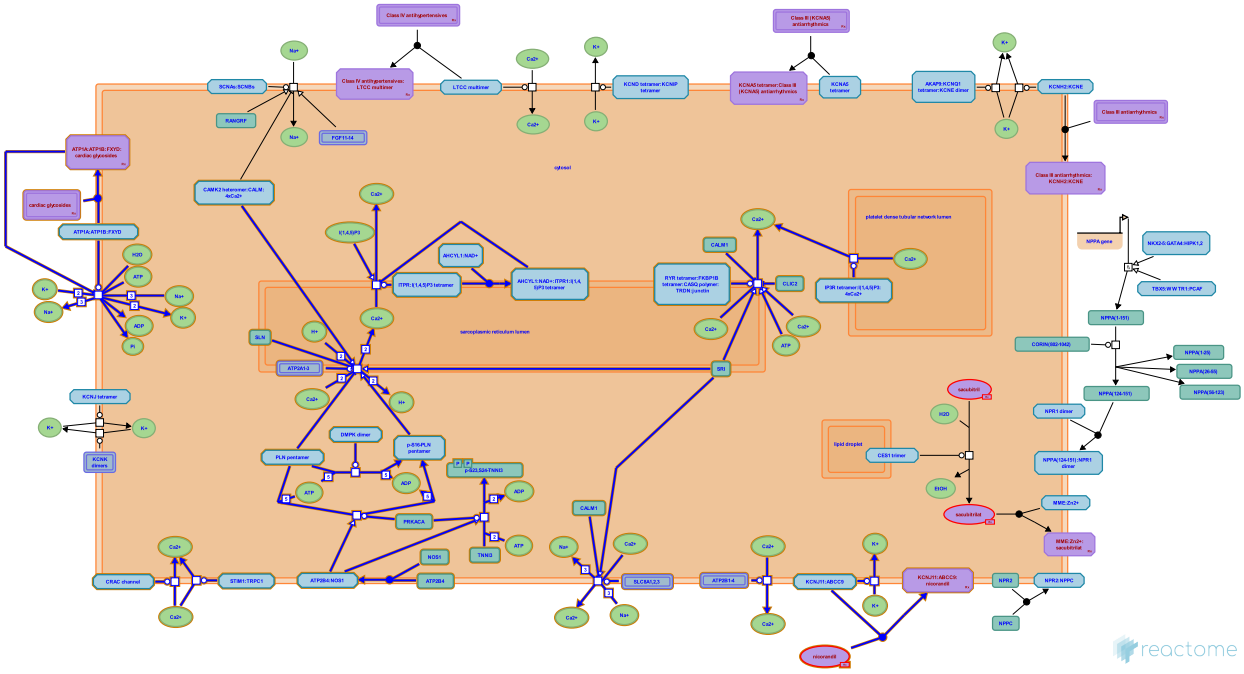
Ion homeostasis



Akkerman, JW., Colotti, G., D'Eustachio, P., Gillespie, ME., He, L., Huddart, R., Jassal, B., Jupe, S., Kunapuli, SP., Le Novere, N., Matthews, L., May, B., Moitra, K., Shoichet, BK., Wienands, J.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

03/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

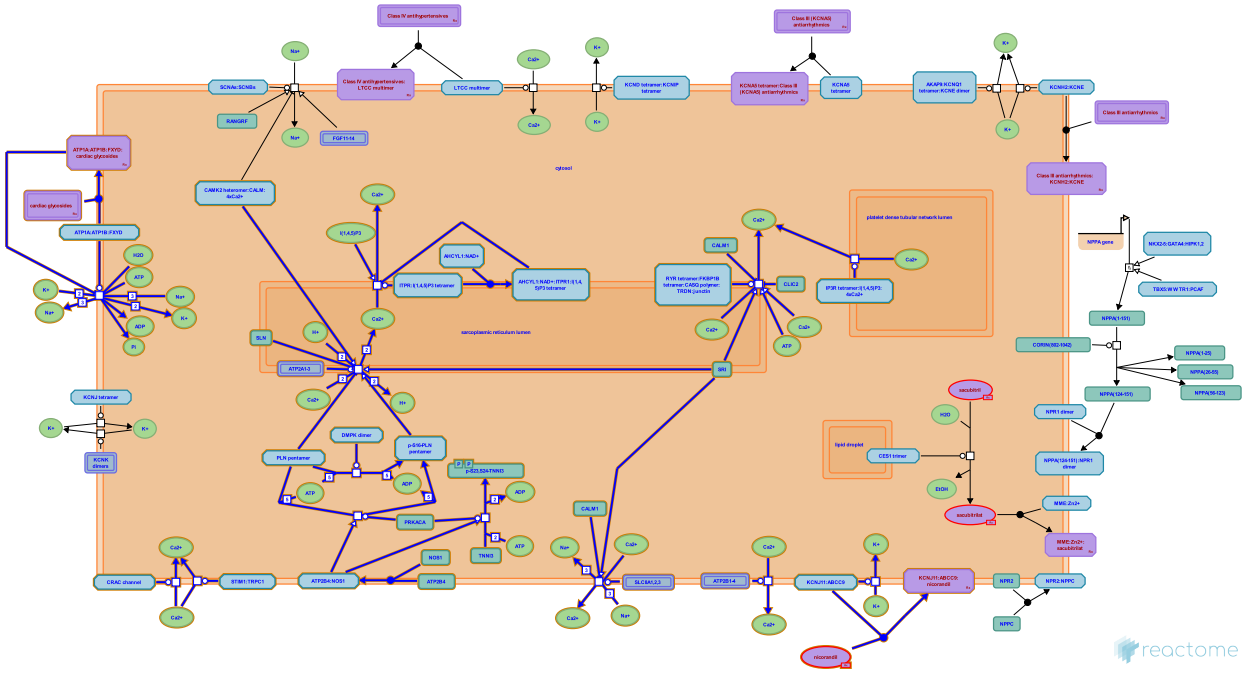
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Ion homeostasis

Stable identifier: R-HSA-5578775



Ion channels and ion homeostasis in relation to cardiac conduction is described in this section (Couette et al. 2006, Bartos et al. 2015).

Literature references

Marger, L., Couette, B., Mangoni, ME., Nargeot, J. (2006). Physiological and pharmacological insights into the role of ionic channels in cardiac pacemaker activity. *Cardiovasc Hematol Disord Drug Targets, 6*, 169-90.

Grandi, E., Ripplinger, CM., Bartos, DC. (2015). Ion Channels in the Heart. *Compr Physiol, 5*, 1423-64.

Editions

2014-06-02	Authored, Edited	Jassal, B.
2015-11-09	Reviewed	Colotti, G.

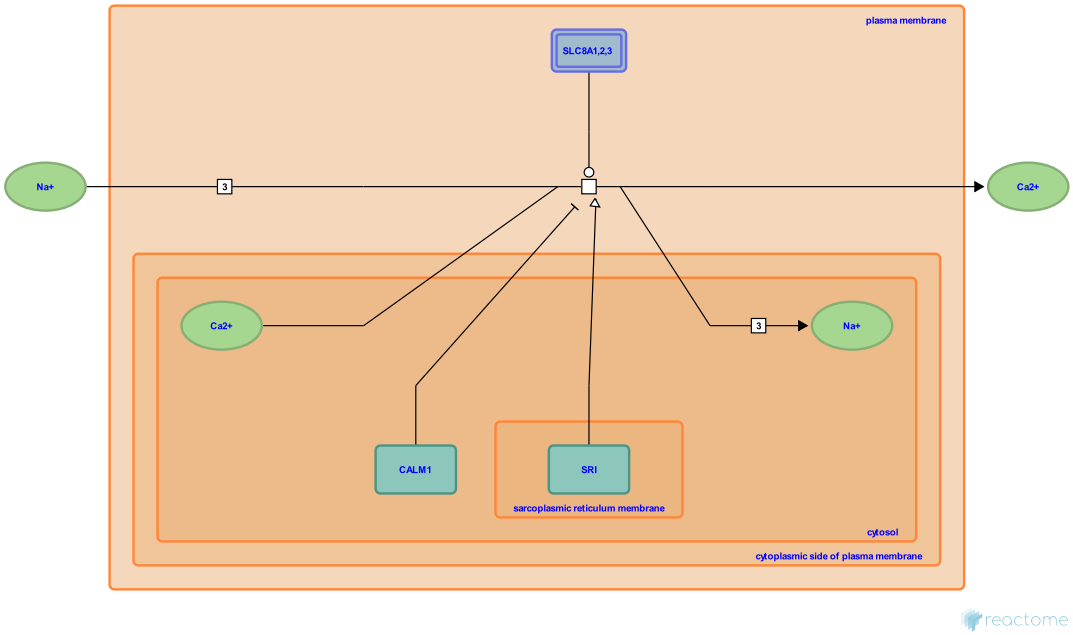
SLC8A1,2,3 exchange 3Na+ for Ca2+ ↗

Location: Ion homeostasis

Stable identifier: R-HSA-425661

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The sodium/calcium exchangers 1, 2 and 3 (SCL8A1,2,3 aka NCX1,2,3) belong to one of three families that control Ca2+ flux across the plasma membrane or intracellular compartments. They extrude Ca2+ from the cell, using the electrochemical gradient of Na+ as it flows into the cell. One Ca2+ is exchanged for three Na+. During this electrogenic exchange, the membrane potential is altered. SLC8A1, 2, 3 play a minor role during phase 2, since they begin to restore ion concentrations. The high concentration of intracellular calcium starts contraction of those cells, which is sustained in the plateau phase. SLC8A1 has a ubiquitous expression profile (highest expression in heart, brain and kidney) and was originally cloned and characterized from human cardiac muscle (Komuro et al. 1992). Both SLC8A2) (Li et al. 1994) and SLC8A3 (Gabellini et al. 2002) are expressed in the brain.
In Rabbits, sorcin (SRI) activates SLC8A1, via the interaction of the respective Ca2+-binding domains (Zamparelli et al. 2010). Calmodulin (CALM1) binds to the cytoplasmic loop of NCX1 to negatively regulate exchange activity (Chou et al. 2015).

