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# Modulation of ryanodine receptor $Ca^{2+}$ channels (Review)

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**Abstract.** Ryanodine-sensitive $Ca^{2+}$ release channels (ryanodine receptors, RyRs) play a crucial role in the mobilization of $Ca^{2+}$ from the sarcoplasmic reticulum (SR) during the excitation-contraction coupling of muscle cells. In skeletal muscle, depolarization of transverse tubules activates the RyR, whereas in cardiac muscle, a $Ca^{2+}$ influx through an L-type $Ca^{2+}$ channel activates the RyR. The RyR is also activated by caffeine, a low concentration (<10 $\mu$M) of ryanodine or cyclic ADP-ribose. RyR activity is inhibited by $Mg^{2+}$, ruthenium red, or higher concentrations (≥100 $\mu$M) of ryanodine. The activity of RyR channels is modulated by phosphorylation and by associated proteins, including calmodulin (CaM), calsequestrin (CSQ) and FK506-binding proteins (FKBPs). In muscle cells, apoCaM ($Ca^{2+}$-free CaM) activates the RyR channel, and $Ca^{2+}$ CaM ($Ca^{2+}$-bound CaM) inhibits the channel. CSQ can bind approximately 40 moles of $Ca^{2+}$/mole of CSQ in the SR lumen of muscle cells, and interacts functionally with RyR protein. When the RyR is stimulated, $Ca^{2+}$ released from the lumen is dissociated from the CSQ-$Ca^{2+}$ complex. A 12-kDa or 12.6-kDa FK506-binding protein (FKBP12 or FKBP12.6, respectively) is associated with RyR protein. When FKBP12 or FKBP12.6 is dissociated from the FKBP-RyR complex, the RyR is modulated (activated). Phosphorylation of the RyR by cAMP-dependent protein kinase (PKA) and $Ca^{2+}$/calmodulin-dependent protein kinase II modulates the channel. PKA phosphorylation of the RyR on the skeletal and cardiac muscle SR dissociates FKBP12 or FKBP12.6 from the RyR complex. This review deals with the modulation mechanisms of RyR proteins by associated proteins and phosphorylation.

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*Abbreviations:* cADPR, cyclic ADP-ribose; CaM, calmodulin; CaMKII, $Ca^{2+}$/calmodulin-dependent protein kinase II; CSQ, calsequestrin; E-C, excitation-contraction; ER, endoplasmic reticulum; FKBP, FK506-binding protein; $IP_3$, D-myo-inositol 1,4,5-trisphosphate; PKA, cAMP-dependent protein kinase; PKG, cGMP-dependent protein kinase; RyR, ryanodine receptor; SR, sarcoplasmic reticulum

*Key words:* ryanodine receptor, calmodulin, calsequestrin, FK506-binding protein, phosphorylation

**Contents**



## 1. Introduction

In many cell types, intracellular $Ca^{2+}$ stores play an essential role in the regulation of cytosolic $Ca^{2+}$ concentration ($[Ca^{2+}]_i$), the elevation of which triggers various cellular events, including muscle contraction, enzyme secretion, cell proliferation and egg fertilization. Two distinct classes of $Ca^{2+}$ release channels, which induce release of $Ca^{2+}$ from the stores into the cytosole, have been identified. One is sensitive to the ubiquitous second messenger inositol 1,4,5-trisphosphate ($IP_3$), which is formed by stimulation of a cell surface receptor with hormones or neurotransmitters (1). $Ca^{2+}$ channels (receptors) sensitive to $IP_3$ are widely distributed on the endoplasmic reticulum (ER) of many tissues. The other is sensitive to the plant alkaloid ryanodine. $Ca^{2+}$ channels (receptors) sensitive to ryanodine are activated by caffeine, ryanodine, $Ca^{2+}$ and an $NAD^+$ metabolite cyclic ADP-ribose (cADPR). Ryanodine receptors (RyRs) were first identified in the skeletal and cardiac muscle sarcoplasmic reticulum (SR) (2,3), and were found to play a major role in $Ca^{2+}$ mobilization during excitation-contraction (E-C) coupling. The channel protein has been purified (4,5) and cloned (6,7) in the skeletal and cardiac muscle SR. RyRs have also been identified in the ER of non-muscle cells, including brain (8,9), liver (10) and exocrine (11) cells. At present, the RyR is thought to play a role in the regulation of $[Ca^{2+}]_i$ in many cell types. The RyR has been shown to be a high molecular weight homotetramer (12). Each subunit of the receptor is a compound with a molecular mass of ~565 kDa (6). Three RyR isoforms (RyR1, 2 and 3) have been found to be expressed (13-15), RyR1 and 2 in skeletal and cardiac muscle, respectively, and RyR3 in the brain and smooth muscle.

