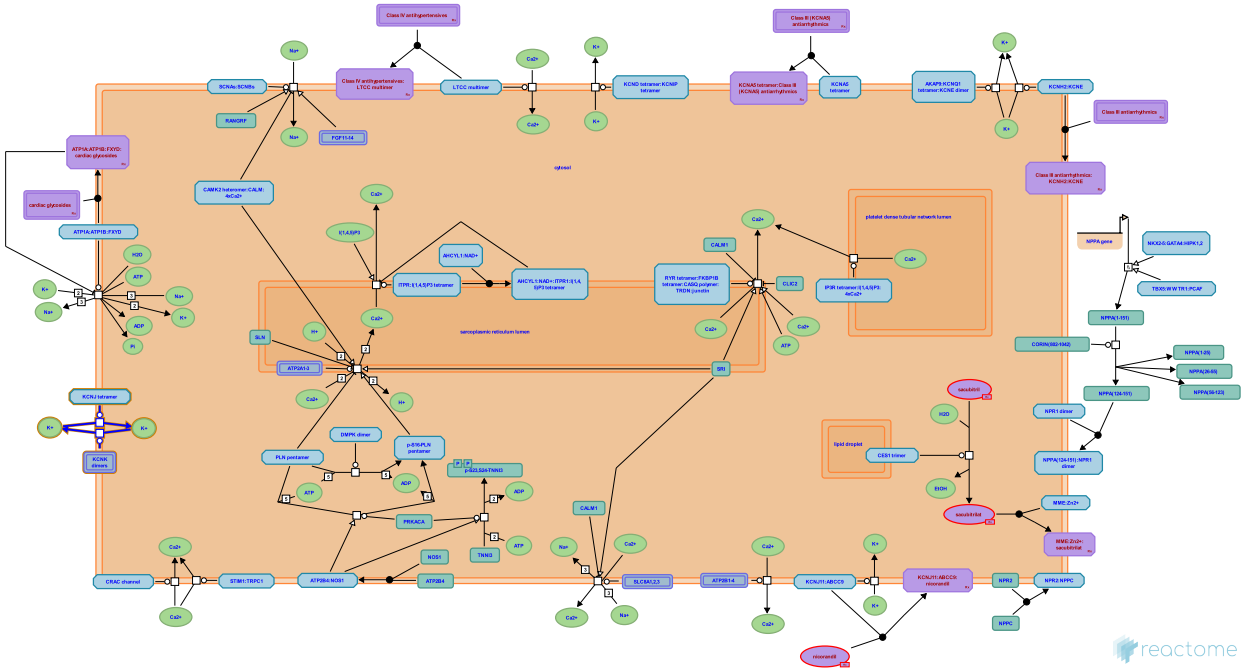
Phase 4 - resting membrane potential



Colotti, G., Jassal, B., Mahajan, SS.

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.

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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. ↗

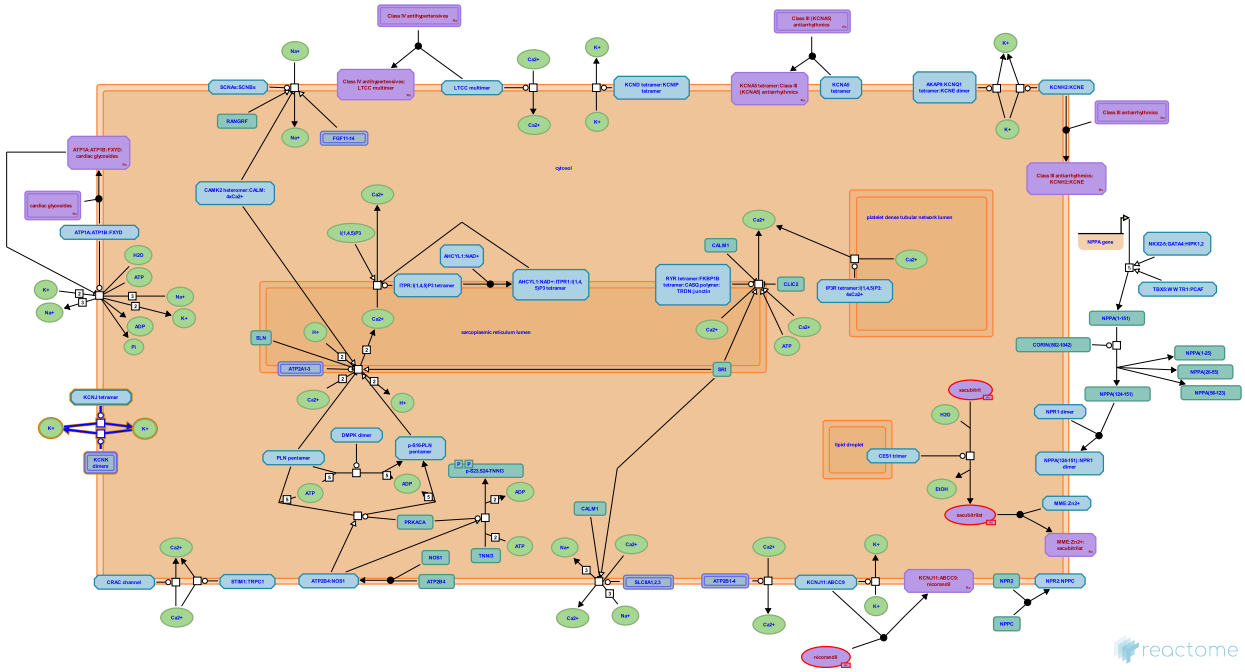
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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 4 - resting membrane potential