Literature references

Wenninger, KE., Philipson, KD., Izumo, S., Komuro, I. (1992). Molecular cloning and characterization of the human cardiac Na+/Ca2+ exchanger cDNA. *Proc Natl Acad Sci U S A, 89*, 4769-73. ↗

Verzili, D., Zamparelli, C., Macquaide, N., Chiancone, E., Seidler, T., Smith, GL. et al. (2010). Activation of the cardiac Na(+)-Ca(2+) exchanger by sorcin via the interaction of the respective Ca(2+)-binding domains. *J. Mol. Cell. Cardiol., 49*, 132-41. ↗

Lifton, RP., Bersohn, MM., Philipson, KD., Burke, EP., Hryshko, LV., Li, Z. et al. (1994). Cloning of the NCX2 isoform of the plasma membrane Na(+)-Ca2+ exchanger. *J Biol Chem, 269*, 17434-9. ↗

Chou, AC., Ju, YT., Pan, CY. (2015). Calmodulin Interacts with the Sodium/Calcium Exchanger NCX1 to Regulate Activity. *PLoS ONE, 10*, e0138856. ↗

Carafoli, E., Gabellini, N., Danieli, GA., Bortoluzzi, S. (2002). The human SLC8A3 gene and the tissue-specific Na+/Ca2+ exchanger 3 isoforms. *Gene, 298*, 1-7. ↗

Editions

2009-06-05	Authored, Edited	Jassal, B.
2009-08-24	Reviewed	He, L.

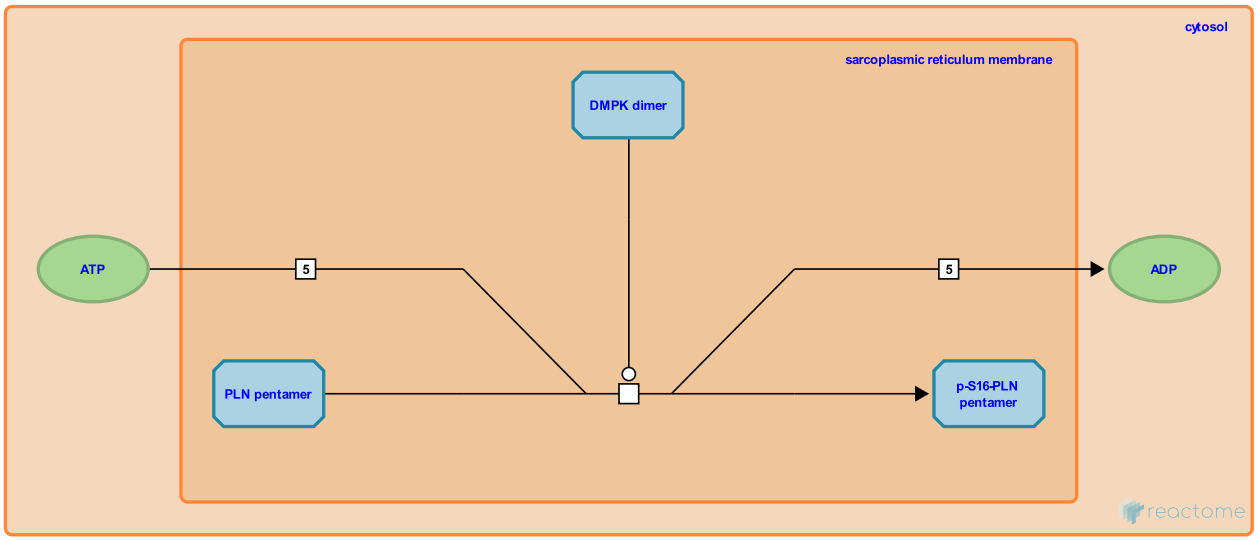
DMPK phosphorylates PLN ↗

Location: Ion homeostasis

Stable identifier: R-HSA-5578777

Type: transition

Compartments: sarcoplasmic reticulum membrane, cytosol



Force generation of the heart and calcium homeostasis are coupled in the myocardium. In the sarcoplasmic reticulum (SR), calcium stores provide the majority of calcium used in muscle contraction-relaxation. During relaxation, an ATP-dependent calcium pump (ATP2A2 aka SERCA) in the SR is essential for the recovery of calcium. The reuptake of calcium by ATP2A2 determines the rate of relaxation and the size of the calcium store available for subsequent contractions. In cardiac muscle, a second protein called phospholamban (PLN) acts as a reversible inhibitor of ATP2A2 and thereby modulates contractility in response to physiological factors. Defects in PLN are associated with lethal dilated cardiomyopathy in humans (Ceholski et al. 2012). PLN is a pentameric protein that, when phosphorylated, alleviates ATP2A2 inhibition and may stimulate SR calcium uptake in cardiomyocytes (Kaliman et al. 2005). Phosphorylation of PLN is mediated by myotonin-protein kinase (DMPK), a SR-bound homodimeric enzyme (Bush et al. 2000, Zhang & Epstein 2003).

Followed by: ATP2A1-3 transport Ca2+ from cytosol to ER lumen

Literature references

Epstein, HF., Zhang, R. (2003). Homodimerization through coiled-coil regions enhances activity of the myotonic dystrophy protein kinase. *FEBS Lett., 546*, 281-7. ↗

Perryman, MB., Helmke, SM., Birnbaum, RA., Bush, EW. (2000). Myotonic dystrophy protein kinase domains mediate localization, oligomerization, novel catalytic activity, and autoinhibition. *Biochemistry, 39*, 8480-90. ↗

Chien, KR., Lam, JT., Ruiz-Lozano, P., Palacin, M., Reddy, S., Kaliman, P. et al. (2005). Myotonic dystrophy protein kinase phosphorylates phospholamban and regulates calcium uptake in cardiomyocyte sarcoplasmic reticulum. *J. Biol. Chem., 280*, 8016-21. ↗

Young, HS., Trieber, CA., Ceholski, DK. (2012). Hydrophobic imbalance in the cytoplasmic domain of phospholamban is a determinant for lethal dilated cardiomyopathy. *J. Biol. Chem., 287*, 16521-9. ↗

Editions

2014-06-02	Authored, Edited	Jassal, B.
2015-11-09	Reviewed	Colotti, G.

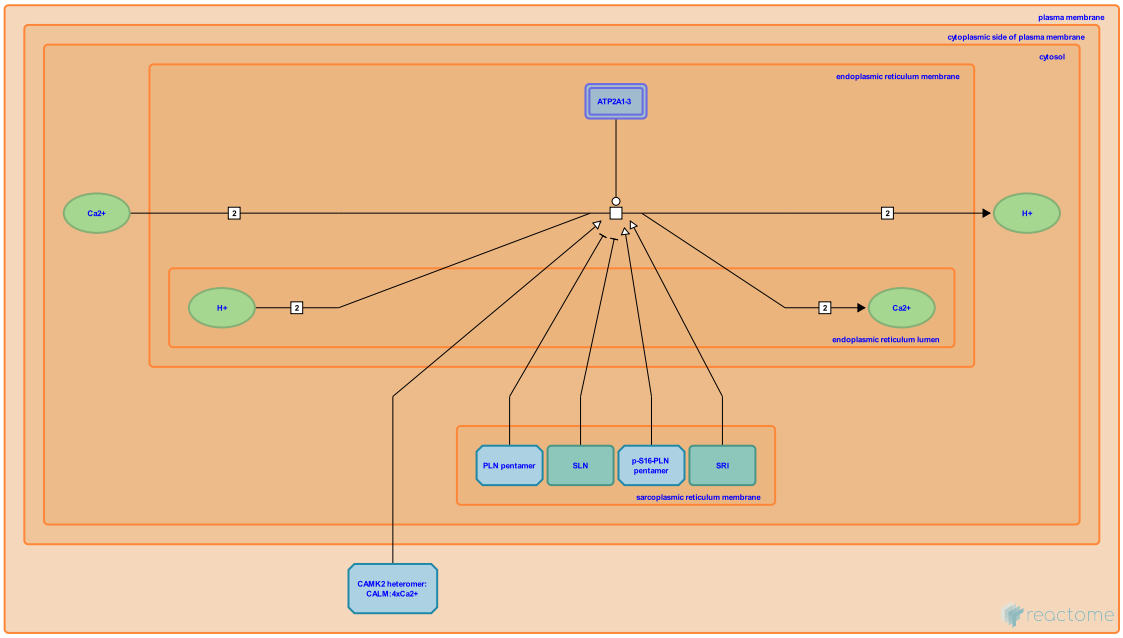
ATP2A1-3 transport Ca2+ from cytosol to ER lumen ↗

