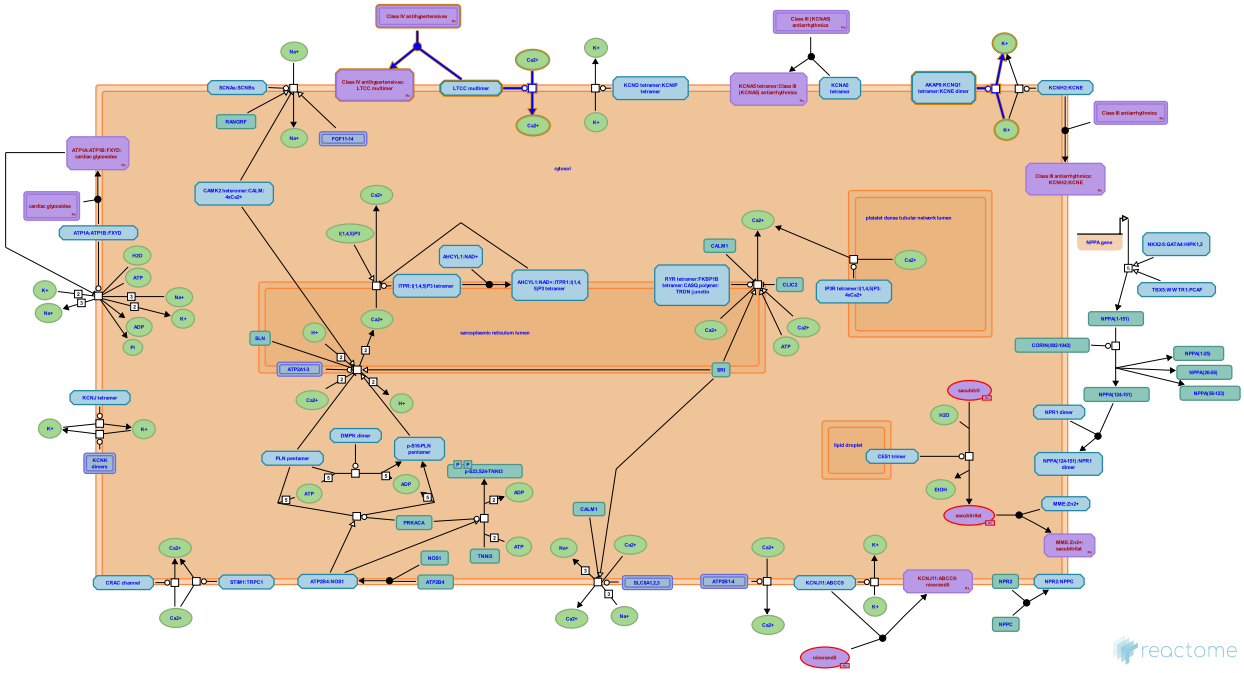
Phase 2 - plateau phase



Colotti, G., Huddart, R., Jassal, B., Matthews, L.

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.