In the skeletal muscle SR, RyR proteins have several binding sites to calmodulin (CaM) (16,17), which is a ubiquitous $Ca^{2+}$-binding protein within cells. CaM is known to modulate $Ca^{2+}$ release through the RyR (18-20). RyR proteins

have been shown to be linked to the $Ca^{2+}$-binding protein calsequestrin (CSQ), located inside the SR, via the action of anchor proteins on the junctional region of the SR membrane (21-23). CSQ is known to activate or inhibit RyR channel activity (24-26). The immunosuppressant drug FK506 is known to modulate RyR proteins. A 12- or 12.6-kDa FK506-binding protein (FKBP12 or FKBP12.6, respectively) has been shown to be associated with RyR proteins on the skeletal or cardiac muscle SR, respectively (27-30). FK506 modulates (activates) the RyR by dissociating FKBP12 or FKBP12.6 from the RyR complex (31-33). RyR proteins on the skeletal and cardiac muscle SR are phosphorylated by cAMP-dependent protein kinase (PKA), cGMP-dependent protein kinase (PKG) or $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII) (34-38). Phosphorylation of the RyR in skeletal and cardiac muscle cells by PKA or CaMKII modulates the channel activity (38-41).

In this review, the activation mechanisms of the RyR are described in brief, and the modulation mechanisms of RyR proteins by associated proteins and by phosphorylation are described in detail.

## 2. Activation of the ryanodine receptor

The activation mechanism of the RyR in E-C coupling of skeletal muscle is different from that of cardiac muscle. In skeletal muscle, RyR1 channels interact with voltage-dependent $Ca^{2+}$ channels (dihydropyridine receptors; DHPRs) located on the transverse tubule (t-tubule) membrane. DHPRs act as voltage sensors for E-C coupling (42). Depolarization of the t-tubule membrane activates RyR1 via a direct physical DHPR-RyR1 linkage (43-45). The activation of RyR1 induces $Ca^{2+}$ release from the SR lumen into the cytosol. In cardiac muscle, depolarization-induced $Ca^{2+}$ influx through DHPR (an L-type $Ca^{2+}$ channel) activates RyR2 and induces $Ca^{2+}$ release from the SR (46-48). This process is referred to as '$Ca^{2+}$-induced $Ca^{2+}$ release'. The $Ca^{2+}$ dependence of $Ca^{2+}$-induced $Ca^{2+}$ release forms a bell-shaped curve with a maximum at 2-20 $\mu$M of cytosolic-free $Ca^{2+}$ concentration (49,50). The activation mechanism of RyRs in $Ca^{2+}$ mobilization in non-muscle cells has not been elucidated. Recently, the endogenous ligand cADPR has been shown to be capable of inducing $Ca^{2+}$ release from the RyR in sea urchin eggs (51,52), and cADPR-induced $Ca^{2+}$ release from RyRs has also been reported in various tissues, including cardiac muscle cells (53), brain cells (54), pancreatic β-cells (55) and pancreatic acinar cells (56,57). This compound is thought to be an intracellular messenger in addition to $IP_3$ (58,59). Caffeine and ryanodine are known to be pharmacological agents for RyRs. Caffeine increases the $Ca^{2+}$ sensitivity of $Ca^{2+}$-induced $Ca^{2+}$ release (60). Ryanodine locks the RyR channel to an 'open state' at low concentrations (<10 $\mu$M) and to a 'closed state' at higher concentrations (≥100 $\mu$M) (61,62). Not only higher concentrations of ryanodine but also millimolar concentrations of $Mg^{2+}$ (49,50,63,64) and micromolar concentrations of ruthenium red (65-67) inhibit the activity of RyRs.