Location: Ion homeostasis

Stable identifier: R-HSA-427910

Type: transition

Compartments: endoplasmic reticulum membrane



Intracellular pools of Ca2+ serve as the source for inositol 1,4,5-trisphosphate (IP3) -induced alterations in cytoplasmic free Ca2+. In most human cells Ca2+ is stored in the lumen of the sarco/endoplastic reticulum by ATPases known as SERCAs (ATP2As). In platelets, ATP2As transport Ca2+ into the platelet dense tubular network. ATP2As are P-type ATPases, similar to the plasma membrane Na+ and Ca+-ATPases. Humans have three genes for SERCA pumps; ATP2A1-3. Studies on ATP2A1 suggest that it binds two Ca2+ ions from the cytoplasm and is subsequently phosphorylated at Asp351 before translocating Ca2+ into the SR lumen. There is a counter transport of two or possibly three protons ensuring partial charge balancing. Sarcolipin (SLN) can reversibly inhibit the activity of ATP2A1 by decreasing the apparent affinity of the ATPase for Ca2+ (Gorski et al. 2013) whereas activated Ca2+/CaM-dependent protein kinase II (CAMK2) and sorcin (SRI) can both stimulate ATP2A1-3 activity (Toyofuku et al. 1994, Matsumoto et al. 2005).

Preceded by: DMPK phosphorylates PLN

Literature references

Ikeda, Y., Inoue, N., Ohkusa, T., Sato, T., Hisamatsu, Y., Matsuzaki, M. et al. (2005). Sorcin interacts with sarcoplasmic reticulum Ca(2+)-ATPase and modulates excitation-contraction coupling in the heart. *Basic Res. Cardiol., 100*, 250-62. ↗

Bokkala, S., Wuytack, F., el-Daher, SS., Kakkar, VV., Authi, KS. (1995). Localization and identification of Ca2+ATPases in highly purified human platelet plasma and intracellular membranes. Evidence that the monoclonal antibody PL/IM 430 recognizes the SERCA 3 Ca2+ATPase in human platelets. *Biochem J, 306*, 837-42. ↗

Gorski, PA., Young, HS., Vangheluwe, P., Glaves, JP. (2013). Sarco(endo)plasmic reticulum calcium ATPase (SERCA) inhibition by sarcolipin is encoded in its luminal tail. *J. Biol. Chem., 288*, 8456-67. ↗

Toyofuku, T., MacLennan, DH., Curotto Kurzydlowski, K., Narayanan, N. (1994). Identification of Ser38 as the site in cardiac sarcoplasmic reticulum Ca(2+)-ATPase that is phosphorylated by Ca2+/calmodulin-dependent protein kinase. *J. Biol. Chem., 269*, 26492-6. ↗

Heilmann, C., Gerok, W., Spamer, C. (1987). Ca2+-activated ATPase in microsomes from human liver. *J Biol Chem, 262*, 7782-9. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2010-11-15	Reviewed	He, L.
2010-11-25	Edited	Jupe, S.

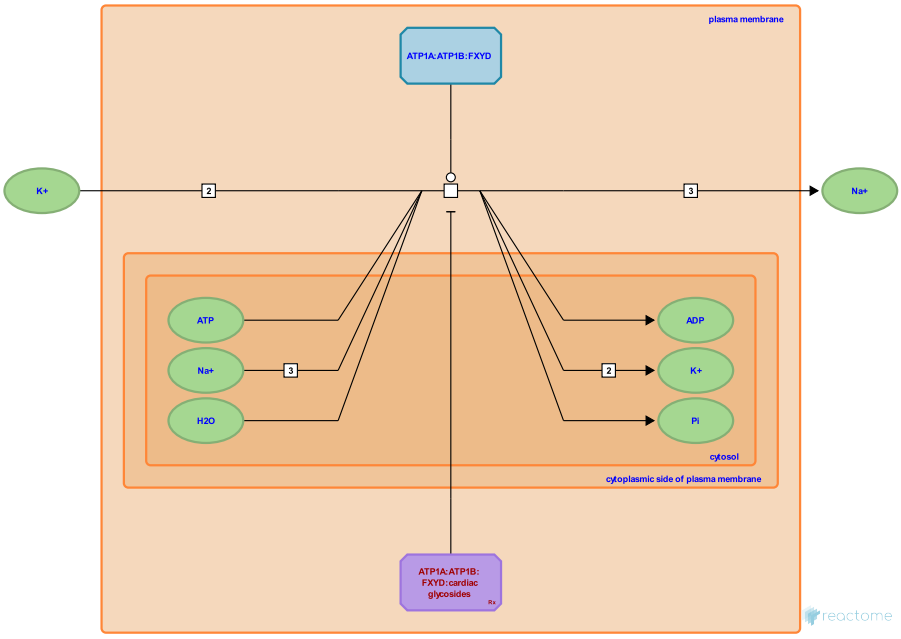
ATP1A:ATP1B:FXYD exchanges 3Na+ for 2K+ ↗

Location: Ion homeostasis

Stable identifier: R-HSA-936897

Type: transition

Compartments: plasma membrane



The sodium/potassium-transporting ATPase (ATP1A:ATP1B:FXYD) is composed of three subunits - alpha (catalytic part), beta and gamma. The trimer catalyzes the hydrolysis of ATP coupled with the exchange of sodium and potassium ions across the plasma membrane, creating the electrochemical gradient which provides energy for the active transport of various nutrients.
Four human genes encode the catalytic alpha subunits, ATP1A1-4 (Kawakami et al, 1986; Shull et al, 1989; Ovchinnikov et al, 1988; Keryanov and Gardner, 2002). Defects in ATP1A2 cause alternating hemiplegia of childhood (AHC) (Swoboda et al, 2004). Another defect in ATP1A2 causes familial hemiplegic migraine type 2 (FHM2) (Vanmolkot et al, 2003). Defects in ATP1A3 are the cause of dystonia type 12 (DYT12) (de Carvalho Aguiar et al, 2004).

Three human genes encode the non-catalytic beta subunits, ATP1B1-3. The beta subunits are thought to mediate the number of sodium pumps transported to the plasma membrane (Lane et al, 1989; Ruiz et al, 1996; Malik et al, 1996). FXYD proteins belong to a family of small membrane proteins that are auxiliary gamma subunits of Na-K-ATPase. At least six members of this family, FYD1-4, 6 and 7, have been shown to regulate Na-K-ATPase activity (Geering 2006, Choudhury et al. 2007). Defects in FXYD2 are the cause of hypomagnesemia type 2 (HOMG2) (Meij et al, 2000). ATP1A1-4 and ATP1B1-4 play a minor role during phase 2, since they begin to restore ion concentrations. The high concentration of intracellular calcium starts contraction of those cells, which is sustained in the plateau phase.

Literature references

Black, DF., Sandkuijl, LA., Kors, EE., van den Maagdenberg, AM., Terwindt, GM., Frants, RR. et al. (2003). Novel mutations in the Na+, K+-ATPase pump gene ATP1A2 associated with familial hemiplegic migraine and benign familial infantile convulsions. *Ann Neurol, 54*, 360-6. ↗

Xaidara, A., Youroukos, S., Swoboda, KJ., Leppert, MF., Ptácek, LJ., Silver, K. et al. (2004). Alternating hemiplegia of childhood or familial hemiplegic migraine? A novel ATP1A2 mutation. *Ann Neurol, 55*, 884-7. ↗

Nadeem, H., McQuillin, A., Johnson, S., Quested, D., Datta, S., Pimm, J. et al. (2007). A genetic association study of chromosome 11q22-24 in two different samples implicates the FXYD6 gene, encoding phosphohippolin, in susceptibility to schizophrenia. *Am. J. Hum. Genet., 80*, 664-72. ↗

Lane, LK., Shull, MM., Whitmer, KR., Lingrel, JB. (1989). Characterization of two genes for the human Na,K-ATPase beta subunit. *Genomics, 5*, 445-53. ↗

Nagano, K., Ohta, T., Kawakami, K., Nojima, H. (1986). Primary structure of the alpha-subunit of human Na,K-ATPase deduced from cDNA sequence. *J Biochem, 100*, 389-97. ↗

Editions

2010-08-24	Authored, Edited	Jassal, B.
2010-11-15	Reviewed	He, L.
2012-12-07	Revised	Jassal, B.