Stable identifier: R-HSA-5576886



Phase 4 describes the membrane potential when a cell is not being stimulated. The normal resting potential in the ventricular myocardium is between -85 to -95 mV. The membrane is most permeable to K+ and relatively impermeable to other ions therefore the K+ gradient across the cell membrane is the key determinant in the normal resting potential (Park & Fishman 2011, Grant 2009). In this phase, K+ currents are generated by inward rectifier potassium channels (KCNJs) and tandem pore domain K+ channels (KCNKs). Some Na+/K+-ATPases and Na+/Ca2+-exchangers can also play roles during this phase.

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.

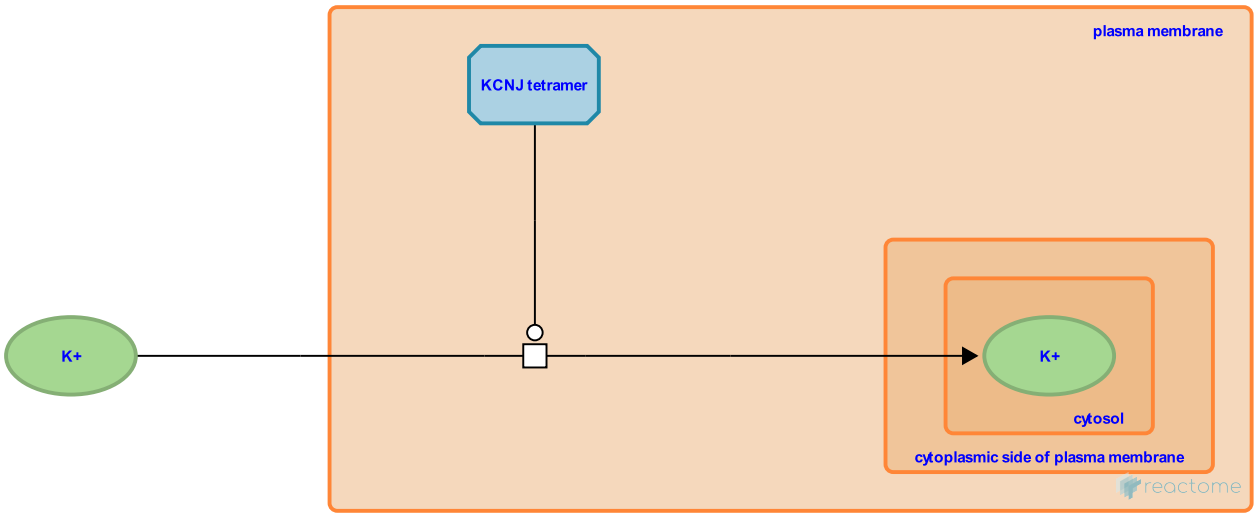
KCNJs transport K+ from the extracellular region to cytosol ↗

Location: Phase 4 - resting membrane potential

Stable identifier: R-HSA-1296046

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Activation of classical Kir (K+ inwardly rectifying) channels (KCNJ2, 4, 12 and 14) results in K+ influx which contributes to the maintenance of the membrane potential (Phase 4 of the action potential). The current created by this flow of K+ is called the inward rectifying current (I_{K1}). A channel that is inwardly-rectifying is one that passes current more easily into the cell than out of the cell. At membrane potentials negative to potassium's reversal potential, KCNJs support the flow of K+ ions into the cell, pushing the membrane potential back to the resting potential. Two factors regulate K+ permeability - cell permeability to K+ is increased at more negative membrane potentials and increasing extracellular K+ concentrations.

When the membrane potential is positive to the channel's resting potential (such as in Phase 3 of the action potential), these channels pass very little charge out of the cell. This may be due to the channel's pores being blocked by internal Mg2+ and endogenous polyamines such as spermine (Shin & Lu 2005).

Inwardly rectifying (Kir) channels contribute to potassium leak, stabilizing cells near the equilibrium reversal potential of potassium (EK). Kir channels pass small outward currents because of pore blockade by internal magnesium and polyamines; at potentials negative to EK, large inward currents are passed upon relief from blockade.