## 3. Modulation of the ryanodine receptor

*Calmodulin*. CaM is a ubiquitous $Ca^{2+}$-binding protein of 16.7 kDa. Early sequence analysis of RyR proteins in the skeletal muscle SR showed that the receptor has several binding sites for CaM (16,17). A study using $^{125}I$ (18) or fluorescently (68) labeled CaM in skeletal muscle has indicated that RyR1 has 4-6 binding sites per subunit of the receptor for apoCaM ($Ca^{2+}$-free CaM), and 1 binding site per subunit of the receptor for $Ca^{2+}$ CaM ($Ca^{2+}$-bound CaM). However, recent studies using $^{35}S$-labeled CaM in both skeletal and cardiac muscle have shown that RyRs have only one binding site per subunit of the receptor for both apoCaM and $Ca^{2+}$ CaM (20,69,70), and that the binding sites for apoCaM and $Ca^{2+}$ CaM are in the same region (amino acid residues 3630-3637) (69). It has been suggested that the larger number of binding sites for apoCaM previously reported may be due to an artificial effect (69). Studies on both $Ca^{2+}$ efflux and single channel activity using lipid bilayer membranes have demonstrated that apoCaM, the concentration of which is increased at nanomolar $Ca^{2+}$ concentrations, activates the RyR1 channels (18-20,71), but not the RyR2 channels (20,72). $Ca^{2+}$ CaM, the concentration of which is increased at micromolar to millimolar $Ca^{2+}$ concentrations, inhibits both the RyR1 (18-20,71-73) and RyR2 (20,50,72) channels. It has also been shown that apoCaM activates the RyR1 channels by increasing the $Ca^{2+}$ sensitivity of $Ca^{2+}$-induced $Ca^{2+}$ release (19,20). The effect of CaM on RyR3 from rabbit uterus expressed in HEK293 cells has also been reported. Similar to RyR1, RyR3 was activated by apoCaM and inhibited by $Ca^{2+}$ CaM (74). It has been shown in sea urchin eggs that caffeine-, ryanodine- or cADPR-induced $Ca^{2+}$ release from microsomal vesicles is enhanced by the presence of exogenously added CaM (75,76), and that CaM can bind to the microsomes (76). This suggests that CaM bound to the RyR of sea uchin eggs can modulate the $Ca^{2+}$ release through the receptor. It has been found in rat pancreatic acinar cells that caffeine-, ryanodine- or cADPR-induced $^{45}Ca^{2+}$ release from microsomal vesicles is stimulated by exogenously added CaM, and is inhibited by the CaM antagonist W-7 (56). It is possible that CaM bound to the RyR of rat pancreatic acinar cells modulates the $Ca^{2+}$ release, since KN-62, a CaMKII inhibitor, was not observed to inhibit the caffeine-induced $^{45}Ca^{2+}$ release from the vesicles (56).

*Calsequestrin*. CSQ is the major $Ca^{2+}$-binding protein located in the terminal cisternae of the skeletal and cardiac muscle SR. The molecular mass of the CSQ monomer is 41-46 kDa (77). The protein has been purified (78-80) and cloned (81,82) in the skeletal and cadiac muscle SR. The protein is acidic and can bind 40-50 moles of $Ca^{2+}$/mole of CSQ for skeletal muscle (78,79,83-85) and 18-40 moles of $Ca^{2+}$/mole of CSQ for cardiac muscle (86,87). CSQ acts as a $Ca^{2+}$ buffer in the lumen of SR $Ca^{2+}$ storage pools to lower free $Ca^{2+}$ concentrations. The conformation of CSQ changes with an increase in the free $Ca^{2+}$ concentration of the lumen (22,23). CSQ monomer polymerizes at $Ca^{2+}$ concentrations over 10 $\mu$M. The polymer is stable at a $Ca^{2+}$ concentration of ~1 mM and is anchored to the SR membrane by binding to the intrinsic membrane proteins triadin and junctin, which have binding sites for RyR protein (21-23). CSQ can interact functionally with the RyR protein via the anchoring proteins or by direct binding (23). Evidence suggests that $Ca^{2+}$ released from the SR lumen is dissociated from the CSQ-$Ca^{2+}$ complex after stimulation of the RyR (24,88,89). Thus, CSQ functions as a regulator of the RyR during muscle contraction. Studies using lipid bilayer membranes have shown that the addition of

CSQ activates (24,25,90) or inhibits (26) the RyR1 channels, whereas CSQ just inhibits the RyR2 channels (91).