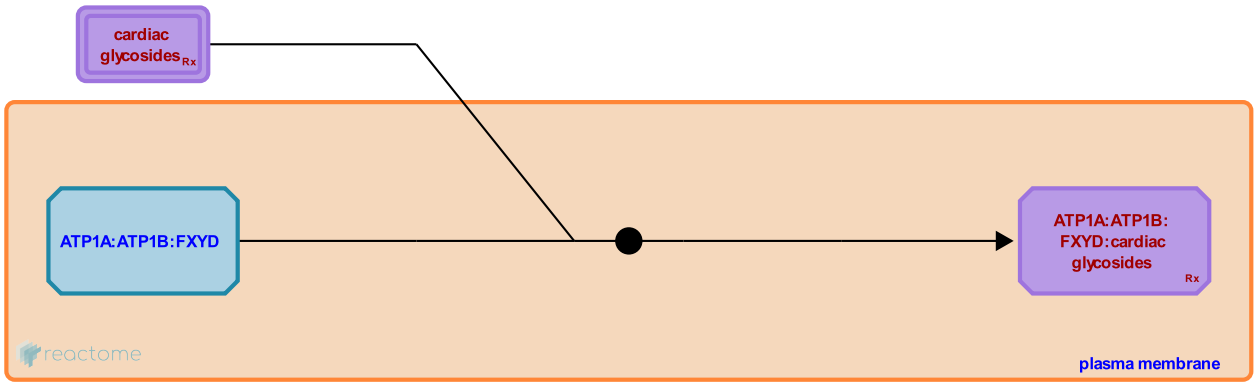
ATP1A:ATP1B:FXYD binds cardiac glycosides ↗

Location: Ion homeostasis

Stable identifier: R-HSA-9684068

Type: binding

Compartments: plasma membrane, extracellular region



Cardiac glycosides are a class of organic compounds that increase the output force of the heart and increase its rate of contractions by inhibition of the cellular sodium-potassium ATPase pump (ATP1A1). Their beneficial medical uses are as treatments for congestive heart failure and cardiac arrhythmias. Cardiac glycosides are primarily derived from foxglove plants or from the venom of the cane toad Bufo marinus. Their toxicity prevents them from being widely used. Changes to heart inotropic and chronotropic activity results in multiple kinds of dysrhythmia and potentially fatal ventricular tachycardia. Different cardiac glycosides show different specificities towards sodium-potassium ATPase pump alpha isoforms (Hauck et al. 2009, Katz et al. 2010, Cherniavsky et al. 2015).

HIV-1 Tat is essential for HIV-1 replication. Tat must escape from the cell in order for it to activate the HIV-1 LTR promoter and facilitate HIV-1 viral replication. Tat utilises the cellular ATP1A1 pump for secretion out of cells. The cardiac glycosides ouabain, digoxin, digitoxin, acetyldigitoxin and deslanoside can all inhibit ATP1A1 (Smith 1984), impairing extracellular Tat release and blocking HIV-1 replication (Agostini et al. 2017).

Literature references

Smith, TW. (1984). The basic mechanism of inotropic action of digitalis glycosides. *J Pharmacol, 15*, 35-51. ↗

Tasciotti, E., Fittipaldi, A., Agostini, S., Giacca, M., Ali, H., Vardabasso, C. et al. (2017). Inhibition of Non Canonical HIV-1 Tat Secretion Through the Cellular Na⁺,K⁺-ATPase Blocks HIV-1 Infection. *EBioMedicine, 21*, 170-181. ↗

Wittwer, T., Schwinger, RH., Wahlers, T., Bartz, M., Müller-Ehmsen, J., McDonough, AA. et al. (2009). Isoform specificity of cardiac glycosides binding to human Na+,K+-ATPase alpha1beta1, alpha2beta1 and alpha3beta1. *Eur. J. Pharmacol., 622*, 7-14. ↗

Garty, H., Cherniavsky Lev, M., Karlish, SJ. (2015). Cardiac glycosides induced toxicity in human cells expressing α1-, α2-, or α3-isoforms of Na-K-ATPase. *Am. J. Physiol., Cell Physiol., 309*, C126-35. ↗

Karlish, SJ., Bab-Dinitz, E., Tal, DM., Katz, A., Kapri-Pardes, E., Lifshitz, Y. et al. (2010). Selectivity of digitalis glycosides for isoforms of human Na,K-ATPase. *J. Biol. Chem., 285*, 19582-92. ↗

Editions

2020-04-20	Authored, Edited	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

CRAC translocates calcium from the extracellular region to the cytosol ↗

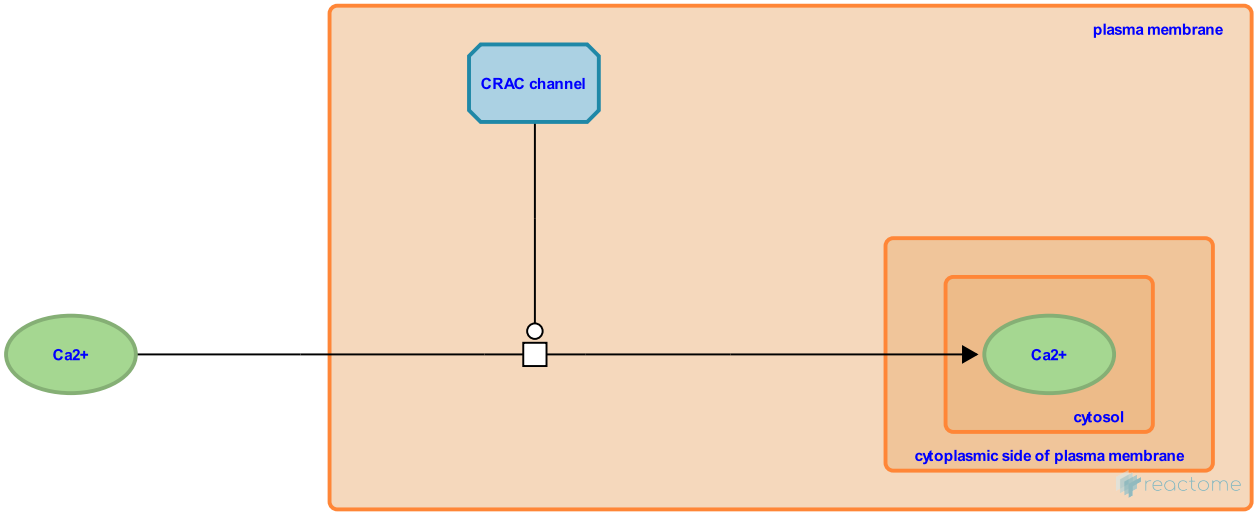
Location: Ion homeostasis

Stable identifier: R-HSA-434798

Type: transition

Compartments: plasma membrane

Inferred from: Calcium influx via CRAC (Drosophila melanogaster)



Activation of Calcium-release-activated (CRAC) channels allows influx of calcium. The Orai component of CRAC is responsible for the selectivity of the channel, while the Stim component is responsible for activation.

Editions

2009-09-04	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

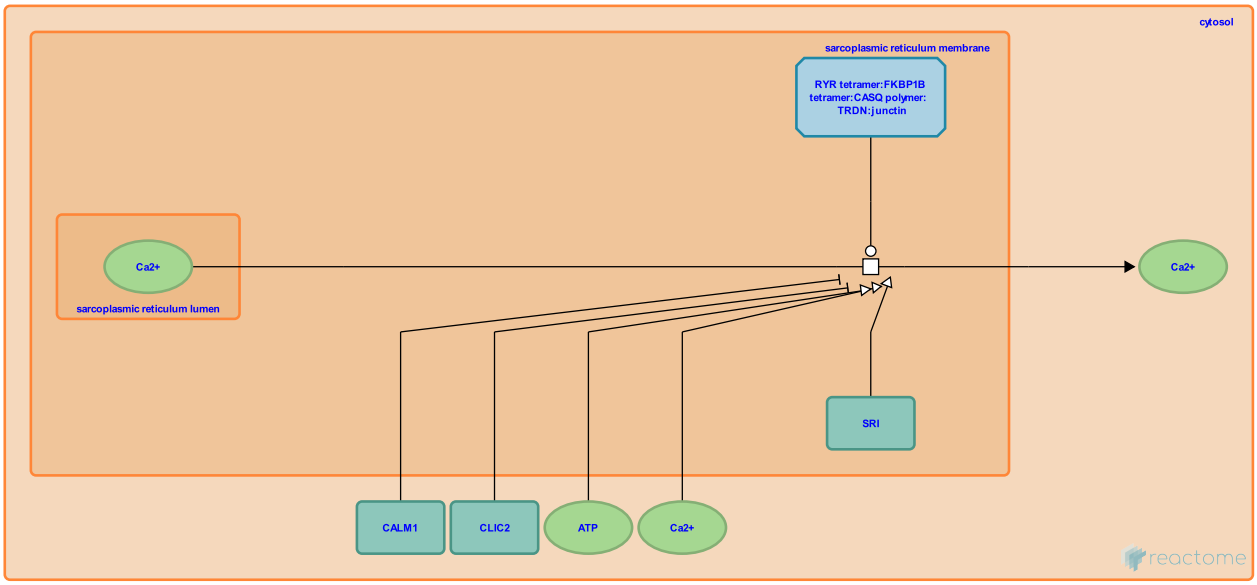
RYR tetramers transport Ca2+ from sarcoplasmic reticulum lumen to cytosol ↗

