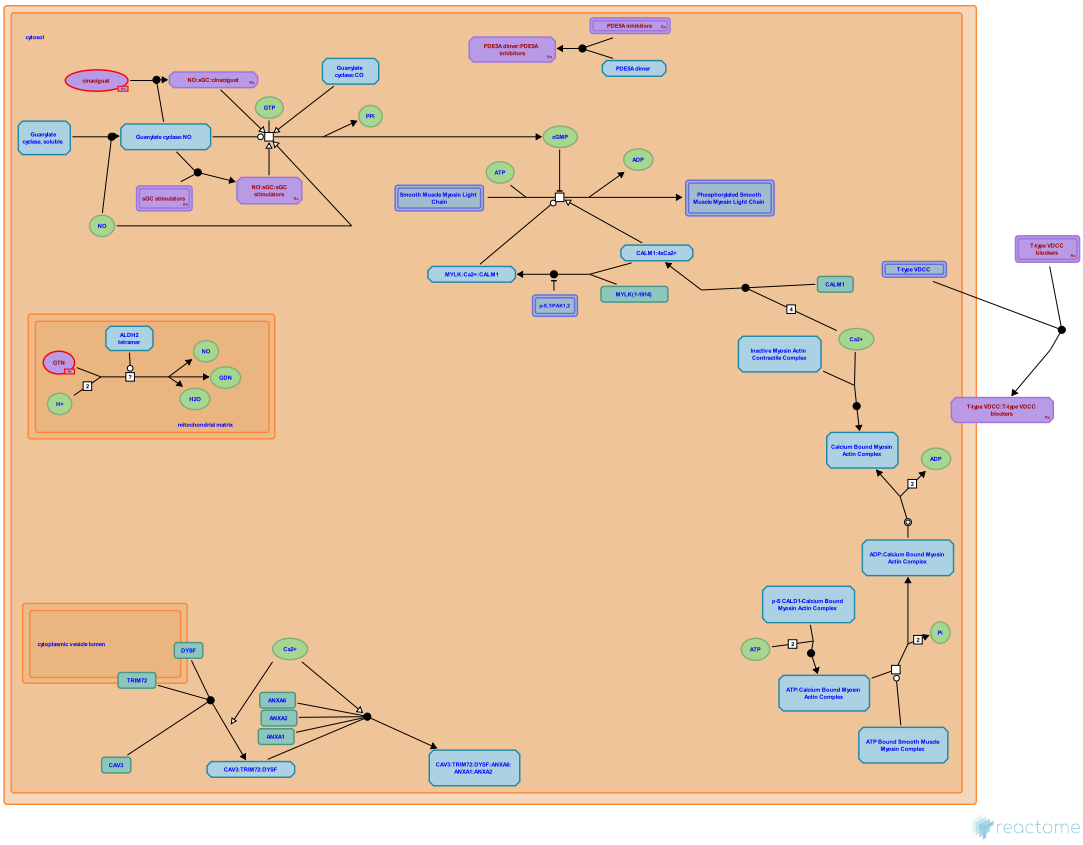
Smooth Muscle Contraction



Akkerman, JW., D'Eustachio, P., Gillespie, ME., Huddart, R., Jassal, B., Jupe, S., Kunapuli, SP., Le Novere, N., Matthews, L., Orlic-Milacic, M., Rivero Crespo, F., Rush, MG.

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

18/04/2024

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. ↗

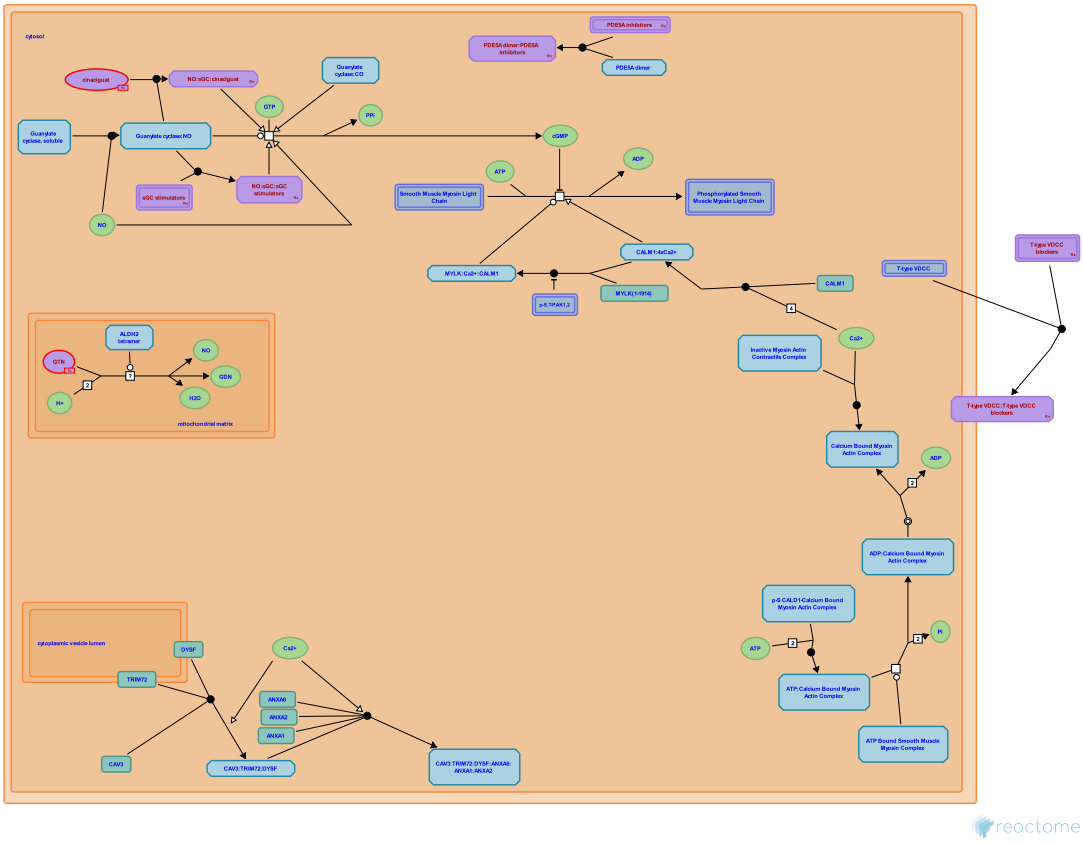
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Smooth Muscle Contraction ↗

Stable identifier: R-HSA-445355

Compartments: cytosol, plasma membrane



Layers of smooth muscle cells can be found in the walls of numerous organs and tissues within the body. Smooth muscle tissue lacks the striated banding pattern characteristic of skeletal and cardiac muscle. Smooth muscle is triggered to contract by the autonomic nervous system, hormones, autocrine/paracrine agents, local chemical signals, and changes in load or length.
Actin:myosin cross bridging is used to develop force with the influx of calcium ions (Ca2+) initiating contraction. Two separate protein pathways, both triggered by calcium influx contribute to contraction, a calmodulin driven kinase pathway, and a caldesmon driven pathway.
Recent evidence suggests that actin, myosin, and intermediate filaments may be far more volatile then previously suspected, and that changes in these cytoskeletal elements along with alterations of the focal adhesions that anchor these proteins may contribute to the contractile cycle.
Contraction in smooth muscle generally uses a variant of the same sliding filament model found in striated muscle, except in smooth muscle the actin and myosin filaments are anchored to focal adhesions, and dense bodies, spread over the surface of the smooth muscle cell. When actin and myosin move across one another focal adhesions are drawn towards dense bodies, effectively squeezing the cell into a smaller conformation. The sliding is triggered by calcium:caldesmon binding, caldesmon acting in an analogous fashion to troponin in striated muscle. Phosphorylation of myosin light chains also is involved in the initiation of an effective contraction.

Literature references

Webb, RC. (2003). Smooth muscle contraction and relaxation. *Adv Physiol Educ, 27*, 201-6. ↗

Editions

2008-01-11	Reviewed	Rush, MG.
2009-03-09	Authored	Gillespie, ME.
2009-11-18	Edited	Gillespie, ME.