*FK506-binding protein*. FKBPs, intracellular receptors for the immunosuppressant drug FK506, are abundant within cells and comprise a family of proteins (92). A 12-kDa FKBP (FKBP12) has been shown to be tightly associated with RyR1 on the SR of skeletal muscle (27,28). One mole of FKBP12 is associated with each protomer of homotetrameric RyR1 (31). In association with RyR1, FKBP12 has been shown to stabilize the closed conformation of the $Ca^{2+}$ channel (31). FK506 has been shown to promote the dissociation of FKBP12 from the RyR1 complex (31). The $EC_{50}$ value for dissociation of FKBP12 from the RyR1 complex in skeletal muscle has been reported to be in the concentration range of 0.12-0.5 $\mu$M FK506 (31). By the removal of FKBP12, RyR1 exhibits subconductance states (93), and the $Ca^{2+}$ or caffeine sensitivity of the channel is enhanced (31,94). Compared with control SR vesicles, FKBP12-deficient SR vesicles in skeletal muscle have been shown to increase open probability and mean open times for single channel recordings of the RyR1 (94-96). Recently, in the skeletal muscle SR, FKBP12 has been found to be dissociated from the RyR1 complex by PKA phosphorylation of the receptor (97) (see *Phosphorylation*). In cardiac type RyR (RyR2), one mole of FKBP12.6 is associated with each protomer of RyR2 (29,30). Activation of RyR2 by dissociation of FKBP12.6 from the RyR2 complex in cardiac muscle is controversial. In some cases, dissociation of FKBP12.6 from the RyR2 complex increased the open probability for single channel recordings of RyR2 (98,99). However, in other cases, dissociation of FKBP12.6 from the RyR2 complex did not activate the RyR2 channel (30,96). Activation of RyR by dissociation of FKBP12.6 from the RyR complex has also been reported in tissues other than cardiac muscle. It has been shown in pancreatic islets that FK506 induces $Ca^{2+}$ release from RyR2 by dissociating FKBP12.6 from the RyR2 complex (32). Although the type of RyR is unclear, FK506 has been shown to increase the open probability of reconstituted RyRs ($Ca^{2+}$ channels) in coronary arterial smooth muscle cells, in which FKBP12.6 has been detected (33). This suggests that FK506 activates the RyR in this tissue by dissociating FKBP12.6 from the receptor. FK506 has been shown to shift the dose-response curve of ryanodine- or caffeine-induced $^{45}Ca^{2+}$ release from the microsomal vesicles of rat pancreatic acinar cells to the left (57). Since an RyR2 isoform has been identified in rat pancreatic acinar cells (100,101), FKBP12.6 may be involved in the modulation of $Ca^{2+}$ release through the RyR by FK506. It has been found that cADPR as well as FK506 can bind to FKBP12.6, and dissociate FKBP12.6 from pancreatic islet microsomes to release $Ca^{2+}$ (32). An antibody against FKBP12.6 has been shown to inhibit the activation of the RyR induced not only by FK506 but also by cADPR in coronary arterial smooth muscle cells (33). These findings suggest that cADPR dissociates FKBP12.6 from the RyR-FKBP12.6 complex to activate the $Ca^{2+}$ channel. It has been found in rat pancreatic acinar cells that cADPR shifts the dose-response curve of ryanodine- or caffeine-induced $^{45}Ca^{2+}$ release to the left by the same extent as that in the case of FK506, and that the stimulatory effects on ryanodine- or caffeine-induced $^{45}Ca^{2+}$ release by cADPR and by FK506 are not additive (57). This suggests that cADPR modulates the RyR in pancreatic acinar cells by the same mechanism as that by which FK506 modulates the RyR. The endogenous ligand cADPR might induce the activation or modulation of the RyR by dissociating FKBP12.6 from the RyR complex under physiological conditions. Recently, it has been shown in the cardiac muscle SR that FKBP12.6 is dissociated from the RyR2 complex by PKA phosphorylation of the receptor (102) (see *Phosphorylation*).