Location: Ion homeostasis

Stable identifier: R-HSA-2855020

Type: transition

Compartments: sarcoplasmic reticulum membrane, cytosol, sarcoplasmic reticulum lumen



Ryanodine receptors (RYRs) are located in the sarcoplasmic reticulum (SR) membrane and mediate the release of Ca2+ from intracellular stores during excitation-contraction (EC) coupling in both cardiac and skeletal muscle. RYRs are the largest known ion channels (>2MDa) and are functional in their homotetrameric forms. There are three mammalian isoforms (RYR1-3); RYR1 is prominent in skeletal muscle (Zorzato et al. 1990), RYR2 in cardiac muscle (Tunwell et al. 1996) and RYR3 is found in the brain (Nakashima et al. 1997, Lanner et al. 2010). The function of RYRs are controlled by peptidyl-prolyl cis-trans isomerase (FKBP1B), intracellular Ca2+-binding proteins calsequestrin 1 and 2 (CASQ1 and 2) and the anchoring proteins triadin (TRDN) and junctin. Together, they make up the Ca2+-release complex. CASQ1 and 2 buffer intra-SR Ca2+ stores in skeletal muscle and cardiac muscle respectively (Fujii et al. 1990, Kim et al. 2007). When Ca2+ concentrations reach 1mM, CASQs polymerise (Kim et al. 2007) and can attach to one end of RYRs, mediated by anchoring proteins TRDN and junctin (Taske et al. 1995). By sequestering Ca2+ ions, CASQs can inhibit RYRs function (Beard et al. 2004, Beard et al. 2009a, Beard et al. 2009b).

A member of the intracellular Cl- channel protein family, CLIC2, has also been determined to inhibit RYR-mediated Ca2+ transport (Board et al. 2004), potentially playing a role in the homeostasis of Ca2+ release from intracellular stores. Inhibition is thought to be via reducing activation of the channels by their primary endogenous cytoplasmic ligands, ATP and Ca2+ (Dulhunty et al. 2005). Protein kinase A (PKA) phosphorylation of RYR2 dissociates FKBP1B and results in defective channel function (Marx et al. 2000). The penta-EF hand protein sorcin (SRI) can modulate Ca2+-induced calcium-release in the heart via the interaction with several Ca2+ channels such as RYRs. A natural ligand, F112L, impairs this modulating activity (Franceschini et al. 2008). Calmodulin (CALM1) is considered a gatekeeper of RYR2. CALM1 acts directly by binding to RYR2 at residues 3583–3603, inhibiting RYR2 both at physiological and higher, pathological Ca2+ concentrations (Smith et al. 1989, Ono et al. 2010).

Literature references

Fujii, J., MacLennan, DH., Willard, HF. (1990). Characterization and localization to human chromosome 1 of human fast-twitch skeletal muscle calsequestrin gene. *Somat. Cell Mol. Genet., 16*, 185-9. ↗

Nishimura, S., Kita, T., Nakashima, Y., Imoto, K., Allen, PD., Nakai, J. et al. (1997). Molecular cloning and characterization of a human brain ryanodine receptor. *FEBS Lett., 417*, 157-62. ↗

Antaramian, A., Verzili, D., Rueda, A., Valdivia, HH., Zamparelli, C., Franceschini, S. et al. (2008). Molecular basis for the impaired function of the natural F112L sorcin mutant: X-ray crystal structure, calcium affinity, and interaction with annexin VII and the ryanodine receptor. *FASEB J., 22*, 295-306. ↗

Dulhunty, AF., Pouliquin, P., Coggan, M., Board, PG., Gage, PW. (2005). A recently identified member of the glutathione transferase structural family modifies cardiac RyR2 substate activity, coupled gating and activation by Ca2+ and ATP. *Biochem. J., 390*, 333-43. ↗

Dulhunty, AF., Watson, S., Coggan, M., Gage, PW., Board, PG. (2004). CLIC-2 modulates cardiac ryanodine receptor Ca2+ release channels. *Int. J. Biochem. Cell Biol., 36*, 1599-612. ↗

Editions

2012-12-14	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.

IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol ↗

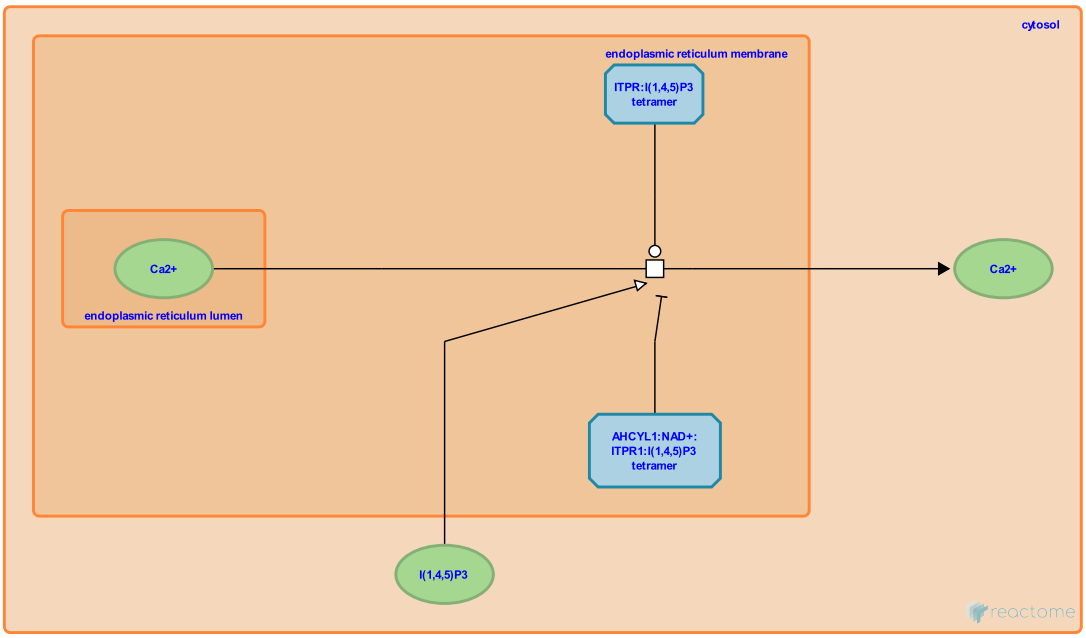
Location: Ion homeostasis

Stable identifier: R-HSA-169683

Type: transition

Compartments: endoplasmic reticulum membrane

Inferred from: Calcium release from intracellular stores by IP3 receptor activation (Rattus norvegicus)



IP3 promotes the release of intracellular calcium.

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2006-10-10	Edited	Jassal, B.
2009-06-02	Reviewed	Gillespie, ME.

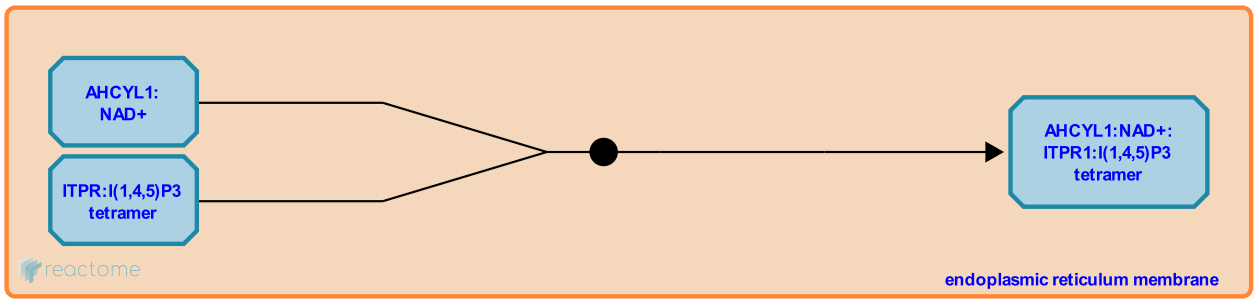
AHCYL1:NAD+ binds ITPR1:I(1,3,5)P3 tetramer, inhibiting it ↗

Location: Ion homeostasis

Stable identifier: R-HSA-5226904

Type: binding

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Putative adenosylhomocysteinase 2 (AHCYL1 aka adenosylhomocysteine hydrolase-like protein 1) (Dekker et al. 2002) possesses 50% homology to adenosylhomocysteine hydrolase (AHCY), an enzyme important for metabolizing S-adenosyl-l-homocysteine. AHCYL1 can bind to the inositol 1,4,5-trisphosphate receptor (ITPR1) tetramer, suggesting that AHCYL1 is involved in modulating intracellular calcium release (Cooper et al. 2006).

