in the ligand-binding domain, whereas the S2 and S3 splice sites are in the regulatory domain (Lin et al. 2000). Both the short and the long form of S1 and S3 appear to coexist in the same tissues, while the expression of the S2 variant differs in neurons and peripheral tissues (Kocan et al. 2002). The S1 splice site formed by splicing in the middle of the ligand binding domain may alter the properties of IP_3R binding, while the presence or absence of the S2 splice site may modify regulation of IP_3Rs-1, probably through the protein kinase A (PKA) phosphorylation sites and changes in kinetics (Danoff et al. 1991). S2 splicing has an effect on ATP sensitivity (Tu et al. 2002). The apparent affinity to potentiation by ATP is reduced approximately six-fold in the non-neuronal (peripheral) IP_3R-1 S2(−) isoform. In contrast, the level of basal activity in the absence of ATP is elevated two-fold for the S2(−) isoform (Tu et al. 2002). The ATPA site is intact in IP_3R-1 S2(−) isoform and the observed changes are likely to be attributable to overall changes in the conformation of the IP_3 coupling domain induced by the S2 splicing event. It is also possible that the additional ATPC site created in IP_3R-1 S2(−) isoform by S2 excision (Ferris and Snyder 1992) is inhibitory, leading to reduction in the apparent affinity of IP_3R-1 for ATP. Boehning et al. (2001) described the single-channel properties of all, the neuronal (S2(+)), non-neuronal (peripheral; S2(−)) and recombinant (S2(+/−) IP_3R-1 in native mammalian membranes. No differences in calcium selectivity and channel gating were observed between S2(+) and S2(−) splice variants (Boehning et al. 2001).

Modulation of the gene expression of IP_3Rs can differ according to the tissue. Therefore, we tested the effect of single immobilisation (which is one of the most potent stressors) for two hours on IP_3R-1 in renal medulla (Zacikova et al. 2000), cardiac atria (Lencesova et al. 2002) and stellate ganglia (Micutkova et al. 2003) of rats. In renal medulla of normotensive rats, immobilisation decreased the gene expression of IP_3Rs significantly within two hours (Zacikova et al. 2000). In

stellate ganglia, single exposure to immobilisation stress had no effect on the gene expression of IP_3R-1 (Micutkova et al. 2003). In cardiac atria, gene expression of IP_3Rs-1 and -2 was upregulated by single immobilisation stress for 2 hours and this increase in gene expression was glucocorticoid-dependent (Lencesova et al. 2002). Nevertheless, when animals were exposed to repeated immobilisation for 7 days, two hours daily, a significant decrease in IP_3Rs-1 occurred in all these tissues.

Downregulation of IP_3R gene expression was observed also in heart failure derived from end-stage dilated cardiomyopathy (Barrans et al. 2002). Nevertheless, it still remains to be elucidated whether downregulation of IP_3Rs is a cause, or a consequence of the pathological stage.

Modulation of IP_3R function by phosphorylation

IP_3Rs contain consensus sequences for phosphorylation and they have been reported to be phosphorylated by cAMP-dependent PKA (Wojcikiewicz and Luo 1998), protein kinase C (PKC), cGMP-dependent protein kinase G (PKG), CaMKII and protein tyrosine kinases (PTKs) (for review see Patel et al. 1999; Thrower et al. 2001). For example, human cerebellum IP_3R-1 has the following total number of consensus phosphorylation sites: 3 for PKA, 6 for PKC, 43 for casein kinase II (CKII), 16 for CaMKII, and 3 for tyrosine kinase (TK) (Patel et al. 1999). This indicates that there is a huge number of combinations of phosphorylated/dephosphorylated sites. For example, if there are seven potential phosphorylated sites (each monomer equally phosphorylated/dephosphorylated), there are 128 different possible phosphorylation stages of the channel. Since phosphorylation/dephosphorylation modulates channel function (Jayaraman et al. 1996; DeSouza et al. 2002), the effects of phosphorylation/dephosphorylation might be very complex.

IP_3R can undergo also autophosphorylation. Ferris et al. (1992) demonstrated autophosphorylation of a purified and reconstituted rat cerebellum IP_3R on a serine residue and found serine protein kinase activity of the IP_3R towards a specific peptide substrate. Stoichiometric levels of the autophosphorylation were 0.4 mol of phosphate/mol of IP_3R. This demonstrated that only a fraction of IP_3Rs was capable of autophosphorylation. Recently, it was reported that protein kinases, melanoma and kidney α-kinases were covalently linked with ion channels (Riazanova et al. 2001). This may indicate that more membrane channels can exhibit kinase activity.

Recent evidence supports a view that IP_3Rs function as multiprotein complexes. Several proteins having phosphorylation or dephosphorylation activity were reported to be associated with IP_3Rs. Schlossmann et al. (2000) identified a 125,000 dalton protein IRAG, which was bound to the IP_3R-1 and to cGMP-dependent protein kinase I (cGKIβ). Stimulation of T-lymphocytes caused a physical association between the non-receptor PTK in the *Src* family and IP_3R-1 (Jayaraman et al. 1996).