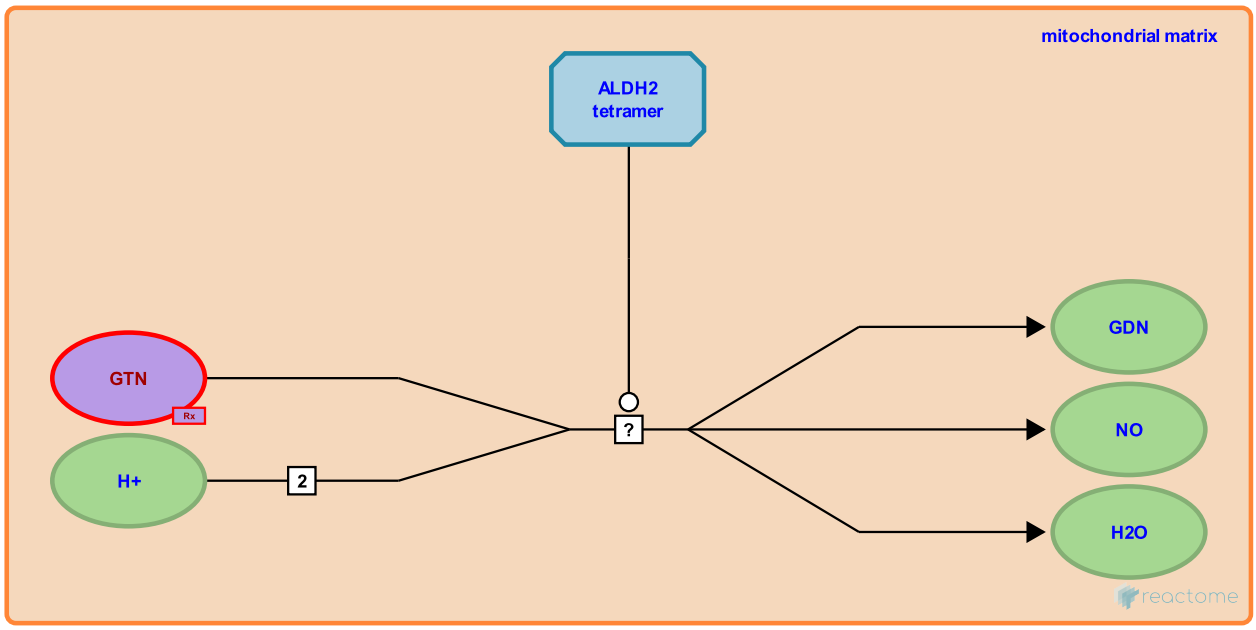
ALDH2 transforms GTN to NO ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-9620103

Type: uncertain

Compartments: mitochondrial matrix



In the mid-19th century, nitroglycerin (nitroglycerine, glyceryl trinitrate, GTN) was synthesised by the Italian chemist Ascanio Sobrero (1812–1888) and was discovered to be a powerful vasodilator (Marsh & Marsh 2000), as well as an active ingredient in the manufacture of explosives, mostly dynamite. It was first used to relieve angina in 1867 and was noted to have pharmacological resistance on repeated doses (Daiber & Münzel 2015). Today, GTN is still the treatment of choice for relieving angina. Other organic esters and inorganic nitrates are also used, but the rapid action of GTN and its established efficacy make it the mainstay of angina pectoris relief.

GTN relaxes blood vessels primarily via activation of the soluble guanylyl cyclase (sGC)/cGMP/cGMP-dependent protein kinase (cGK-I) pathway (see reviews Münzel et al. 2003, Daiber & Münzel 2015). The activation of sGC by nitrate-derived nitric oxide (NO) and/or S-nitrosothiol was identified as the principal mechanism of action of organic nitrates such as GTN (Schulz et al. 2002, Opelt et al. 2016). Nitrate generated within the mitochondria is metabolised further by reduction to NO and/or by conversion to S-nitrosothiol (Chen & Stamler 2006, Chen et al. 2002). However, the exact reaction mechanism of this mitochondrial NO production, as well as the NO form which is conveyed from mitochondria to cytosolic sGC, remain unresolved (Mayer & Beretta 2008, Chen & Stamler 2006). Nitrate drug biotransformation pathways to NO and their effects as NO donors across tissues remain ill defined. GTN-induced vasodilation might be mediated by an NO-related species, for example, iron–nitrosyl or S-nitroso species. A significant increase in iron–nitrosyl or S-nitroso species can be seen minutes after oral intake of GTN in human volunteers and animals (Wenzel et al. 2009, Janero et al. 2004).

Mitochondrial aldehyde dehydrogenase 2 (ALDH2) catalyses the bioactivation of GTN by the formation of a reactive NO or NO-related intermediate that activates sGC. Conversion of GTN into GDN (1,2-glycerol dinitrate) and nitrite by mitochondrial ALDH2 may be an essential pathway of GTN bioactivation in blood vessels (Kollau et al. 2005). NO binds to a heme group of sGC. Activation of sGC leads to increased bioavailability of cyclic guanosine-3′,-5′-monophosphate (cGMP) and activation of cGMP-dependent protein kinases, such as the cGMP-dependent protein kinase I (cGK-I). cGK-I inhibits the inositol-1,4,5-trisphosphate (IP3)-dependent calcium release from the ER, inhibiting myosin light chain kinase (MLCK) and thereby vasoconstriction. cGKI also phosphorylates Rho and interferes with Rho kinase inhibition of myosin light chain phosphatase (MLCP). MLCP dephosphorylates MLC and enhances SMC relaxation. It is well known that GTN can inhibit mitochondrial ALDH2 activity (Mukerjee & Pietruszko 1994). Chen et al. (Chen et al. 2002) were the first to provide evidence that prolonged treatment with GTN results in GTN tolerance and simultaneous inhibition of mitochondrial ALDH2 in vascular preparations.

For simplification, the probable NO production from GTN is described as a single event, collating the probable denitrification and reduction steps involved.

Literature references

Kollau, A., Keung, WM., Schmidt, K., Hofer, A., Mayer, B., Brunner, F. et al. (2005). Contribution of aldehyde dehydrogenase to mitochondrial bioactivation of nitroglycerin: evidence for the activation of purified soluble guanylate cyclase through direct formation of nitric oxide. *Biochem. J., 385*, 769-77. ↗

Reiter, B., Wendt, M., Walter, U., Reichenspurner, H., Schulz, E., Meinertz, T. et al. (2002). Functional and biochemical analysis of endothelial (dys)function and NO/cGMP signaling in human blood vessels with and without nitroglycerin pretreatment. *Circulation, 105*, 1170-5. ↗

Opelt, M., Mayer, B., Fassett, JT., Waldeck-Weiermair, M., Eroglu, E., Malli, R. et al. (2016). Formation of Nitric Oxide by Aldehyde Dehydrogenase-2 Is Necessary and Sufficient for Vascular Bioactivation of Nitroglycerin. *J. Biol. Chem., 291*, 24076-24084. ↗

Stamler, JS., Chen, Z. (2006). Bioactivation of nitroglycerin by the mitochondrial aldehyde dehydrogenase. *Trends Cardiovasc. Med., 16*, 259-65. ↗

Stamler, JS., Zhang, J., Chen, Z. (2002). Identification of the enzymatic mechanism of nitroglycerin bioactivation. *Proc. Natl. Acad. Sci. U.S.A., 99*, 8306-11. ↗

Editions

2021-03-25	Authored	Jassal, B.
2021-10-27	Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