Literature references

Cooper, BJ., Angel, NZ., Budhia, S., Hart, DN., Dekker, JW., Clark, GJ. et al. (2002). Identification of an S-adenosyl-homocysteine hydrolase-like transcript induced during dendritic cell differentiation. *Immunogenetics, 53*, 993-1001. ↗

Cooper, BJ., Angel, NZ., Key, B., Hart, DN., Kato, M., Carter, A. (2006). Suppression and overexpression of adenosyl-homocysteine hydrolase-like protein 1 (AHCYL1) influences zebrafish embryo development: a possible role for AHCYL1 in inositol phospholipid signaling. *J. Biol. Chem., 281*, 22471-84. ↗

Editions

2014-01-09	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

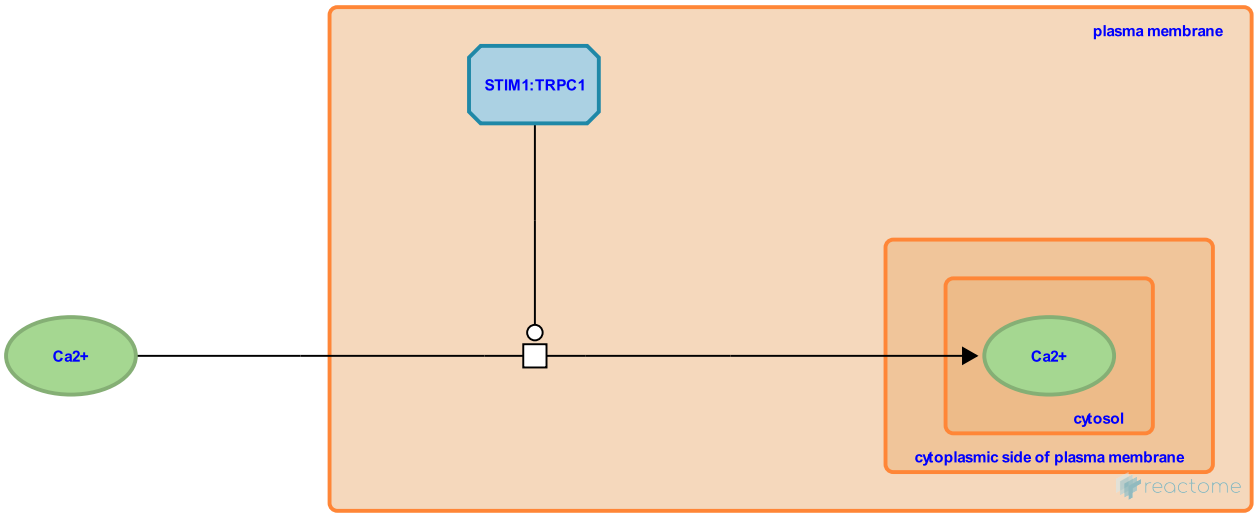
TRPC1 translocates calcium from the extracellular region to the cytosol ↗

Location: Ion homeostasis

Stable identifier: R-HSA-2089943

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



TRPC1 forms a channel that transports Ca2+ across the plasma membrane. TRPC1 is gated by STIM1 (Ong et al. 2007).

Literature references

Yuan, JP., Muallem, S., Kim, MS., Huang, GN., Choi, YJ., Zeng, W. et al. (2008). STIM1 gates TRPC channels, but not Orai1, by electrostatic interaction. *Mol Cell, 32,* 439-48. ↗

Yuan, JP., Muallem, S., Huang, GN., Zeng, W., Worley, PF. (2007). STIM1 heteromultimerizes TRPC channels to determine their function as store-operated channels. *Nat Cell Biol, 9,* 636-45. ↗

Freichel, M., Tiruppathi, C., Yuan, JP., Malik, AB., Vogel, SM., Sundivakkam, PC. et al. (2011). The Ca2+ Sensor STIM1 is Necessary and Sufficient for the Store-Operated Ca2+ Entry Function of TRPCs in Endothelial Cells. *Mol Pharmacol.* ↗

Gwack, Y., Ong, HL., Bandyopadhyay, BC., Ambudkar, IS., Srikanth, S., Liu, X. et al. (2007). Dynamic assembly of TRPC1-STIM1-Orai1 ternary complex is involved in store-operated calcium influx. Evidence for similarities in store-operated and calcium release-activated calcium channel components. *J Biol Chem, 282,* 9105-16. ↗

Editions

2012-02-01	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

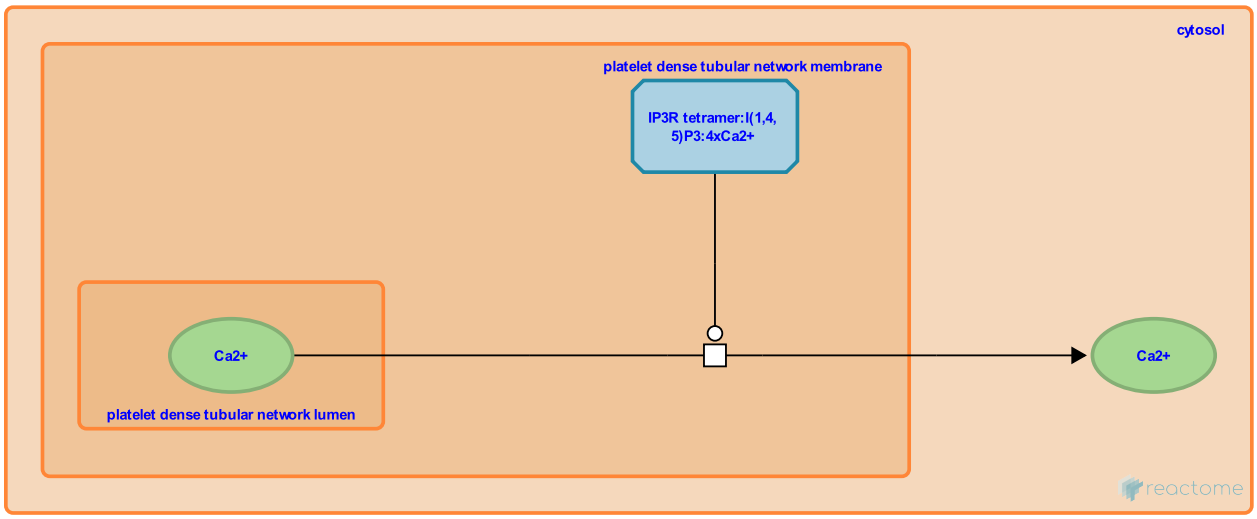
IP3R tetramer:I(1,4,5)P3:4xCa2+ transports Ca2+ from platelet dense tubular system to cytosol ↗

Location: Ion homeostasis

Stable identifier: R-HSA-139854

Type: transition

Compartments: platelet dense tubular network membrane



The IP3 receptor (IP3R) is an intracellular calcium release channel that mobilizes Ca2+ from internal stores in the ER to the cytoplasm. Though its activity is stimulated by IP3, the principal activator of the IP3R is Ca2+. This process of calcium-induced calcium release is central to the mechanism of Ca2+ signalling. The effect of cytosolic Ca2+ on IP3R is complex: it can be both stimulatory and inhibitory and can the effect varies between IP3R isoforms. In general, the IP3Rs have a bell-shaped Ca2+ dependence when treated with low concentrations of IP3; low concentrations of Ca2+ (100–300 nM) are stimulatory but above 300 nM, Ca2+ becomes inhibitory and switches the channel off. The stimulatory effect of IP3 is to relieve Ca2+ inhibition of the channel, enabling Ca2+ activation sites to gate it.
Functionally the IP3 receptor is believed to be tetrameric, with results indicating that the tetramer is composed of 2 pairs of protein isoforms.

Literature references

Rink, TJ., Sage, SO., Mahaut-Smith, MP. (1990). Receptor-activated single channels in intact human platelets. *J Biol Chem, 265*, 10479-83. ↗

Editions

2009-09-09	Edited	Jupe, S.

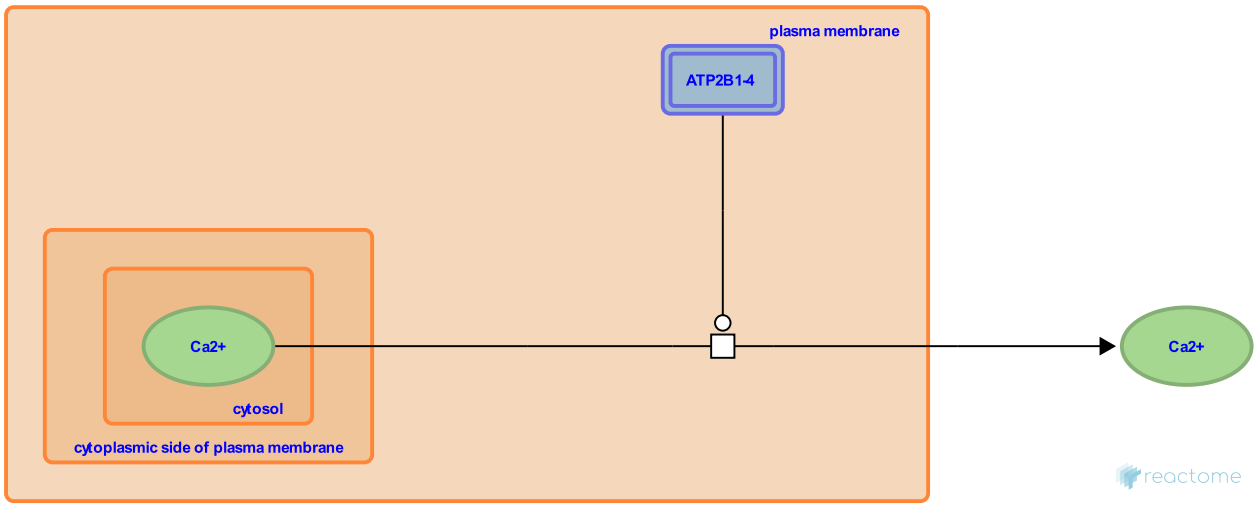
ATP2B1-4 transport cytosolic Ca2+ to extracellular region ↗

Location: Ion homeostasis

Stable identifier: R-HSA-418309

Type: transition

Compartments: plasma membrane



The plasma membrane Ca-ATPases 1-4 (ATP2B1-4, PMCAs) are P-type Ca2+-ATPases regulated by calmodulin. The PMCA also counter-transports a proton. PMCA is important for Ca2+ homeostasis and function.