18/05/2024

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. ↗

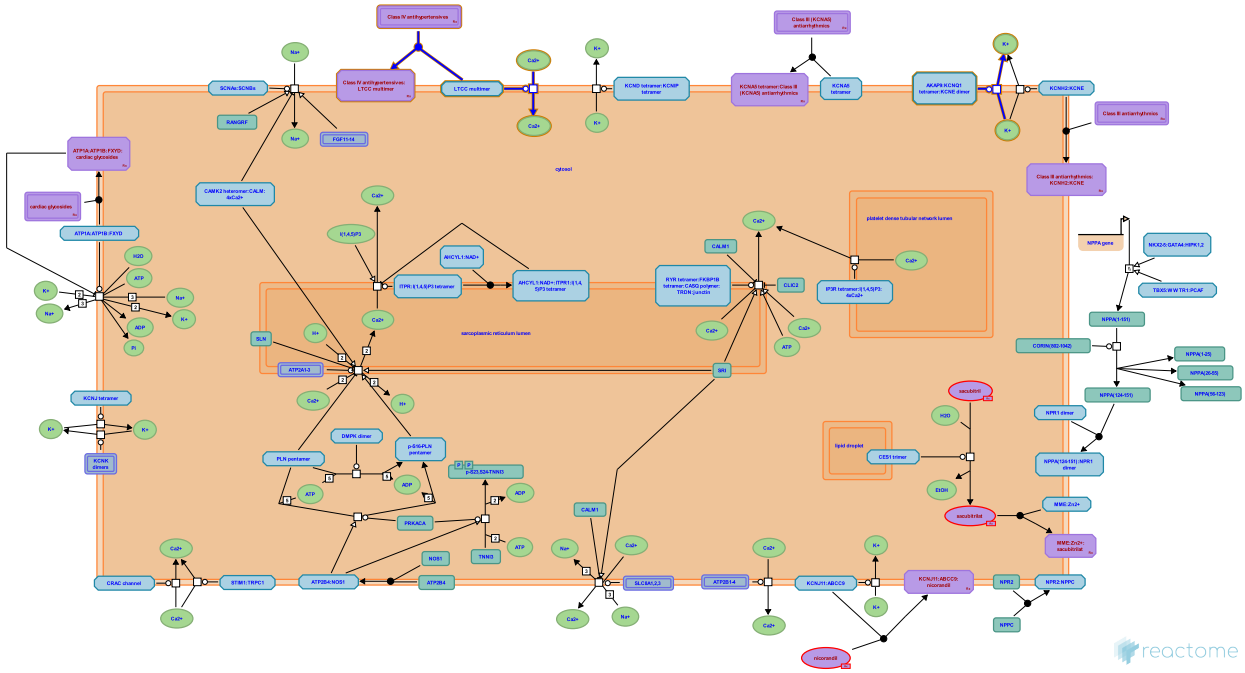
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Phase 2 - plateau phase ↗

Stable identifier: R-HSA-5576893



Phase 2 of the cardiac action potential is the plateau phase which is sustained by a balance of Ca2+ influx through L-type Ca2+ channels (LTCCs) and K+ efflux through the slow delayed rectifier K+ channel 1 (KCNQ1). This phase sustains muscle contraction (Park & Fishman 2011, Grant 2009).

Literature references

Park, DS., Fishman, GI. (2011). The cardiac conduction system. *Circulation, 123*, 904-15. ↗

Grant, AO. (2009). Cardiac ion channels. *Circ Arrhythm Electrophysiol, 2*, 185-94. ↗

Editions

2014-05-27	Authored, Edited	Jassal, B.
2015-11-09	Reviewed	Colotti, G.

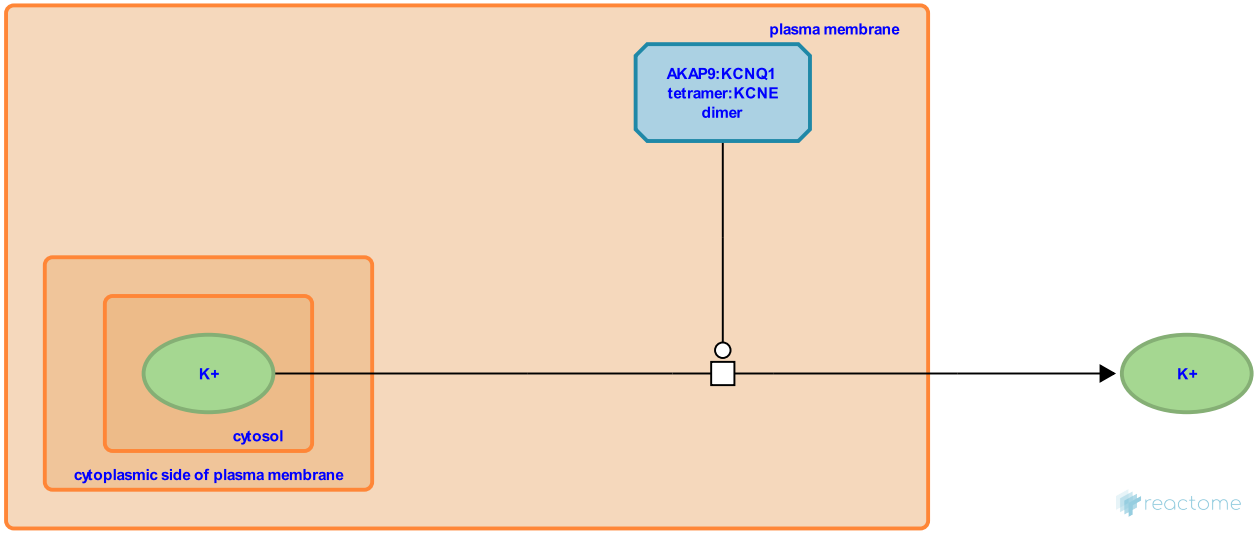
AKAP9:KCNQ1 tetramer:KCNE dimer transports K+ from cytosol to extracellular region ↗