NO binds to Guanylate Cyclase ↗

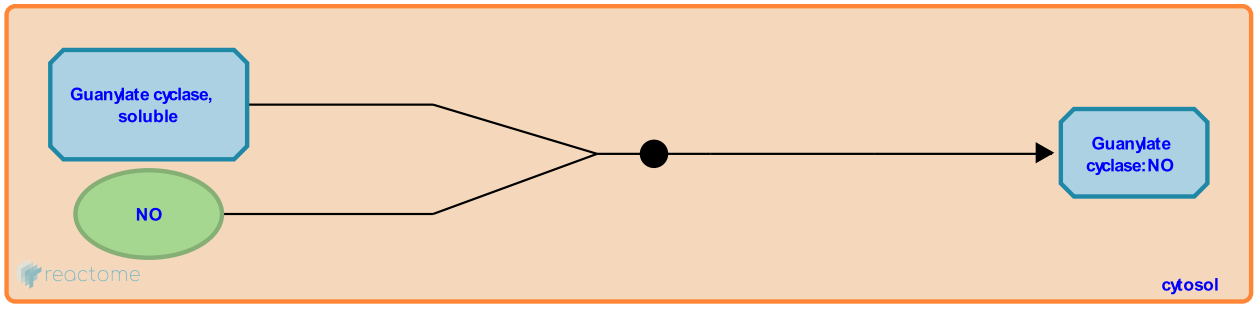
Location: Smooth Muscle Contraction

Stable identifier: R-HSA-392143

Type: binding

Compartments: cytosol

Inferred from: NO binds to Guanylate Cyclase (Rattus norvegicus)



Soluble guanylate cyclase (sGC) is a heterodimeric hemoprotein that selectively binds Nitric Oxide (NO). NO binding stimulates the synthesis of cGMP, which then binds to phosphodiesterases (PDE), ion-gated channels, and cGMP-dependent protein kinases (cGK) to regulate several physiological functions including vasodilation, platelet aggregation and neurotransmission.

Followed by: Soluble guanylate cyclase converts GTP to cGMP

Editions

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

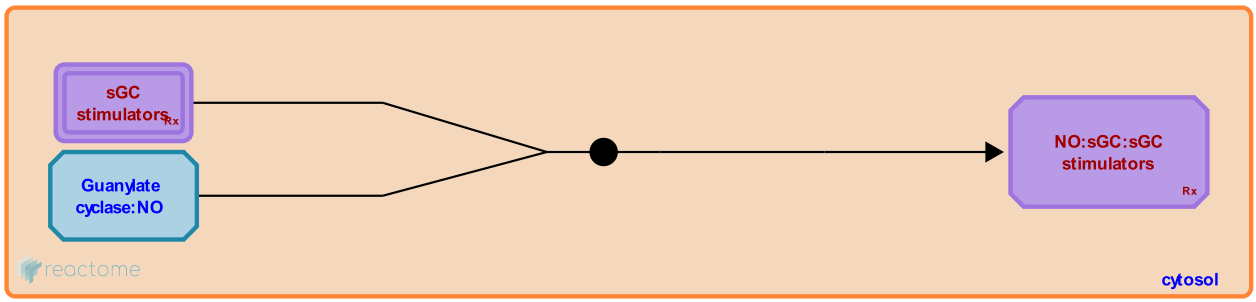
sGC stimulators bind sGC:NO ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-9620456

Type: binding

Compartments: cytosol



Soluble guanylate cyclase (sGC) modulators are small-molecule drugs that bind sGC and enhance nitric oxide (NO)-mediated cGMP signalling, resulting in vasodilation and inhibition of platelet aggregation. The suffix “ciguat” is the unique identifier for this drug class. There are two types of "ciguats"; NOsGC stimulators, which act through allosteric regulation and NOsGC activators, which occupy the heme binding site and work additively with NO (Kraehling & Sessa 2017).

NOsGC stimulators activate sGC independently of NO. This was demonstrated in human platelets by the first allosteric activator lificiguat (YC-1), a benzyl indazol derivative (Friebe et al. 1998). Lificiguat, synergistically with NO, stimulates sGC activity 200-800 fold to result in inhibition of platelet aggregation. A regulatory site on sGC was discovered to be the probable binding site (C239 and C244 regions) for sGC stimulators using the pyrazolopyridine BAY 41-2272, a lificiguat analog (Stasch et al. 2001). BAY 41-2272 induces vasodilation without developing nitrate tolerance, possesses antiplatelet activity and reduces mortality. Optimisation experiments on lificiguat led to the development of riociguat (BAY 63-252, Adempas). Riociguat, activates NOsGC 70-fold at therapeutic concentrations and is the only "ciguat" so far to be approved for the treatment of pulmonary arterial hypertension (PAH) and inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (Schermuly et al. 2008).

Another NOsGC stimulator, vericiguat, shows an optimized pharmacokinetic profile and allows a once daily dosing regimen, unlike riociguat (3 times a day) (Breitenstein et al. 2017). Vericiguat is in clinical trials to determine its efficacy in heart failure, in patients with chronic failure and reduced ejection fraction (Gheorghiade et al. 2015). Praliciguat (IW-1973) is a novel clinical-stage NOsGC stimulator under clinical investigation for the treatment of heart failure with preserved ejection fraction and diabetic nephropathy (Tobin et al. 2018, Breitenstein et al. 2017).

Literature references

Schröder, H., Minuth, T., Pleiss, U., Stahl, E., Stasch, JP., Straub, A. et al. (2001). NO-independent regulatory site on soluble guanylate cyclase. *Nature, 410*, 212-5. ↗

Koesling, D., Schultz, G., Smolenski, A., Friebe, A., Müllershausen, F., Walter, U. (1998). YC-1 potentiates nitric oxide- and carbon monoxide-induced cyclic GMP effects in human platelets. *Mol. Pharmacol., 54*, 962-7. ↗

Editions

2018-09-24	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

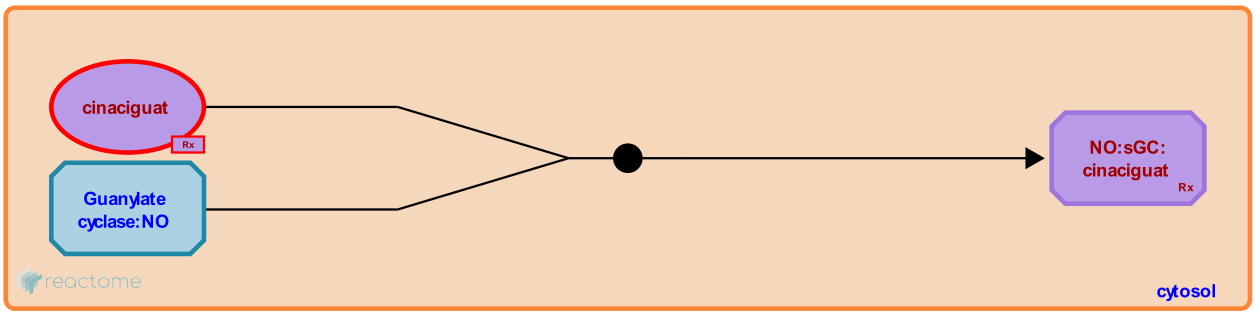
Cinaciguat binds sGC:NO ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-9621179

Type: binding

Compartments: cytosol



Soluble guanylate cyclase (sGC) modulators are small-molecule drugs that bind sGC and enhance nitric oxide (NO)-mediated cGMP signalling. The suffix “ciguat” is the unique identifier for this drug class. There are two types of "ciguats"; NOsGC stimulators, which act through allosteric regulation and NOsGC activators, which occupy the heme binding site and work additively with NO (Kraehling & Sessa 2017).

In the early 2000s, cinaciguat (BAY 58-2667) was identified as a novel NOsGC activator (Stasch et al. 2002). Cinaciguat has been shown to unload the heart in patients with acute decompensated heart failure (ADHF). However, high doses of cinaciguat are associated with hypotension (Erdmann et al. 2013).