B-cell scaffold protein with ankyrin repeats (BANK), a substrate of TK is associated with PTK-Lyn and IP_3R. BANK promotes PTK-Lyn mediated tyrosine phosphorylation of IP_3R (Yokoyama et al. 2002). A physical association of the protein phosphatase calcineurin with the IP_3R *via* an immunophilin protein FKBP12 was reported (Cameron et al. 1995). On the other hand, Bultynck et al. (2001) did not find a specific, high-affinity interaction between IP_3R-1 or -2 with FKBP12. Regulation of IP_3R by calcineurin and FKBP12 remains controversial.

Recently it was shown that PKA and the protein phosphatases PP1 and PP2A are components of the IP_3R-1 macromolecular signalling complex (DeSouza et al. 2002; Tang et al. 2003). This finding points to the similarities between this complex and that of the closely related ryanodine calcium release channels (RyR1 and RyR2; Marx et al. 2001). They showed that the RyR1 and RyR2 macromolecular complexes involve targeting of kinases and phosphatases to the channels *via* targeting proteins that specifically bind to leucine/isoleucine zippers on the RyRs. Since the IP_3Rs are phosphorylated or dephosphorylated by associated and free kinases or phosphatases, the regulation of IP_3R by phosphorylation or dephosphorylation in the intact cells may be different from the regulation of purified receptors in reconstituted systems.

Phosphorylation by PKA

Phosphorylation of IP_3Rs by PKA is relatively well characterised (Danoff et al. 1991; Ferris et al. 1991; Nakade et al. 1994; Wojcikiewicz and Luo 1998; Haug et al. 1999; Giovannucci et al. 2000; Pieper et al. 2001; Tang et al. 2003). However, modulation of IP_3R function by phosphorylation is still not fully understood. There is not full consensus regarding the effects of PKA on the activity of IP_3Rs. Several reports demonstrate that PKA phosphorylation of IP_3Rs either increase or decrease the channel activity.

The isolated neuronal IP_3R-1 from rat cerebellum is phosphorylated by cAMP- and cGMP-dependent protein kinases on two distinct sites, Ser-1589 and Ser-1756 (Ferris et al. 1991). PKA phosphorylated both sites with the same time course and same stoichiometry, whereas PKG phosphorylated Ser-1755 with a higher velocity and a higher stoichiometry than Ser-1589 (Haug et al. 1999). IP_3R-2 and -3 lack these consensus PKA phosphorylation sites, although they do contain other putative PKA phosphorylation sites. To monitor IP_3R phosphorylation *in vivo*, Pieper et al. (2001) developed antibodies that differentiated IP_3R-1 phosphorylated at Ser-1755 from the unphosphorylated form. They demonstrated that IP_3R-1 was phosphorylated by PKA at Ser-1589 and Ser-1755, with Ser-1755 phosphorylation greatly predominating in the brain. Striking variations in the regional and subcellular distribution of IP_3R-1 phosphorylation were found, which were regulated by excitatory neurotransmission, excitotoxic insult and neuronal ischaemia-reperfusion. In non-neuronal tissues alternative splicing results in deletion of a 40 amino acid exon that affects PKA phosphorylation of the channel resulting in a preferential phosphorylation of serine 1589 in some tissues (Danoff et al. 1991).

PKA in the presence of cAMP and of the catalytic subunit of PKA increased the extent of IICR from canine cerebellum membrane fractions by 35 % without interfering with the binding of IP_3 to its receptor sites (Volpe and Alderson-Lang 1990). Phosphorylation of an immunoaffinity-purified IP_3R-1 from mouse cerebellar microsomal fraction was studied after reconstitution into phospholipid vesicles. The catalytic subunit of PKA stoichiometrically phosphorylated the IP_3R-1 protein and it increased the rate and extent of $^{45}Ca^{2+}$ influx into proteoliposomes by 20 % (Nakade et al. 1994). PKA phosphorylation of IP_3R-1 augmented Ca^{2+} release (Pieper et al. 2001) and increased channel activity in planar lipid bilayers (DeSouza et al. 2002; Tang et al. 2003). Phosphorylation of IP_3R in intact hepatocytes cells was associated with an increase of its sensitivity to Ca^{2+} and IP_3 (Joseph and Ryan 1993). IP_3R-1, -2 and -3 were differentially susceptible to PKA phosphorylation and were phosphorylated in intact human neuroblastoma, rat pancreatoma and rat insulinoma cells (Wojcikiewicz and Luo 1998). PKA enhanced IP_3-induced Ca^{2+} mobilisation by $\approx$ 20 % in a range of permeabilised cell types, irrespective of whether the type 1, 2, or 3 receptor was predominant. PKA phosphorylated IP_3R-2 in parotid acinar cells and dramatically potentiated Ca^{2+} release (Bruce et al. 2002). The interpretation of indirect studies of IP_3R activation by PKA phosphorylation may be complicated by the findings that cAMP can raise intracellular calcium independently of PKA (den Dekker et al. 2002).