Location: Phase 2 - plateau phase

Stable identifier: R-HSA-5577050

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Two potassium currents, I_{Ks} and I_{Kr}, provide the principal repolarising currents in cardiac myocytes for the termination of action potentials. Potassium voltage-gated channel subfamily KQT member 1 (KCNQ1 aka Kv7.1) is the pore-forming alpha subunit of a complex also containing an ancillary protein from potassium voltage-gated channel subfamily E members (KCNE) that assemble as a beta subunit. The stoichiometry is believed to be 4 KCNQ1 subunits to 2 KCNE subunits (Plant et al. 2014). A-kinase anchor protein 9 (AKAP9) is an essential anchoring protein that binds to KCNQ1. Defects in KCNQ1 that disrupt this binding can result in type 1 long-QT syndrome (LQT1), a hereditary, potentially lethal arrhythmia syndrome (Chen et al. 2007). The AKAP9:KCNQ1:KCNE complex creates the slowly activating delayed rectifier cardiac potassium current I_{Ks} by the efflux of K+ from cardiac cells (Schroeder et al. 2000).

Literature references

Tester, DJ., Sampson, KJ., Chen, L., Kass, RS., Marquardt, ML., Ackerman, MJ. (2007). Mutation of an A-kinase-anchoring protein causes long-QT syndrome. *Proc. Natl. Acad. Sci. U.S.A., 104*, 20990-5. ↗

Goldstein, SA., Dai, H., Xiong, D., Plant, LD. (2014). Individual IKs channels at the surface of mammalian cells contain two KCNE1 accessory subunits. *Proc. Natl. Acad. Sci. U.S.A., 111*, E1438-46. ↗

Greger, R., Jentsch, TJ., Bleich, M., Schroeder, BC., Warth, R., Fehr, S. et al. (2000). A constitutively open potassium channel formed by KCNQ1 and KCNE3. *Nature, 403*, 196-9. ↗

Editions

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2015-11-09	Reviewed	Colotti, G.

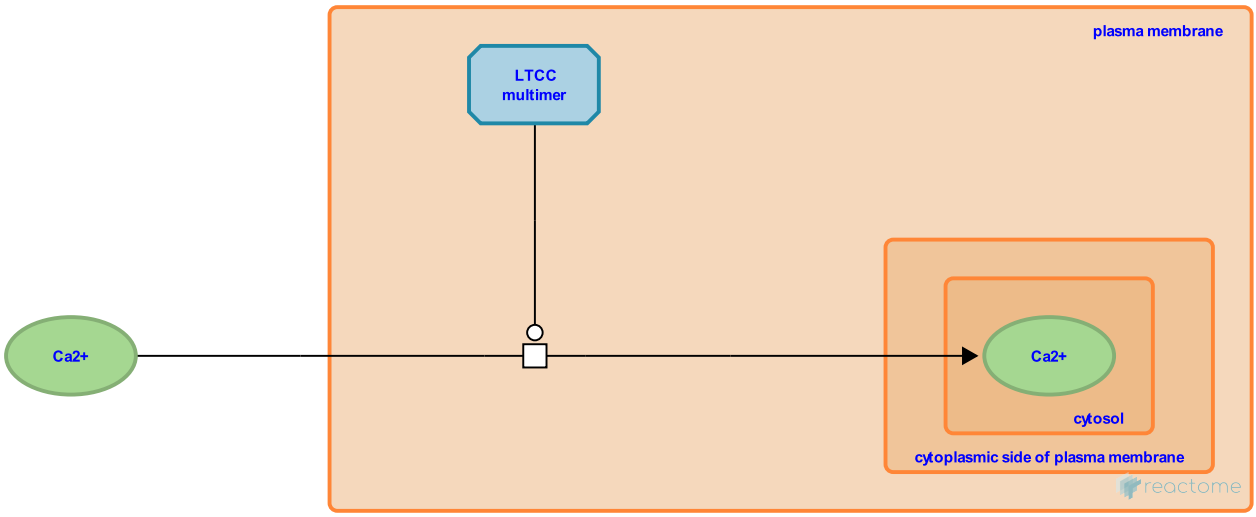
LTCC multimer transports Ca2+ from extracellular region to cytosol ↗