Literature references

Mebazaa, A., Nieminen, MS., Semigran, MJ., Mitrovic, V., Agrawal, R., Gheorghiade, M. et al. (2013). Cinaciguat, a soluble guanylate cyclase activator, unloads the heart but also causes hypotension in acute decompensated heart failure. *Eur. Heart J., 34*, 57-67. ↗

Editions

2018-09-26	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

Soluble guanylate cyclase converts GTP to cGMP ↗

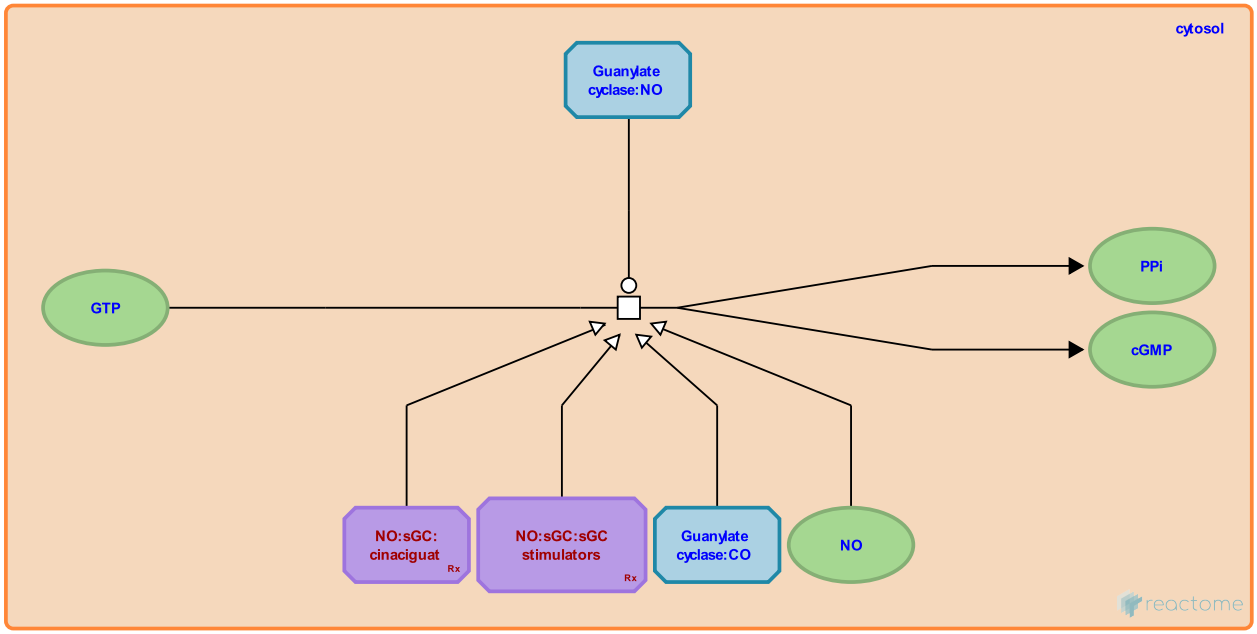
Location: Smooth Muscle Contraction

Stable identifier: R-HSA-392152

Type: transition

Compartments: cytosol

Inferred from: Soluble guanylate cyclase converts GTP to cGMP (Rattus norvegicus)



Soluble guanylate cyclase (sGC) is a heterodimeric hemoprotein that selectively binds Nitric Oxide (NO). NO binding stimulates the synthesis of cGMP, which then binds to phosphodiesterases (PDE), ion-gated channels, and cGMP-dependent protein kinases (cGK) to regulate several physiological functions including vasodilation, platelet aggregation and neurotransmission.

Preceded by: NO binds to Guanylate Cyclase

Editions

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

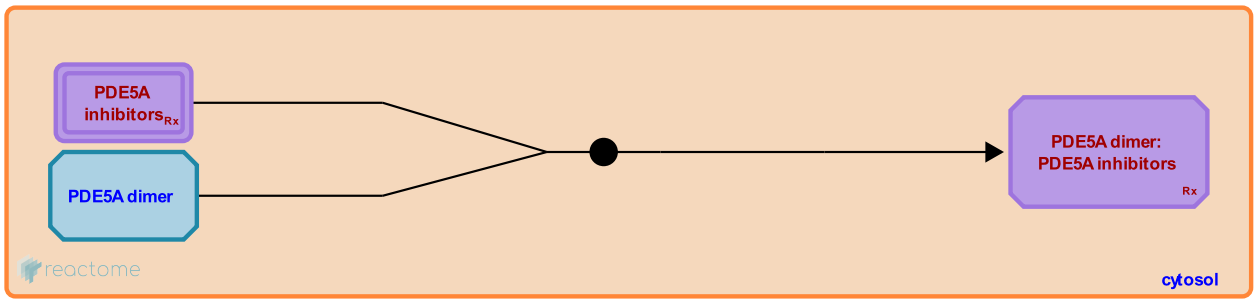
PDE5A dimer binds PDE5A inhibitors ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-9708104

Type: binding

Compartments: cytosol



The cGMP-specific phosphodiesterase PDE5A is highly expressed in vascular and bronchial smooth muscle, in renal tubules and in platelets. It is prominent in the retina and the corpus cavernosa, the pair of erectile tissues in the penis. It catalyses the degradation of cGMP in these tissues, facilitating muscle contraction. Clinically used PDE5A inhibitors target PDE5A in vascular muscle to treat erectile dysfunction (Ventimiglia et al. 2016, Gong et al. 2017) and bronchial smooth muscle to treat pulmonary arterial hypertension (Palacios et al. 2020).

Erectile dysfunction drugs such as Viagra (sildenafil), Cialis (tadalafil) and Levitra (vardenafil) inhibit PDE5A (Boolell et al. 1996, Ballard et al. 1998, Moreland et al. 1998), increasing cGMP levels and thereby allowing smooth muscle relaxation and vasodilation. This allows blood flow into the corpus cavernosa leading to erection (Raheem & Kell 2009).

Literature references

Tang, K., Naylor, AM., Turner, LA., Ballard, SA., Gingell, CJ., Price, ME. (1998). Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol, 159*, 2164-71. ↗

Goldstein, I., Traish, A., Moreland, RB. (1998). Sildenafil, a novel inhibitor of phosphodiesterase type 5 in human corpus cavernosum smooth muscle cells. *Life Sci, 62*, PL 309-18. ↗

Boolell, M., Naylor, AM., Muirhead, GJ., Gingell, C., Gepi-Attee, S., Ballard, SA. et al. (1996). Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res, 8*, 47-52. ↗

Gong, B., Huang, Y., Yang, X., Huang, J., Xie, W., Sun, T. et al. (2017). Direct comparison of tadalafil with sildenafil for the treatment of erectile dysfunction: a systematic review and meta-analysis. *Int Urol Nephrol, 49*, 1731-1740. ↗

Editions

2021-03-25	Authored	Jassal, B.
2021-10-27	Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

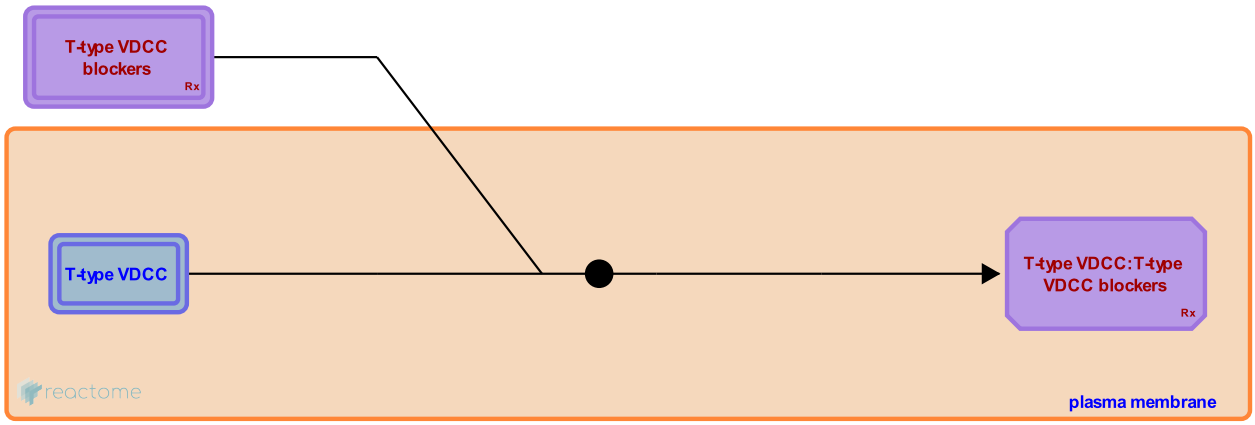
T-type VDCC bind T-type VDCC blockers ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-9700701

Type: binding

Compartments: plasma membrane, extracellular region



Voltage-dependent calcium channels (VDCCs) mediate the entry of calcium ions (Ca2+) into excitable cells as well as being involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division and cell death. The CACN isoforms alpha-1G, alpha-1H and alpha1I give rise to T-type calcium currents which mediate pacemaking functions in both neurons and cardiac nodal cells and support calcium signaling in secretory cells and vascular smooth muscle.