Phosphorylation of IP_3R-1 from cerebellum caused a decrease in Ca^{2+} release (Supattapone et al. 1988). Phosphorylation of IP_3R-1 by endogenous kinases in intact platelets resulted in high IICR, whereas additional PKA phosphorylation inhibited IICR (Quinton et al. 1996). Elevation of cAMP in intact single megakaryocytes inhibited IP_3-induced rise in intracellular Ca^{2+} and PKA inhibitors blocked the inhibitory effect, indicating that the inhibition was induced by PKA (Tertyshnikova and Fein 1998). PKA-dependent phosphorylation of IP_3R-3 inhibited Ca^{2+} release in pancreatic acinar cells at a low concentration of IP_3, whereas PKA had little effect on the release at high doses of IP_3 (Giovannucci et al. 2000). PKA shaped oscillations in pancreatic acinar cells by phosphorylation of IP_3R-3 (Straub et al. 2002).

The discrepancy between the effects of PKA phosphorylation on IP_3R activity observed by various investigators may be partially explained by misinterpretation of the Ca^{2+} release activity due to the confounding opposing contribution of increased ER Ca^{2+} pump (uptake) activity in response to PKA phosphorylation as well as by different "phosphorylation stages" of the IP_3R complex in different experiments.

Phosphorylation by PKG

PKG phosphorylation of IP_3R-1 decreased IP_3-induced calcium release. Activation of PKG effectively suppressed thrombin-induced stimulation of IP_3 production (Ruth et al. 1993). IICR was inhibited by cGMP in intact rat megakaryocytes *via* PKG and PKA (Tertyshnikova and Fein 1998). In permeabilised and intact rabbit stomach muscle cells, PKG inhibited IICR (Murthy 2001). IRAG and cGKIβ are part of the multicomponent complex physically interacting with IP_3R-1 (Schloss-

mann et al. 2000). They are involved in regulation of IICR. By phosphorylation of IRA, cGKIβ decreased the IP_3-dependent release through IP_3R-1. Up to four serine residues in IRAG were phosphorylated cGKIβ, but phosphorylation of Ser-696 was necessary to decrease calcium release (Ammendola et al. 2001).

Phosphorylation by PTK

PTK phosphorylation of IP_3R-1 increased IP_3-induced calcium release. IP_3R-1 contains two potential tyrosine phosphorylation sites at residues 482 and 2617 (Michikawa et al. 1994). Thrombin activation of human platelets was accompanied by tyrosine phosphorylation of IP_3R and by a transient enhancement in platelet cytosolic Ca^{2+}, but this enhancement was attenuated by subsequent dephosphorylation. Jayaraman et al. (1996) observed that stimulation of T-lymphocytes caused a physical association between the PTK-Fyn and IP_3R, followed by tyrosine phosphorylation of IP_3R-1 and resulting in an increase in the open probability of the channel. PTK-Lyn mediated tyrosine phosphorylation of IP_3R in B-cells, resulting in its increased activity (Yokoyama et al. 2002). Major cell adhesion molecules, CD44v10 and Rho-kinase (ROK) are physically associated as a complex in aortic endothelial cells. Activation of the cells promoted RhoA-mediated ROK activity, which, in turn, increased phosphorylation of IP_3R-1 and, to a lesser extent, of IP_3R-2 and -3. The phosphorylated IP_3R-1 is enhanced in its binding to IP_3, which subsequently stimulates IP_3-mediated Ca^{2+} flux (Singleton and Bourguignon 2002).

Phosphorylation by other kinases

CaMKII can phosphorylate IP_3R-1 but the exact site of phosphorylation is still unknown (Ferris et al. 1991). An IICR in permeabilised 3T6 fibroblasts was activated probably by CaMKII and inhibited by Ca^{2+}-dependent protein phosphatase 2B (Zhang et al. 1993). Cerebellar membranes containing IP_3R-1 phosphorylated by PKC or CaMKII displayed a greater potency for IP_3 in stimulating Ca^{2+} flux compared with membranes treated with a specific inhibitor of CaMKII (Cameron et al. 1995).

Conclusion

Modulation of both transcription and phosphorylation affects the function of IP_3Rs. As it can be seen from this minireview, both processes are very complex. Despite a huge amount of information there is still plenty of ambiguity in IP_3R research, from regulatory aspects to the function of these systems. To analyse the precise function of the IP_3R-1, IP_3R-1 deficient mice have been generated by gene targeting (Matsumoto et al., 1996). Most of the homozygous IP_3R-1 deficient mice died *in utero* and the rest suffered of ataxia and convulsion and died before the weaning period. Ogura and co-workers (2001) examined the heterozygous IP_3R deficient mice and found that IP_3R-1 plays a substantial role in the motor coordination.

The function of IP_3R-2 and -3 is still not known. Further research is certainly needed to clarify unknown aspects of these channels.

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