Location: Phase 2 - plateau phase

Stable identifier: R-HSA-5577213

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Voltage-dependent L-type calcium channels (LTCCs) transport Ca2+ into excitable cells. Isoforms CACNA1C, D, F and S form long-lasting (L-type) inward Ca2+ currents (I_{CaL}) and play an important role in excitation-contraction coupling in the heart. LTCCs are multisubunit complexes consisting of alpha-1, alpha-2/delta, beta and gamma subunits in a 1:1:1:1 ratio (Brust et al. 1993). The alpha-2 and delta subunits in these complexes are chains of differing length cleaved from the same gene product (CACNA2D), linked by a disulfide bond (Calderon-Rivera et al. 2012). Pore-forming alpha1 subunits are supported by the auxiliary alpha-2, delta and beta subunits which aid the membrane trafficking of the alpha1 subunit and modulate the kinetic properties of the channel (Klugbauer et al. 2003, Yang et al. 2011). The binding of various gamma subunits to alpha1 subunits may differentially modulate alpha1 subunit function in the heart (Yang et al. 2011). In heart pacemaker cells, phase 0 of the action potential depends upon LTCC-mediated Ca2+ current rather than the fast Na+ current. In cardiac pacemaker cells, phase 1 is due to the closure of LTCCs (and rapid efflux of K+). Specific subunits can form the LTCC in the heart are CACNA1C (pore-forming alpha subunit), CACNA2D2 (alpha-2:delta-2 subunit), CACNB1 and CANCNB2 (either of these beta subunits) and CACNG4, 6, 7 and 8 (any of these gamma subunits).

Literature references

Marx, SO., Yang, L., Morrow, JP., Doshi, D., Katchman, A. (2011). Cardiac L-type calcium channel (Cav1.2) associates with gamma subunits. *FASEB J., 25*, 928-36. ↗

Schoonmaker, S., Simerson, S., Johnson, EC., Brust, PF., Harpold, MM., Ellis, SB. et al. (1993). Human neuronal voltage-dependent calcium channels: studies on subunit structure and role in channel assembly. *Neuropharmacology, 32*, 1089-102. ↗

Klugbauer, N., Marais, E., Hofmann, F. (2003). Calcium channel alpha2delta subunits: differential expression, function, and drug binding. *J. Bioenerg. Biomembr., 35*, 639-47. ↗

Rivera, M., Gomora, JC., Calderón-Rivera, A., Felix, R., González-Ramírez, R., Andrade, A. et al. (2012). Identification of a disulfide bridge essential for structure and function of the voltage-gated Ca(2+) channel ?(2)?-1 auxiliary subunit. *Cell Calcium, 51*, 22-30. ↗

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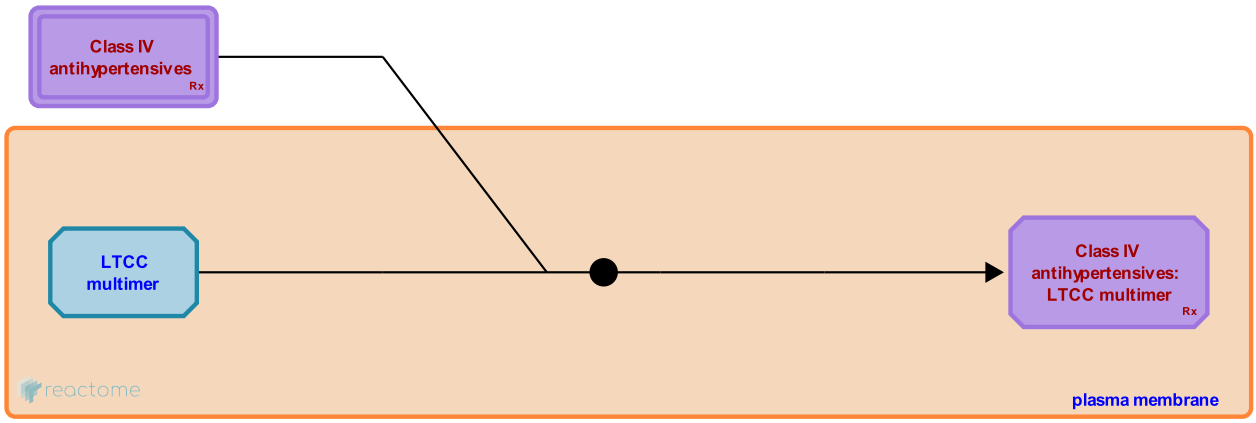
Class IV antihypertensives bind LTCC multimer ↗