Small molecules that block these channels (Perez-Reyes et al. 2009) are generally used to treat hypertension (Triggle 1997, Martin et al. 2000, Godfraind 2014), seizures in epilepsy (Zamponi 2016, Powell et al. 2014), vomiting, nausea and motion sickness (Zamponi et al. 2015).

Literature references

Lee, JH., Perez-Reyes, E., Cribbs, LL., Hanck, DA., Martin, RL. (2000). Mibefradil block of cloned T-type calcium channels. *J. Pharmacol. Exp. Ther., 295*, 302-8. ↗

Dolphin, AC., Striessnig, J., Koschak, A., Zamponi, GW. (2015). The Physiology, Pathology, and Pharmacology of Voltage-Gated Calcium Channels and Their Future Therapeutic Potential. *Pharmacol. Rev., 67*, 821-70. ↗

O'Brien, TJ., Snutch, TP., Cain, SM., Powell, KL. (2014). Low threshold T-type calcium channels as targets for novel epilepsy treatments. *Br J Clin Pharmacol, 77*, 729-39. ↗

Godfraind, T. (2014). Calcium channel blockers in cardiovascular pharmacotherapy. *J. Cardiovasc. Pharmacol. Ther., 19*, 501-15. ↗

Triggle, DJ. (1997). Cardiovascular T-type calcium channels: physiological and pharmacological significance. *J Hypertens Suppl, 15*, S9-15. ↗

Editions

2020-09-16	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

Calcium binds calmodulin ↗

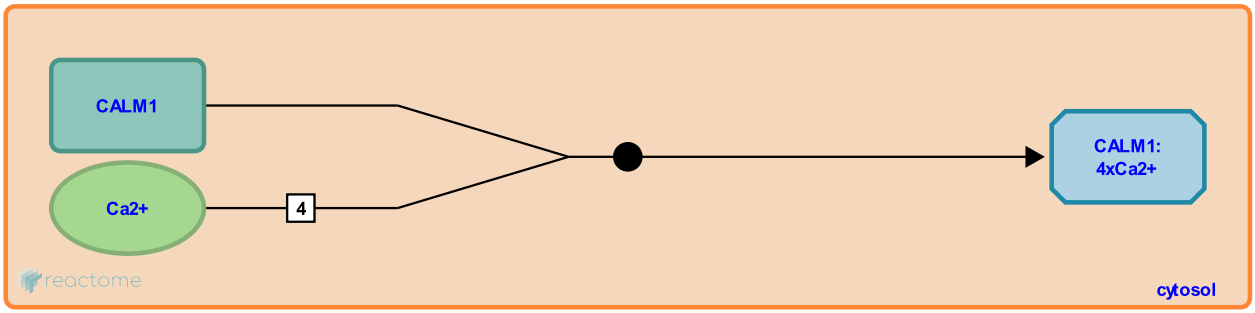
Location: Smooth Muscle Contraction

Stable identifier: R-HSA-74448

Type: binding

Compartments: cytosol

Inferred from: Calcium binds calmodulin (Bos taurus)



Upon increase in calcium concentration, calmodulin (CaM) is activated by binding to four calcium ions (Crouch and Klee 1980).

Followed by: MYLK (MLCK) Active Calmodulin Binding

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-01-11	Reviewed	Rush, MG.
2008-11-06	Edited	Jassal, B.

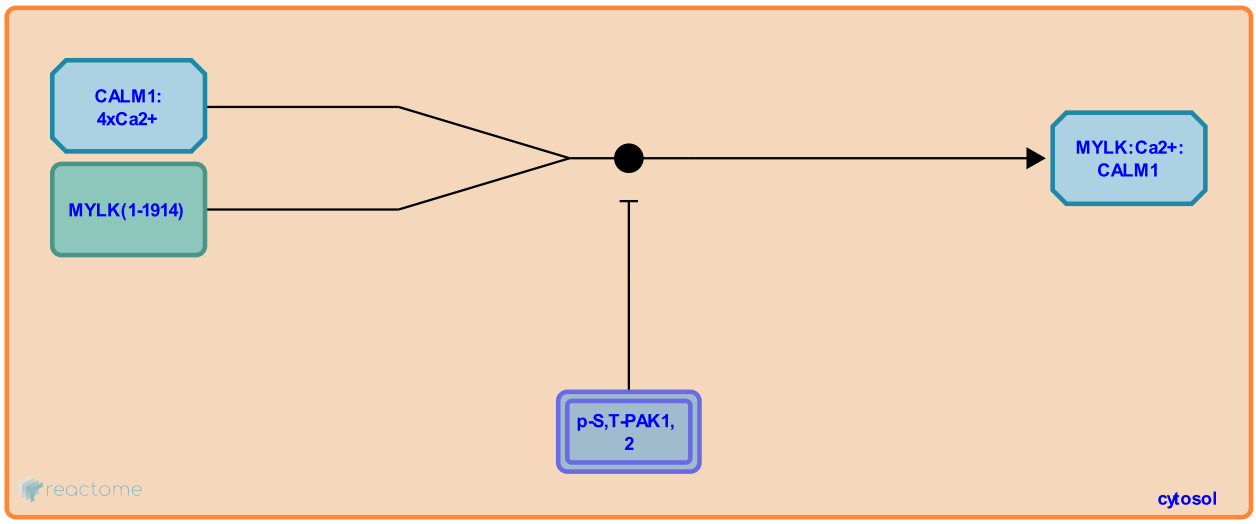
MYLK (MLCK) Active Calmodulin Binding ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-445797

Type: binding

Compartments: cytosol



Once calcium influx occurs, calmodulin is activated by the binding of calcium. The active calmodulin complex binds and activates the smooth muscle myosin light chain kinase (Hathaway and Adelstein 1979, Webb 2003).

Preceded by: Calcium binds calmodulin

Followed by: Phosphorylation of Smooth Muscle Myosin Light Chains

Literature references

Webb, RC. (2003). Smooth muscle contraction and relaxation. *Adv Physiol Educ, 27*, 201-6. ↗

Hathaway, DR., Adelstein, RS. (1979). Human platelet myosin light chain kinase requires the calcium-binding protein calmodulin for activity. *Proc. Natl. Acad. Sci. U.S.A., 76*, 1653-7. ↗

Editions

2008-01-11	Reviewed	Rush, MG.
2009-02-10	Authored	Gillespie, ME.
2009-11-18	Edited	Gillespie, ME.
2014-12-26	Reviewed	Rivero Crespo, F.
2015-02-02	Edited	Orlic-Milacic, M.