*Phosphorylation*. RyR proteins have many phosphorylation sites (6,103). In the skeletal muscle SR, RyR1 has been found to be phosphorylated by PKA, PKG and CaMKII (34,36,37,104). The phosphorylation site of RyR1 is serine 2843 (36,105). The channel activity of RyR1 incorporated into planar lipid bilayers has been shown to be enhanced by PKA or CaMKII phosphorylation (39,106,107). It has also been demonstrated that depolarization-induced $Ca^{2+}$ release from the skeletal muscle SR is stimulated by cAMP (108). This suggests that endogenous PKA modulates the $Ca^{2+}$ release via the phosphorylation of RyR1 during the E-C coupling of skeletal muscle. Recently, it has been shown that PKA phosphorylation of RyR1 at serine 2843 dissociates FKBP12 (see *FK506-binding protein*) from the receptor (97), and increases the open probability of the channel (97). In the cardiac muscle SR, RyR2 has been shown to be phosphorylated by PKA, PKG and CaMKII (34,35,37,38,109). Witcher *et al* reported that the phosphorylation site of RyR2 is serine 2809 (38). It is well known that the PKA activity of cardiac muscle cells is increased via the elevation of intracellular cAMP after β-adrenergic stimulation (110). The β-adrenergic agonist isoproterenol and cAMP have been shown to stimulate the ATP-induced PKA phosphorylation of RyR2 in cardiac myocytes (111). It has also been shown that PKA activates the RyR2 $Ca^{2+}$ channel on planar lipid bilayers (40,112). The activation of RyR2 via PKA phosphorylation may induce a positive inotropic action during β-adrenergic stimulation of cardiac muscle cells. It has been shown that PKA phosphorylation of RyR2 at serine 2809 dissociates FKBP12.6 (see *FK506-binding protein*) from the receptor (102), and increases the open probability of the channel (102,113). In heart failure, the β-adrenergic receptor is chronically stimulated. The phosphorylation of RyR2 by PKA in failing hearts is increased by ~4-fold compared with that in non-failing hearts (102). The hyperphosphorylation of RyR2 by PKA in failing hearts induces a depletion of FKBP12.6 from the RyR2 complex (102,114) and an abnormal $Ca^{2+}$ leak from RyR2 (115,116). In cardiac muscle, CaMKII has been shown to activate (38,40) or inhibit (41) the RyR2 $Ca^{2+}$ channel on planar lipid bilayers. A recent study in cardiac muscle cells has indicated that the CaMKII phosphorylation site on RyR2 is serine 2815, not serine 2809 (117). Phosphorylation of RyR2 by CaMKII at serine 2815 activates the $Ca^{2+}$ channel without dissociating FKBP12.6 from the receptor (117). In addition, the CaMKII phosphorylation of RyR2 showed a positive correlation with heart rate (117). The time-averaged $[Ca^{2+}]_i$ is increased at higher heart rates. The increased $[Ca^{2+}]_i$ enhances the activity of CaMKII in cardiac muscle cells and induces the phosphorylation of RyR2. The phosphorylation of RyR2 by CaMKII increases the open probability of the channel (117), and also increases $Ca^{2+}$ release from RyR2 (118). Thereby, the 'positive force-frequency relationship' (119) may be explained.

Phosphorylation of RyR by CaMKII has also been observed in brain cells (120). It has been shown in rat parotid acinar cells that cAMP induces $Ca^{2+}$ release from microsomal vesicles, and that the release is inhibited by a high concentration of ryanodine and the potent PKA inhibitor, H-89 (121). These results suggest that endogenous PKA phosphorylates the RyR of rat parotid acinar cells to activate $Ca^{2+}$ release from the receptor. In rat pancreatic islets, cADPR-induced $Ca^{2+}$ release from the microsomes has been shown to be enhanced by exogenously added CaM and inhibited by the CaMKII inhibitor KN-62 (122). These results suggest that endogenous CaMKII phosphorylates the RyR of pancreatic islets and mediates the cADPR-induced $Ca^{2+}$ release from the receptor.

## 4. Conclusion

Depolarization of the t-tubule membrane triggers $Ca^{2+}$ release from RyRs in muscle cells. In addition to depolarization, RyRs are activated by $Ca^{2+}$, caffeine, ryanodine and cADPR. The $Ca^{2+}$ release through RyRs is modulated by phosphorylation of the receptors and by the proteins bound to the receptors. As for the associated proteins, CaM and CSQ had been considered important modulators of RyRs. It is thought that CSQ functions as a regulator of the RyR inside the SR of muscle cells. Recent studies on the modulation of RyRs have focused on the presence of FKBPs. The activity of the RyR channel is enhanced by the dissociation of FKBP from the RyR complex, and the $Ca^{2+}$ release through the channel is modulated (activated). Modulation of RyRs by PKA phosphorylation in muscle cells can be explained by the dissociation of FKBP from the RyR complex. Further studies are required to elucidate the role and function of FKBPs in $Ca^{2+}$ mobilization from RyRs.

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