Location: Phase 2 - plateau phase

Stable identifier: R-HSA-9614031

Type: binding

Compartments: plasma membrane, extracellular region



L-type calcium channels are responsible for the excitation-contraction coupling of skeletal, smooth and cardiac muscles and for aldosterone secretion in endocrine cells of the adrenal cortex. Class IV agents are L-type calcium channel blockers used in the treatment of hypertension. In cardiac muscle, they decrease conduction through the AV node, and shorten phase 2 (the plateau) of the cardiac action potential. There are three main chemical classes of class IV agents: Dihydropyridines (prototype nifedipine), phenylalkylamines (prototype verapamil) and benzothiazepines (prototype diltiazem). Despite their different structures, they all bind within a single overlapping drug binding region close to the pore and to the proposed activation gate of the channel's α1 subunit (Striessnig et al. 2015). Dihydropyridines (nifedipine, amlodipine, cilnidipine, clevidipine, felodipine, isradipine, nicardipine, nimodipine, nisoldipine, nitrendipine) all block Ca2+-channels and are usually the first-line therapy in hypertension.

nifedipine is the prototypical dihydropyridine used in the treatment of angina and hypertension (Mueller et al. 1981, Snider et al. 2008). Amlodipine blocks Ca2+-channels in peripheral vascular and coronary smooth muscles, producing marked vasodilation. It has an intrinsically long duration of action (Murdoch & Heel 1991). Cilnidipine is a slow-acting Ca2+ antagonist, blocking L-type and N-type Ca2+ channels. It is used in the treatment of mild to moderate essential hypertension (Lohn et al. 2002, Minami et al. 2000). Clevidipine is a short-acting Ca2+-blocking agent given intravenously which is highly selective for vascular, as opposed to myocardial smooth muscle and, therefore, has little or no effect on myocardial contractility or cardiac conduction. It reduces mean arterial blood pressure by decreasing systemic vascular resistance (Prlesi & Cheng-Lai 2009). Felodipine is a vascualr smooth muscle-selective Ca2+-channel blocker used in the treatment of moderate to severe hypertension (Muir & Wathen, Cheung et al. 1998, Walton & Symes 1993).

Isradipine is a Ca2+-channel blocker used in the management of hypertension by producing peripheral vasodilation (Cheung et al. 1998, Walton & Symes 1993). Nicardipine is used in treatment of stable angina and mild to moderate hypertension (Sorkin & Clissold 1987). Nimodipine is mainly used in the control of blood pressure in patients with cerebral hemorrhage (vasospasm) (Li et al. 2015). Nisoldipine is used to treat chronic stable angina pectoris and mild to moderate essential hypertension (Friedel & Sorkin 1988).Nitrendipine is used to treat primary (essential) hypertension (Goa & Sorkin 1987, Santiago & Lopez 1990).

Phenylalkylamine Ca2+ channel blockers are relatively selective for myocardium, reduce myocardial oxygen demand and have minimal vasodilatory effects compared with dihydropyridines and therefore cause less reflex tachycardia, making it appealing for treatment of angina. The prototypical phenylalkylamine drug verapamil is used to treat high blood pressure, angina, supraventricular tachycardia and migraine headaches (Benjamin et al. 1988, Pedersen 1981, Vohra 1982, Sigurd & Hansen 1984, Markley 1991).

Benzothiazepine calcium channel blockers possess both cardiac depressant and vasodilator actions, therefore benzothiazepines are able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines. The prototypical benzothiazepine diltiazem is used in the treatment of hypertension, angina pectoris and some types of arrhythmia (Chaffman & Borgden 1985, O'Connor et al. 1999). It is also used off-label as a preventive medication for migraine (Kim 1991).

Additional L-type calcium channel blockers of the dihydropyridine class all exhibit antihypertensive activity and are identified by the suffix "-dipine"; aranidipine, azelnidipine, barnidipine, dexniguldipine, efonidipine, lacidipine, lercanidipine, levamlodipine, mandipine and nivaldipine.

Literature references

Striessnig, J., Ortner, NJ., Pinggera, A. (2015). Pharmacology of L-type Calcium Channels: Novel Drugs for Old Targets?. *Curr Mol Pharmacol, 8*, 110-22. ↗

Editions

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2022-03-01	Reviewed	Huddart, R.
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