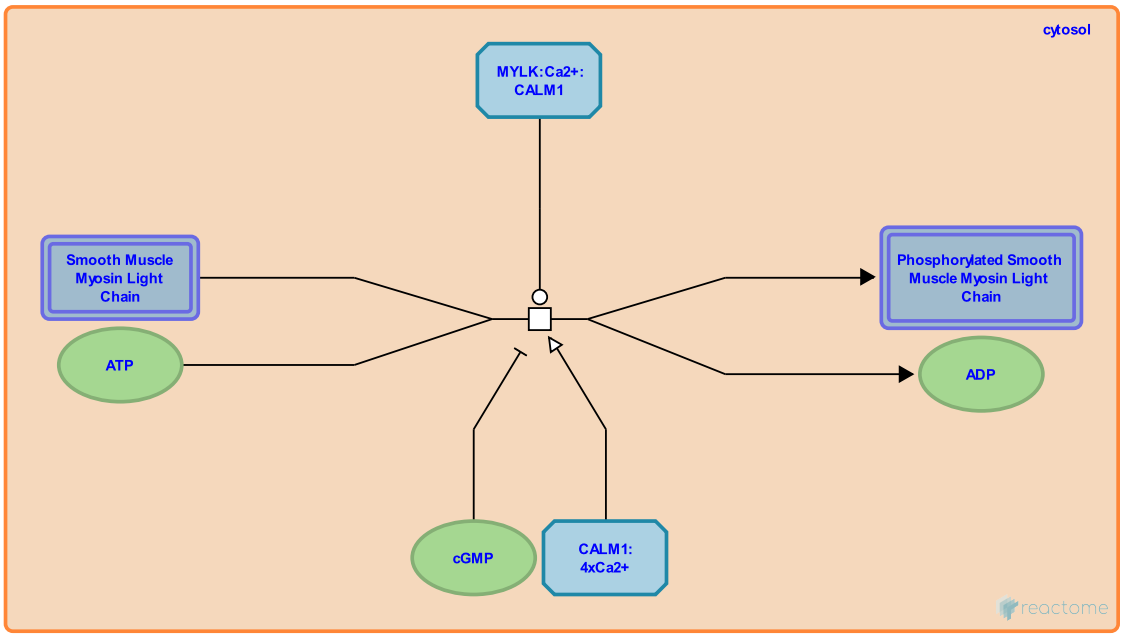
Phosphorylation of Smooth Muscle Myosin Light Chains ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-445813

Type: transition

Compartments: cytosol



The smooth muscle light chain kinase phosphorylates the smooth muscle light chains. This phosphorylation activates the myosin lights chains, effectively allowing contraction to begin.

Preceded by: MYLK (MLCK) Active Calmodulin Binding

Followed by: Release Of ADP From Myosin

Literature references

Kumar, CC., Leibowitz, PJ., Zavodny, PJ., Mohan, SR., Narula, SK. (1989). Characterization and differential expression of human vascular smooth muscle myosin light chain 2 isoform in nonmuscle cells. *Biochemistry, 28*, 4027-35 . ↗

d'Albis, A., Ropert, S., Janmot, C., Cavaillé, F. (1986). Isoforms of myosin and actin in human, monkey and rat myometrium. Comparison of pregnant and non-pregnant uterus proteins. *Eur J Biochem, 160*, 507-13. ↗

Mohammad, MA., Sparrow, MP. (1989). The distribution of heavy-chain isoforms of myosin in airways smooth muscle from adult and neonate humans. *Biochem J, 260*, 421-6. ↗

Editions

2008-01-11	Reviewed	Rush, MG.
2009-11-18	Authored, Edited	Gillespie, ME.

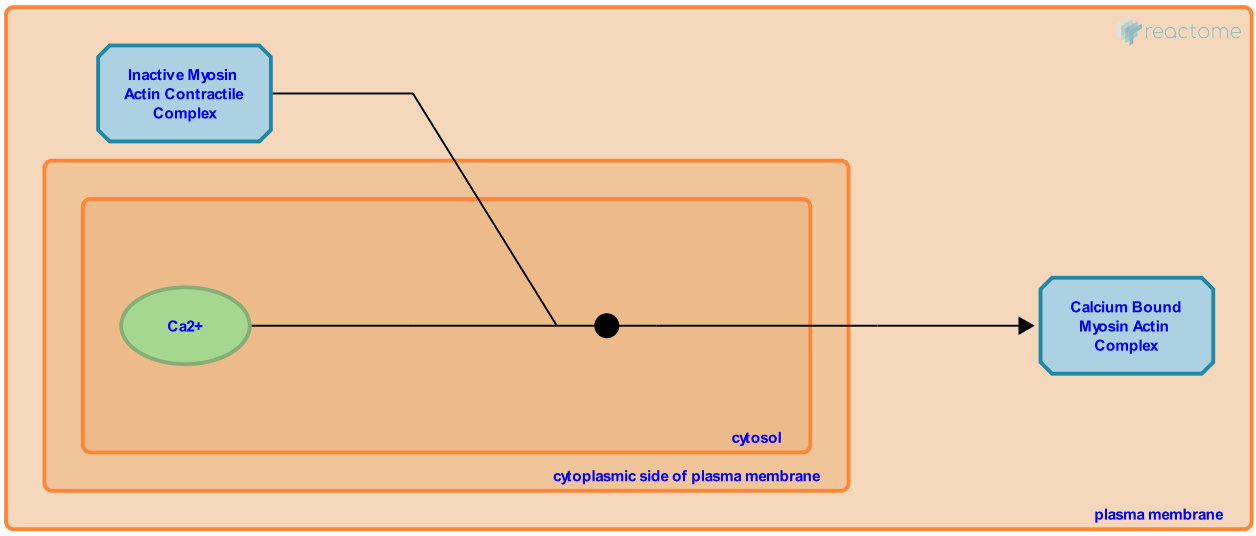
Calcium Binds Caldesmon ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-445704

Type: binding

Compartments: cytosol



Caldesmon functions in an analogous fashion to troponin in striated muscle. Once calcium has entered the smooth muscle cell, calcium levels slowly rise. Caldesmon binds calcium, freeing tropomyosin, allowing the tropomyosin to move exposing the active sites on actin for myosin binding.

Followed by: Release Of ADP From Myosin

Literature references

Gangopadhyay, SS., Morgan, KG. (2001). Invited review: cross-bridge regulation by thin filament-associated proteins. *J Appl Physiol, 91*, 953-62. ↗

Marston, SB., Redwood, CS. (1991). The molecular anatomy of caldesmon. *Biochem J, 279*, 1-16. ↗

Editions

2003-07-01	Authored	Gillespie, ME.
2008-01-11	Reviewed	Rush, MG.
2009-03-11	Edited	Gillespie, ME.

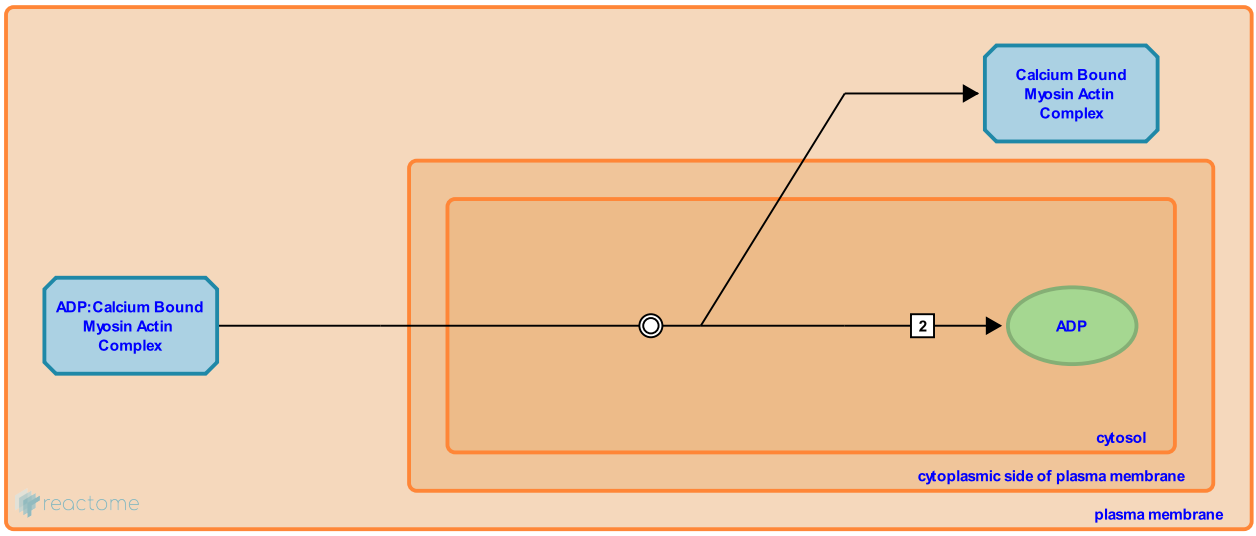
Release Of ADP From Myosin ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-445705

Type: dissociation

Compartments: cytosol



As soon as the actin and myosin filaments become competent for contraction, the swiveling head of myosin pulls itself along the actin filament. This movement changes the shape of the pocket to which ADP is bound, freeing the ADP molecule.

