Ryanodine receptor

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RyR domain Identifiers

Symbol RyR

Pfam PF02026

InterPro IPR003032

TCDB 1.A.3

[show]Available protein structures:

Ryanodine receptors (RyRs) form a class of intracellular calcium channels in various forms of excitable animal tissue like muscles and neurons. It is the major cellular mediator of calcium-induced calcium release (CICR) in animal cells.

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[edit] Etymology

The receptors are named after the plant alkaloid ryanodine, to which they show high affinity:

Ryanodine

[edit] Isoforms

There are multiple isoforms of ryanodine receptors:

RyR1 is primarily expressed in skeletal muscle

RyR2 in myocardium (heart muscle)

A third form, RyR3, is expressed more widely, but especially in the brain.[1]

There is also a fourth form found only in fish.

ryanodine receptor 1 (skeletal) Identifiers

Symbol RYR1

Alt. symbols MHS, MHS1, CCO

Entrez 6261

HUGO 10483

OMIM 180901

RefSeq NM_000540

[1] Riccardo Zucchi and Simonetta Ronca-Testoni, “The Sarcoplasmic Reticulum Ca2+ Channel/Ryanodine Receptor: Modulation by Endogenous Effectors, Drugs and Disease States," *Pharmacological Reviews* 49, no.1 (1997): 1–52.

UniProt P21817

Other data

Locus Chr. 19 q13.1

ryanodine receptor 2 (cardiac) Identifiers

Symbol RYR2

Entrez 6262

HUGO 10484

OMIM 180902

RefSeq NM_001035

UniProt Q92736

Other data

Locus Chr. 1 q42.1-q43

ryanodine receptor 3 Identifiers

Symbol RYR3

Entrez 6263

HUGO 10485

OMIM 180903

RefSeq NM_001036

UniProt Q15413

Other data

Locus Chr. 15 q14-q15

[edit] Physiology

Ryanodine receptors mediate the release of calcium ions from the sarcoplasmic reticulum, an essential step in muscle contraction. In skeletal muscle, it is thought that activation occurs via a physical coupling to the dihydropyridine receptor, whereas, in cardiac muscle, the primary mechanism is calcium-induced calcium release from the sarcoplasmic reticulum.[2]

It has been shown that calcium release from a number of ryanodine receptors in a ryanodine receptor cluster results in a spatiotemporally-restricted rise in cytosolic calcium that can be visualised as a calcium spark.[3]

Ryanodine receptors are similar to the inositol trisphosphate (IP3) receptor, and stimulated to transport Ca2+ into the cytosol by recognizing Ca2+ on its cytosolic side, thus establishing a positive feedback mechanism; a small amount of Ca2+ in the cytosol near the receptor will cause it to release even more Ca2+ (calcium-induced calcium release/CICR.[4]

RyRs are especially important in neurons and muscle cells. In heart and pancreas cells, another second messenger (cyclic ADP-ribose) takes part in the receptor activation.

The localized and time-limited activity of Ca2+ in the cytosol is also called a Ca2+ wave. The building of the wave is done by

the feedback mechanism of the ryanodine receptor

the activation of phospholipase C by GPCR or TRK, which leads to the production of inositol trisphosphate, which in turn activates the InsP3 receptor.

[edit] Associated proteins

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[2] Alexandre Fabiato,“Calcium-Induced Calcium Release of Calcium from the Cardiac Sarcoplasmic Reticulum,” *American Journal of Physiology: Cell Physiology* 245, no. 1 (1983): C1–C14.
[3] H. Cheng, W.J. Lederer, and M.B. Cannell,“Calcium Sparks: Elementary Events Underlying Excitation-Contraction Coupling in Heart Muscle," *Science* 262 (5134): 740–744.
[4] Riccardo Zucchi and Simonetta Ronca-Testoni,“The Sarcoplasmic Reticulum Ca2+ Channel/Ryanodine Receptor: Modulation by Endogenous Effectors, Drugs and Disease States," *Pharmacological Reviews* 49 (1): 1– 52.

Many other proteins with various functions are associated with RyR. For instance in RyR2 from luminal side it is calsequestrin which forms quaternary structure of RyR along with junctin and triadin. Calsequestrin has multiple Ca2+ binding sites and binds Ca2+ ions with very low affinty so they can be easily released.

Ryanodine receptors are usually found in clusters of 3 or 4 (i.e. they are associated with each other)and it was observed that they are to some extent able to open and close simultaneously. This happens more often in physiological conditions and is less observed in vitro.

[edit] Pharmacology

Antagonists[5]:

Ryanodine locks the RyRs at half-open state at nanomolar concentrations, yet fully closes them at micromolar concentration.

Dantrolene the clinically-used antagonist

Ruthenium red

procaine, tetracaine, etc. (local anesthetics)

Activators[6]:

Agonist: 4-chloro-m-cresol and suramin are direct agonists, i.e., direct activators.

Xanthines like caffeine and pentifylline activate it by potentiating sensitivity to native ligand Ca.

Physiological agonist: Cyclic ADP-ribose can act as a physiological gating agent. It has been suggested that it may act by making FKBP12.6 (12.6 kilodalton FK506 binding protein, as opposed to 12 kDa FKBP12 which binds to RyR1) which normally bind (and blocks) RyR2 channel tetramer in an average

[5] A.M. Vites and A. J. Pappano, "Distinct Modes of Inhibition by Ruthenium Red and Ryanodine of Calcium-Induced Calcium Release in Avian Atrium," *The Journal of Pharmacology and Experimental Therapeutics* 268, no.3 (1994): 1476–1484, http://jpet.aspetjournals.org.proxy2.cl.msu.edu/content/268/3/1476.abstract.