Literature references

Schatzmann, HJ. (1966). ATP-dependent Ca++-extrusion from human red cells. *Experientia, 22*, 364-5. ↗

Strehler, EE., Heim, R., Verma, AK., Filoteo, AG., Mathews, S., Fischer, R. et al. (1988). Complete primary structure of a human plasma membrane Ca2+ pump. *J Biol Chem, 263*, 14152-9. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

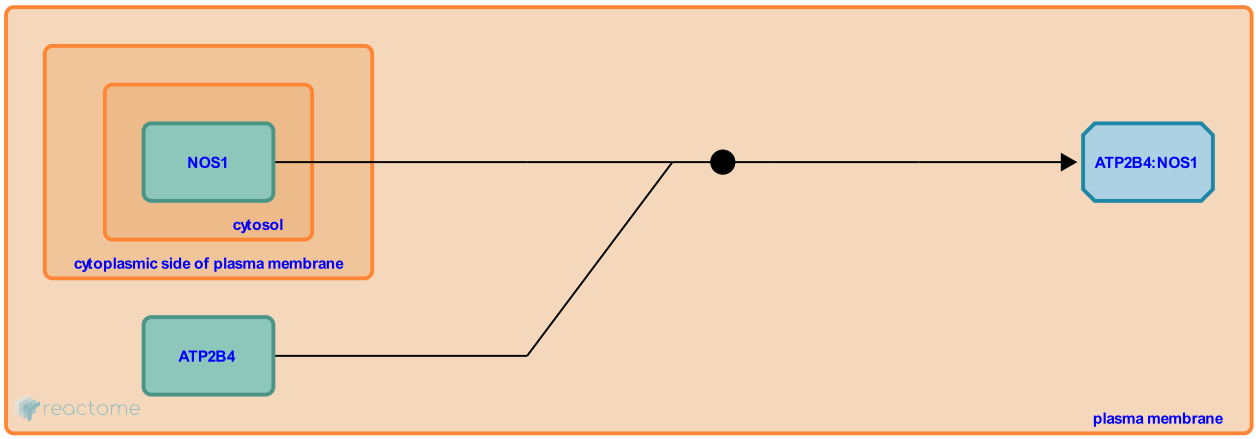
ATP2B4 binds to NOS1, inhibiting it ↗

Location: Ion homeostasis

Stable identifier: R-HSA-5617178

Type: binding

Compartments: plasma membrane, cytosol



Plasma membrane calcium-transporting ATPase 4 (ATP2B4 aka PMCA4) binds and inhibits cardiac neuronal nitric-oxide synthase (NOS1 aka nNOS, a powerful regulator of the beta-adrenergic contractile response in the heart) by changing local calcium concentration (Duan et al. 2013). Reduced nNOS activity leads to a reduction in cGMP which in turn results in the reduction of phosphodiesterase (PDE) activity. As a result, cAMP degradation is prevented, increasing protein kinase A (PKA) activity, which can lead to increased phosphorylation of proteins involved in the excitation-contraction coupling process such as cardiac phospholamban (PLN aka PLB) and of cardiac muscle troponin I (TNNI3 aka cTnI) (Mohamed et al. 2009).

Literature references

Oceandy, D., Cartwright, EJ., Baudoin, FM., Nadif, R., Pickard, A., Neyses, L. et al. (2009). Specific role of neuronal nitric-oxide synthase when tethered to the plasma membrane calcium pump in regulating the beta-adrenergic signal in the myocardium. *J. Biol. Chem., 284*, 12091-8. ↗

Zhou, T., Duan, W., Li, W., Wei, T., Zhou, J., Yang, F. et al. (2013). Plasma membrane calcium ATPase 4b inhibits nitric oxide generation through calcium-induced dynamic interaction with neuronal nitric oxide synthase. *Protein Cell, 4*, 286-98. ↗

Editions

2014-08-05	Authored, Edited	Jassal, B.
2015-11-09	Reviewed	Colotti, G.

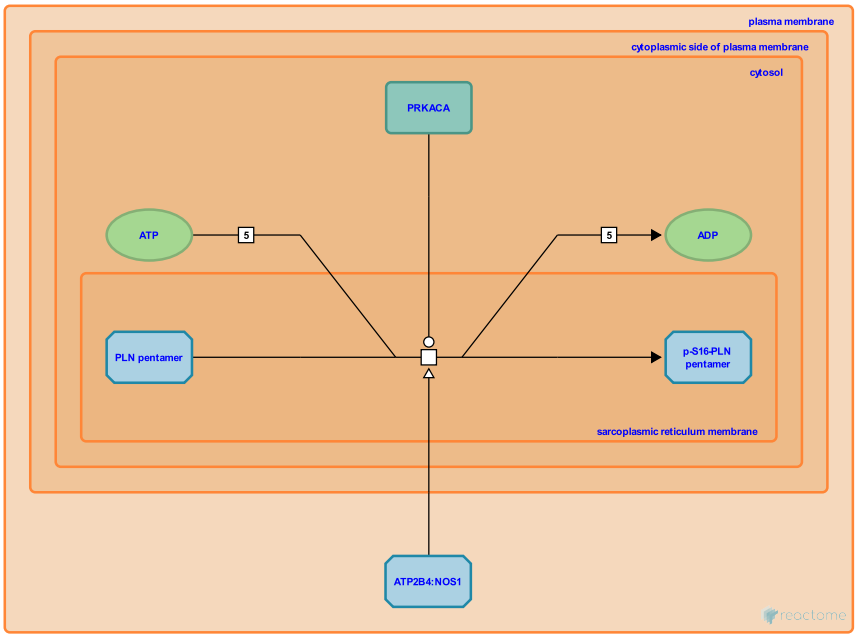
PRKACA phosphorylates PLN ↗

Location: Ion homeostasis

Stable identifier: R-HSA-5617182

Type: transition

Compartments: sarcoplasmic reticulum membrane, cytosol



Cardiac muscle phospholamban (PLN aka PLB) modulates cardiac contractility by inhibiting the sarcoplasmic reticulum calcium pump (ATP2A2 aka SERCA). This process is dynamically regulated by beta-adrenergic stimulation and phosphorylation of PLN. Protein kinase A (PRKACA) is able to phosphorylate PLN at serine 16, relieving its inhibition of ATP2A2 and modulating cardiac contractility (Glaves et al. 2011, Ceholski et al. 2012). The ATP2B4:NOS1 complex, via cAMP, increases PRKACA activity, thereby regulating the response of the heart to beta-adrenergic agonists.

Literature references

Young, HS., Stokes, DL., Trieber, CA., Ceholski, DK., Glaves, JP. (2011). Phosphorylation and mutation of phospholamban alter physical interactions with the sarcoplasmic reticulum calcium pump. *J. Mol. Biol., 405*, 707-23. ↗

Young, HS., Trieber, CA., Holmes, CF., Ceholski, DK. (2012). Lethal, hereditary mutants of phospholamban elude phosphorylation by protein kinase A. *J. Biol. Chem., 287*, 26596-605. ↗

Editions

2014-08-05	Authored, Edited	Jassal, B.
2015-11-09	Reviewed	Colotti, G.