Preceded by: Calcium Binds Caldesmon, ATP Hydrolysis By Myosin, Phosphorylation of Smooth Muscle Myosin Light Chains

Followed by: Myosin Binds ATP

Literature references

Kumar, CC., Leibowitz, PJ., Zavodny, PJ., Mohan, SR., Narula, SK. (1989). Characterization and differential expression of human vascular smooth muscle myosin light chain 2 isoform in nonmuscle cells. *Biochemistry, 28*, 4027-35 . ↗

d'Albis, A., Ropert, S., Janmot, C., Cavaillé, F. (1986). Isoforms of myosin and actin in human, monkey and rat myometrium. Comparison of pregnant and non-pregnant uterus proteins. *Eur J Biochem, 160*, 507-13. ↗

Editions

2003-07-01	Authored	Gillespie, ME.
2008-01-11	Reviewed	Rush, MG.
2009-03-11	Edited	Gillespie, ME.

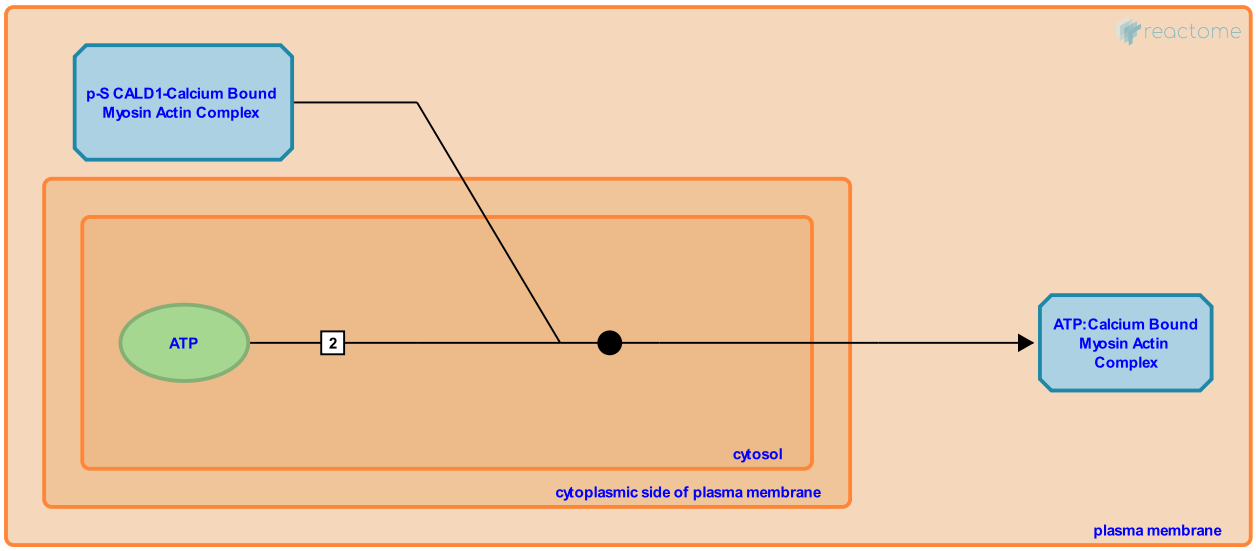
Myosin Binds ATP ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-445700

Type: binding

Compartments: cytosol



With the expulsion of ADP from the nucleotide binding pocket, ATP, if available will immediately bind.

Preceded by: Release Of ADP From Myosin

Followed by: ATP Hydrolysis By Myosin

Literature references

Kumar, CC., Leibowitz, PJ., Zavodny, PJ., Mohan, SR., Narula, SK. (1989). Characterization and differential expression of human vascular smooth muscle myosin light chain 2 isoform in nonmuscle cells. *Biochemistry, 28*, 4027-35 . ↗

d'Albis, A., Ropert, S., Janmot, C., Cavaillé, F. (1986). Isoforms of myosin and actin in human, monkey and rat myometrium. Comparison of pregnant and non-pregnant uterus proteins. *Eur J Biochem, 160*, 507-13. ↗

Mohammad, MA., Sparrow, MP. (1989). The distribution of heavy-chain isoforms of myosin in airways smooth muscle from adult and neonate humans. *Biochem J, 260*, 421-6. ↗

Editions

2003-07-01	Authored	Gillespie, ME.
2008-01-11	Reviewed	Rush, MG.
2009-03-11	Edited	Gillespie, ME.

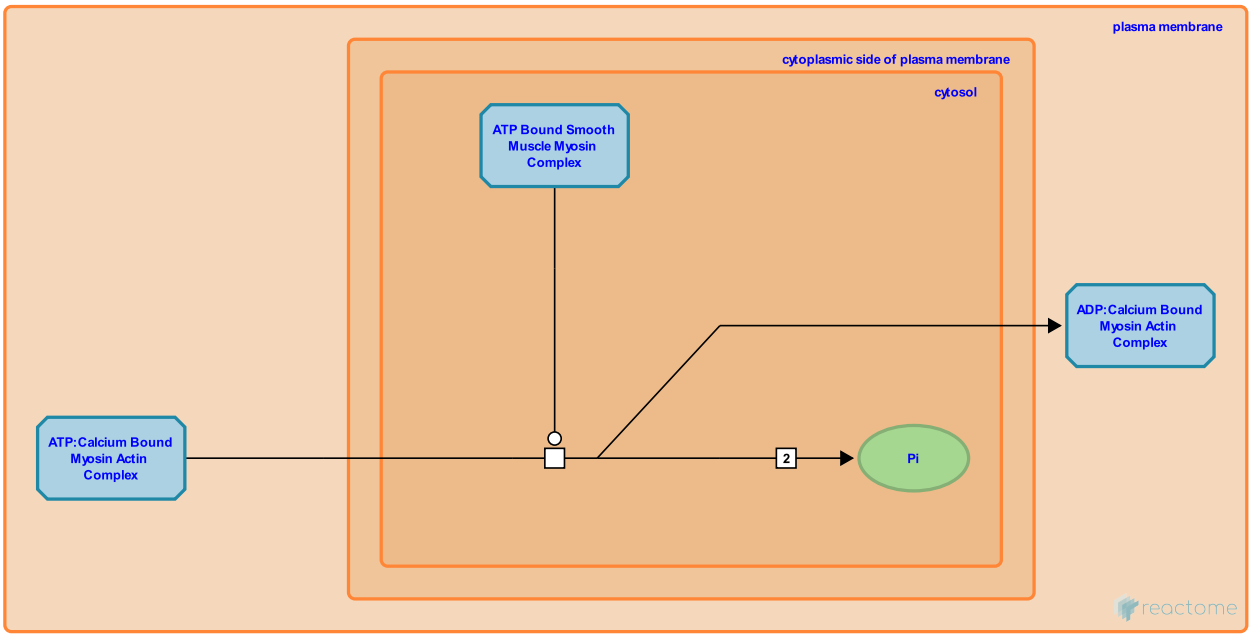
ATP Hydrolysis By Myosin ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-445699

Type: transition

Compartments: cytosol



Once ATP is bound, myosin, which is an ATPase, uses the energy from the cleavage of the terminal phosphate to pivot the myosin head back, away from the actin filamentous chain. This change in conformation "resets" the myosin molecule, leaving it ready to bind the actin filament once more and slide the myosin filament along the actin filament, continuing the contractile cycle.