[6] Le Xu, Ashutosh Tripathy, Daniel A. Pasek, and Gerhard Messiner, "Potential for Pharmacology of Ryanodine Receptor/Calcium Release Channels," *Annals of the New York Academy of Sciences* 853, no.1 (1998): 130–148,doi: 10.1111/j.1749-6632.1998.tb08262.x.

stoichiometry of 3.6, to fall off RyR2 (which is the predominant RyR in pancreatic beta cells, cardiomyocytes and smooth muscles).[7]

A variety of other molecules may interact with and regulate Ryanodine receptor. For example: Dimerized Homer physical tether linking inositol trisphosphate receptors (IP3R) and ryanodine receptors on the intracellular calcium stores with cell surface group 1 metabotropic Glutamate Receptors and the alpha 1D adrenergic receptor.[8]

[edit] Ryanodine

The plant alkaloid ryanodine, for which this receptor was named, has become an invaluable investigative tool. It can block the phasic release of calcium, but at low doses may not block the tonic cumulative calcium release. The binding of ryanodine to RyRs is use-dependent, that is the channels have to be in the activated state. At low (<10 MicroMolar, works even at nanomolar) concentrations, ryanodine binding locks the RyRs into a long-lived subconductance (half-open) state and eventually depletes the store, while higher (~100 MicroMolar) concentrations irreversibly inhibit channel-opening.

[edit] Caffeine

RyRs are activated by millimolar caffeine concentrations. High (greater than 5 mmol/L) caffeine concentrations cause a pronounced increase (from micromolar to picomolar) in the sensitivity of RyRs to Ca2+ in the presence of caffeine, such that basal Ca2+ concentrations become activatory. At low millimolar caffeine concentrations, the receptor opens in a quantal way, but has complicated behavior in terms of repeated use of caffeine or dependence on cytosolic or luminal calcium concentrations.

[edit] Role in disease

RyR1 mutations are associated with malignant hyperthermia and central core disease. RyR2 mutations play a role in stress-induced polymorphic ventricular tachycardia (a form of cardiac arrhythmia) and ARVD.[9] It has also been shown that levels of type RyR3 are greatly increased in PC12 cells overexpressing

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[7] Yong-Xiao Wang, Yun-Min Zheng, Qi-Bing Mei, Quinq-Song Wang, Mei Lin Collier, Sidney Flescher, Hong-Bo Xin, and Michael I. Kotlikoff. “FKBP12.6 and cADPR Regulation of Ca2+ Release in Smooth Muscle Cells," *American Journal of Physiology: Cell Physiology* 286, no.3 (2004): C538–C546, doi:10.1152/ajpcell.00106.2003.

[8] Jian Cheng Tu, Bo Xiao, Joseph P. Yuan, Anthony A. Lanahan, Kathleen Leoffert, Min Li, David J. Linden, and Paul F Worley, "Homer Binds a Novel Proline-Rich Motif and Links Group 1 Metabotropic Glutamate Receptors with IP3 Receptors," *Neuron* 21, no. 4 (1998): 717–726, doi: 10.1016/S0896-6273(00)80589-9.

[9] Riccardo Zucchi and Simonetta Ronca-Testoni, “The Sarcoplasmic Reticulum Ca2+ Channel/Ryanodine Receptor: Modulation by Endogenous Effectors, Drugs and Disease States,” *Pharmacological Reviews* 49, no. 1 (1997): 1–52.

mutant human Presenilin 1, and in brain tissue in knockin mice that express mutant Presenilin 1 at normal levels, and thus may play a role in the pathogenesis of neurodegenerative diseases, like Alzheimer's disease.

The presence of antibodies against ryanodine receptors in blood serum has also been associated with myasthenia gravis.

[edit] Human proteins containing this domain

RYR1; RYR2; RYR3;

[edit] References

[edit] References

Cheng, H., W. J. Lederer, and M. B. Cannell. “Calcium Sparks: Elementary Events Underlying Excitation-Contraction Coupling in Heart Muscle." *Science* 262, no. 5134 (1993): 740–744. <http://www.jstor.org.proxy2.cl.msu.edu/stable/2882684>.

Fabiato, Alexandre. “Calcium-Induced Calcium Release of Calcium from the Cardiac Sarcoplasmic Reticulum.” *American Journal of Physiology: Cell Physiology* 245, no. 1 (1983): C1–C14. <http://ajpcell.physiology.org/content/245/1/C1.full.pdf+html>.

Tu, Jian Cheng, Bo Xiao, Joseph P. Yuan, Anthony A. Lanahan, Kathleen Leoffert, Min Li, David J. Linden, and Paul F. Worley. "Homer Binds a Novel Proline-Rich Motif and Links Group 1 Metabotropic Glutamate Receptors with IP3 Receptors." *Neuron* 21, no. 4 (1998): 717–726. doi: 10.1016/S0896-6273(00)80589-9.

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Wang, Yong-Xiao, Zheng, Yun-Min, Qi-Bing Mei, Quinq-Song Wang, Mei Lin Collier, Sidney Flescher, Hong-Bo Xin, and Michael I. Kotlikoff. “FKBP12.6 and cADPR Regulation of Ca2+ Release in Smooth Muscle Cells." *American Journal of Physiology: Cell Physiology* 286, no.3 (2004): C538–C546. doi:10.1152/ajpcell.00106.2003.

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Zucchi, Riccardo, and Simonetta Ronca-Testoni. “The Sarcoplasmic Reticulum Ca2+ Channel/Ryanodine Receptor: Modulation by Endogenous Effectors, Drugs and Disease States.” *Pharmacological Reviews* 49, no. 1(1997):1–52. http://pharmrev.aspetjournals.org/content/49/1/1.full.pdf+html.