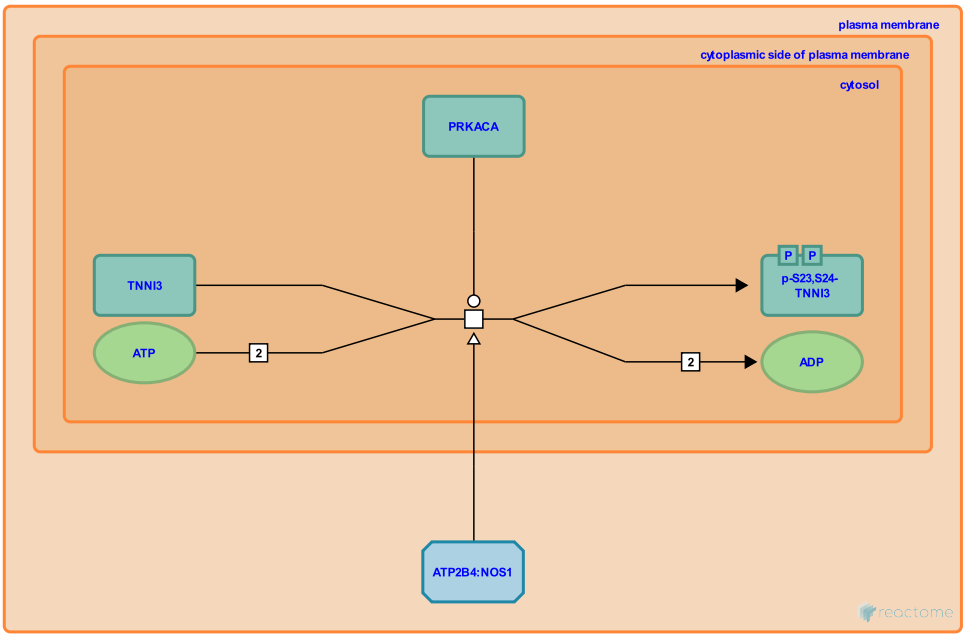
PRKACA phosphorylates TNNI3 ↗

Location: Ion homeostasis

Stable identifier: R-HSA-5617179

Type: transition

Compartments: cytosol



Human cardiac troponin I (TNNI3) is known to be phosphorylated at multiple amino acid residue sites by several kinases. Protein kinase A (PRKACA) can phosphorylate serine 23 and 24 sites on TNNI3. Phosphorylation of TNNI3 reduces myofilament calcium sensitivity (Mittmann et al. 1990, Keane et al. 1997, Zhang et al. 2012). Defects in TNNI3 can cause a range of cardiomyopathies (Lu et al. 2013). The ATP2B4:NOS1 complex, via cAMP, increases PRKACA activity, thereby regulating the response of the heart to beta-adrenergic agonists.

Literature references

Wu, XY., Lu, QW., Morimoto, S. (2013). Inherited cardiomyopathies caused by troponin mutations. *J Geriatr Cardiol, 10*, 91-101. ↗

Heilmeyer, LM., Mittmann, K., Jaquet, K. (1990). A common motif of two adjacent phosphoserines in bovine, rabbit and human cardiac troponin I. *FEBS Lett., 273*, 41-5. ↗

dos Remedios, CG., Murphy, AM., Van Eyk, JE., Kirk, JA., Ji, W., Kass, DA. et al. (2012). Multiple reaction monitoring to identify site-specific troponin I phosphorylated residues in the failing human heart. *Circulation, 126*, 1828-37. ↗

Perry, SV., Quirk, PG., Levine, BA., Gao, Y., Patchell, VB., Keane, NE. (1997). The ordered phosphorylation of cardiac troponin I by the cAMP-dependent protein kinase--structural consequences and functional implications. *Eur. J. Biochem., 248*, 329-37. ↗

Editions

2014-08-05	Authored, Edited	Jassal, B.
2015-11-09	Reviewed	Colotti, G.

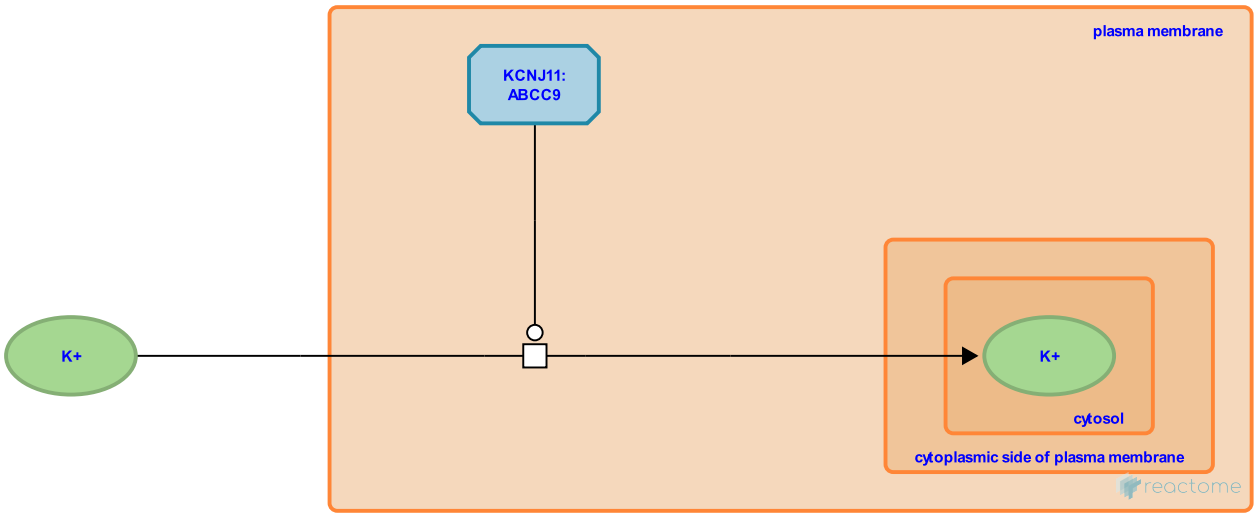
KCNJ11:ABCC9 transports K+ from extracellular region to cytosol ↗

Location: Ion homeostasis

Stable identifier: R-HSA-5678261

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



ATP-sensitive inward rectifier potassium channel 11 (KCNJ11) is an inward rectifier potassium channel, favouring potassium flow into the cell rather than out of it. KCNJ11 can complex with ATP-binding cassette sub-family member 9 (ABCC9) to form cardiac and smooth muscle-type K+(ATP) channels. KCNJ11 forms the channel pore while ABCC9 is required for activation and regulation (Babenko et al. 1998, Tammaro & Ashcroft 2007).

Literature references

Ashcroft, FM., Tammaro, P. (2007). A mutation in the ATP-binding site of the Kir6.2 subunit of the KATP channel alters coupling with the SUR2A subunit. *J. Physiol. (Lond.), 584*, 743-53. ↗

Bryan, J., Gonzalez, G., Aguilar-Bryan, L., Babenko, AP. (1998). Reconstituted human cardiac KATP channels: functional identity with the native channels from the sarcolemma of human ventricular cells. *Circ. Res., 83*, 1132-43. ↗

Editions

2015-02-23	Authored, Edited	Jassal, B.
2015-04-28	Reviewed	Moitra, K.

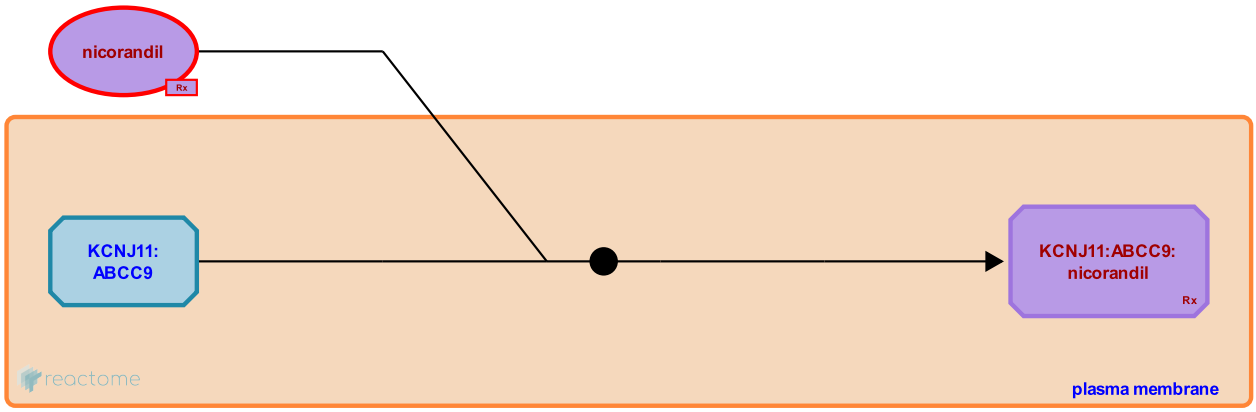
KCNJ11:ABCC9 binds nicorandil ↗

Location: Ion homeostasis

Stable identifier: R-HSA-9691566

Type: binding

Compartments: plasma membrane, extracellular region



Nicorandil, a nicotinamide derivative, is an oral antianginal drug possessing a nitrate moiety in its structure. This drug is an effective and well-tolerated treatment for various types of angina pectoris. Its structure is characterised by a dual mechanism of action. The nicotinamide moiety acts as an agonist for ATP-sensitive inward rectifier potassium channel 11 (KCNJ11, in complex with its regulatory subunit ABCC9) (Hambrock et al. 1999) and the nitrate group explains its nitrate-like properties (Kinoshita & Sakai 1990, Ahmed 2019).

Literature references

Löffler-Walz, C., Delabar, U., Quast, U., Horio, Y., Hambrock, A., Kloor, D. et al. (1999). ATP-Sensitive K+ channel modulator binding to sulfonylurea receptors SUR2A and SUR2B: opposite effects of MgADP. *Mol. Pharmacol., 55,* 832-40. ↗

Editions

2020-06-17	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

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