Preceded by: Myosin Binds ATP

Followed by: Release Of ADP From Myosin

Literature references

Kumar, CC., Leibowitz, PJ., Zavodny, PJ., Mohan, SR., Narula, SK. (1989). Characterization and differential expression of human vascular smooth muscle myosin light chain 2 isoform in nonmuscle cells. *Biochemistry, 28*, 4027-35 . ↗

d'Albis, A., Ropert, S., Janmot, C., Cavaillé, F. (1986). Isoforms of myosin and actin in human, monkey and rat myometrium. Comparison of pregnant and non-pregnant uterus proteins. *Eur J Biochem, 160*, 507-13. ↗

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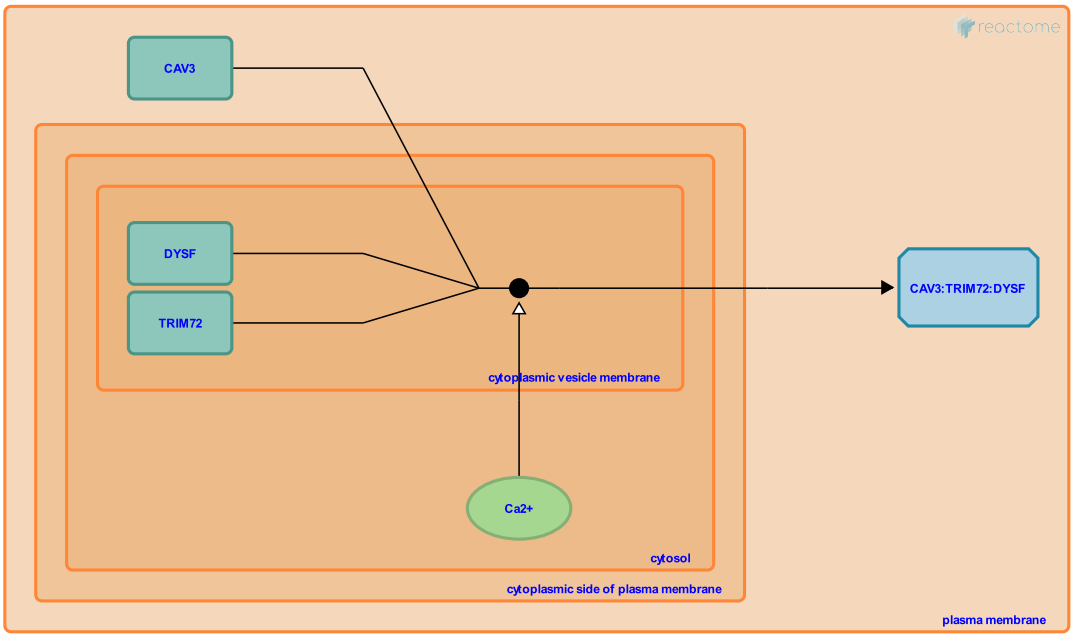
DYSF, CAV3 and TRIM72 bind ↗

Location: Smooth Muscle Contraction

Stable identifier: R-HSA-5263633

Type: binding

Compartments: cytoplasmic vesicle membrane, plasma membrane



Mechanical stress and repetitive muscle contraction often causes membrane disruption to the sarcolemma. Healthy muscle is able to repair these disruptions by a Ca2+-dependent pathway. The combination of dysferlin (DYSF), caveolin 3 (CAV3) and tripartite motif-containing protein 72 TRIM72 aka MG53) appears to be essential for the repair of muscle membrane damage (Cai et al. 2009). CAV3 probably acts as a scaffolding protein in caveolar membranes and can interact with DYSF (Matsuda et al. 2001), a surface membrane protein which promotes the fusion of intracellular vesicles with each other and with the sarcolemma at the site of injury. TRIM72 is required for transport of DYSF to the site of injury.

Literature references

Arahata, K., Hayashi, YK., Murayama, K., Aoki, M., Ogawa, M., Nonaka, I. et al. (2001). The sarcolemmal proteins dysferlin and caveolin-3 interact in skeletal muscle. *Hum. Mol. Genet., 10*, 1761-6. ↗

Cai, C., Nishi, M., Ko, JK., Sunada, Y., Weisleder, N., Takeshima, H. et al. (2009). Membrane repair defects in muscular dystrophy are linked to altered interaction between MG53, caveolin-3, and dysferlin. *J. Biol. Chem., 284*, 15894-902. ↗

Editions

2014-02-12	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.

CAV3:TRIM72:DYSF binds ANXAs ↗

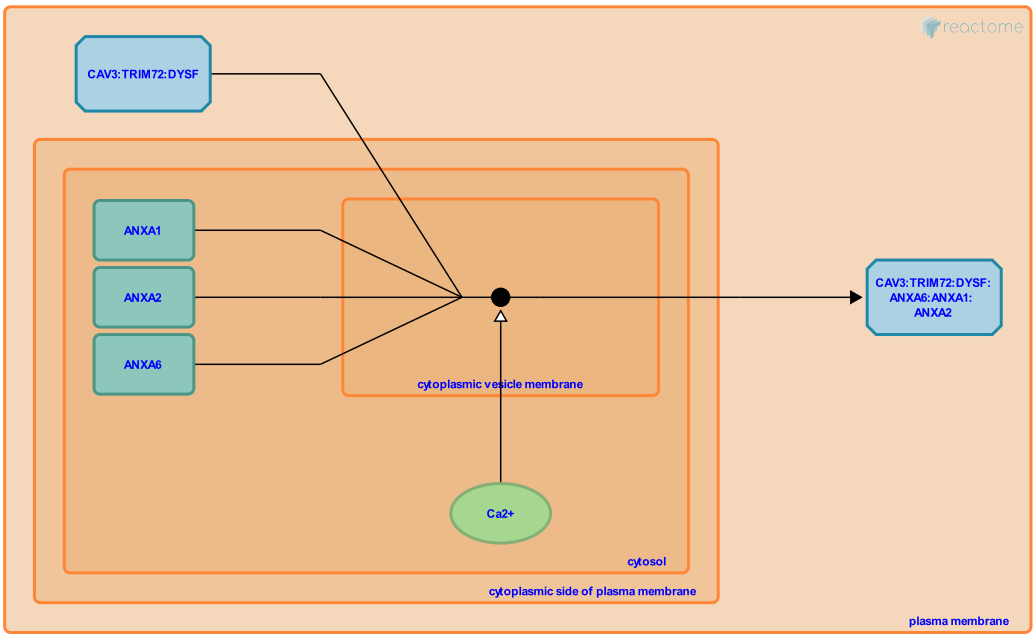
Location: Smooth Muscle Contraction

Stable identifier: R-HSA-5263628

Type: binding

Compartments: cytoplasmic vesicle membrane, plasma membrane, cytosol

Inferred from: Cav3:Trim72:Dysf binds Anxas (Mus musculus)



Mechanical stress and repetitive muscle contraction often causes membrane disruption to the sarcolemma. Healthy muscle is able to repair these disruptions by a Ca2+-dependent pathway. The combination of dysferlin (DYSF), caveolin 3 (CAV3) and tripartite motif-containing protein 72 (TRIM72 aka MG53) appears to be essential for the repair of muscle membrane damage (Cai et al. 2009). DYSF subsequently binds annexin A6 (ANXA6), a member of a family of phospholipid-binding proteins in a Ca2+-dependent manner. This interaction has been demonstrated in imaging experiments in zebrafish (Roostalu U & Strahle 2012). This interaction creates a platform for interacting proteins at the sarcolemma membrane surface and sequential recruitment of annexin A1 and A2 (ANXA1 and 2) to the repair site. The human event is deduced on the basis of experiments performed in mice (Lennon et al. 2003).

Literature references

Strähle, U., Roostalu, U. (2012). In vivo imaging of molecular interactions at damaged sarcolemma. *Dev. Cell, 22*, 515-29. ↗

Brown, RH., Hyman, BT., Bacskai, BJ., Perlmutter, SL., Kho, A., Lennon, NJ. (2003). Dysferlin interacts with annexins A1 and A2 and mediates sarcolemmal wound-healing. *J. Biol. Chem., 278*, 50466-73. ↗

Cai, C., Nishi, M., Ko, JK., Sunada, Y., Weisleder, N., Takeshima, H. et al. (2009). Membrane repair defects in muscular dystrophy are linked to altered interaction between MG53, caveolin-3, and dysferlin. *J. Biol. Chem., 284*, 15894-902. ↗

Editions

2014-02-12	Authored, Edited	Jassal, B.
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