Literature references

Shin, HG., Lu, Z. (2005). Mechanism of the voltage sensitivity of IRK1 inward-rectifier K+ channel block by the polyamine spermine. *J. Gen. Physiol., 125*, 413-26. ↗

Editions

2010-09-23	Reviewed	Jassal, B.
2011-05-19	Authored	Mahajan, SS.
2011-05-23	Edited	Mahajan, SS.

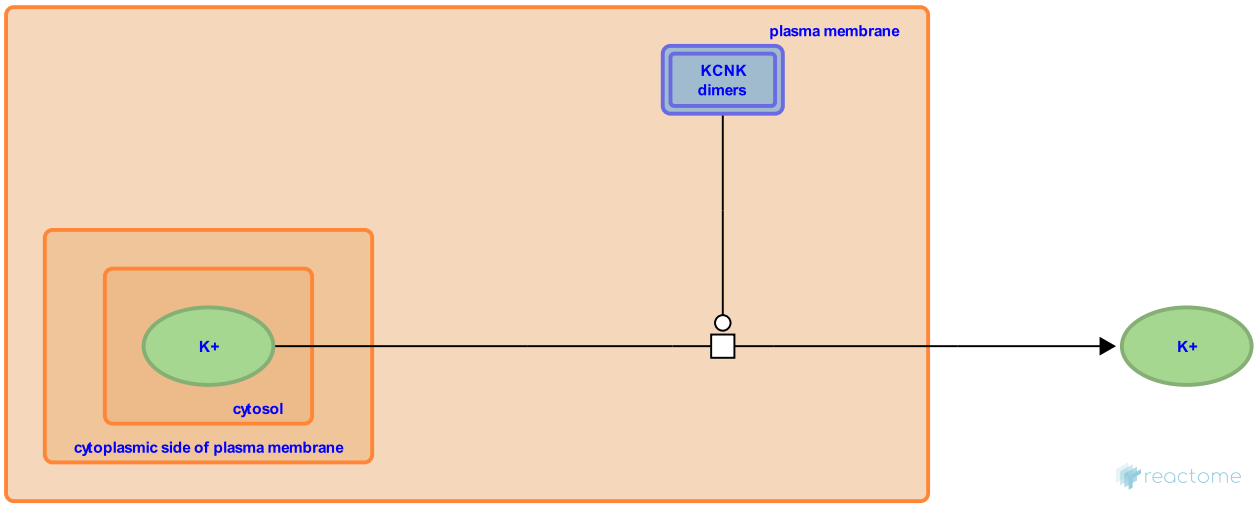
KCNK dimers transport K+ from cytosol to extracellular region ↗

Location: Phase 4 - resting membrane potential

Stable identifier: R-HSA-5578910

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Potassium channels control neuronal excitability through influence over the duration, frequency and amplitude of action potentials. Potassium channels that are active at rest inhibit depolarization toward firing threshold, and thus suppress excitation. Conversely, potassium channels activated at depolarized potentials do not interfere with rise to threshold, but do facilitate recovery and repetitive firing. Tandem pore domain K+ channels (K2p) produce leak K+ current which stabilizes negative membrane potential and counter balances depolarization. These channels are regulated by voltage independent mechanisms such as membrane stretch, pH, temperature (Goldstein et al. 2005, Lotshaw 2007, Enyedi & Czirja 2010). Tandem pore domain K+ channels have been classified into six subfamilies; tandem pore domains in weak rectifying K+ channel (TWIK), TWIK-related K+ channel (TREK), TWIK-related acid-sensitive K+ channel (TASK), TWIK-related alkaline pH-activated K+ channel (TALK), tandem pore domain halothane-inhibted K+ channel (THIK), TWIK-releated spinal cord K+ channel). outwardly rectifying channel that is sensitive to changes in extracellular pH and is inhibited by extracellular acidification. Also referred to as an acid-sensitive potassium channel, it is activated by the anesthetics halothane and isoflurane.

Literature references

Kim, D., Goldstein, SA., Rajan, S., Plant, LD., Bayliss, DA., Lesage, F. (2005). International Union of Pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. *Pharmacol. Rev., 57*, 527-40. ↗

Czirják, G., Enyedi, P. (2010). Molecular background of leak K+ currents: two-pore domain potassium channels. *Physiol Rev, 90*, 559-605. ↗

Lotshaw, DP. (2007). Biophysical, pharmacological, and functional characteristics of cloned and native mammalian two-pore domain K+ channels. *Cell Biochem. Biophys., 47*, 209-56. ↗

Editions

2014-06-05	Authored, Edited	Jassal, B.
2015-11-09	Reviewed	Colotti, G.

Table of Contents