



## 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.

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## Literature references

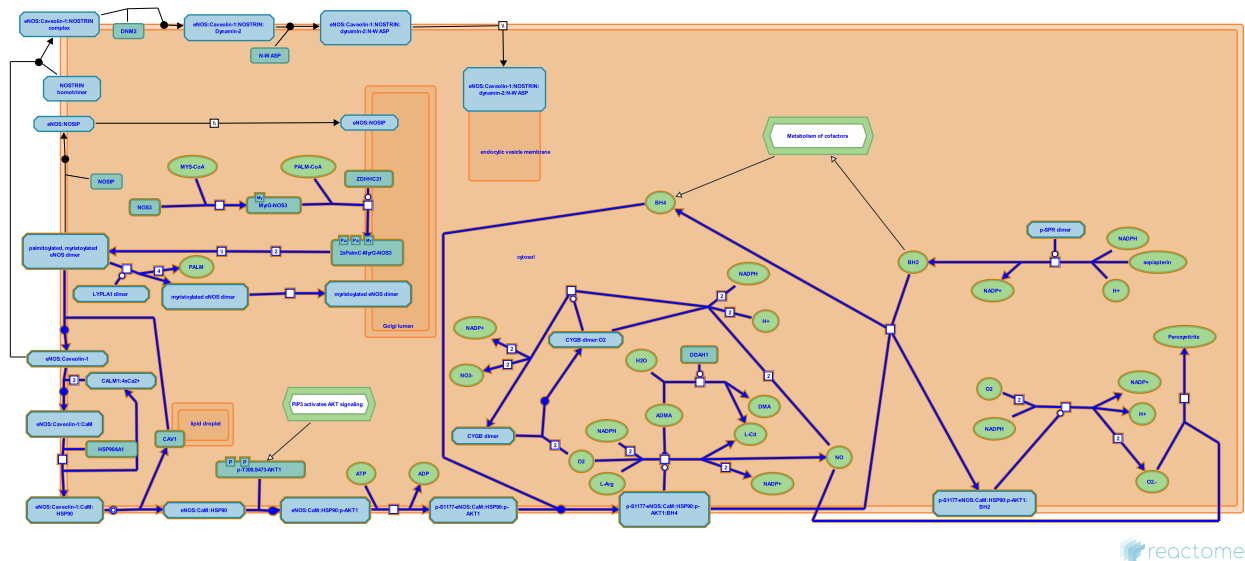
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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, 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. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 20 reactions ([see Table of Contents](#))

## eNOS activation ↗

Stable identifier: R-HSA-203615



eNOS activity is regulated by numerous post-translational modifications including phosphorylation and acylation, which also modulate its interactions with other proteins and its subcellular localization.

In general, following myristoylation and palmitoylation, eNOS localizes to caveolae in the plasma membrane, where in resting cells, it is bound to caveolin and remains inactive. Several agonists that raise intracellular calcium concentrations promote calmodulin binding to eNOS and the dissociation of caveolin from the enzyme, leading to an activated eNOS-calmodulin complex.

Phosphorylation plays a significant role in regulating eNOS activity, especially the phosphorylation of Ser1177, located within the reductase domain, which increases enzyme activity by enhancing reductase activity and calcium sensitivity. In unstimulated, cultured endothelial cells, Ser1177 is rapidly phosphorylated following a variety of stimuli: fluid shear stress, insulin, estrogen, VEGF, or bradykinin. The kinases involved in this process depend upon the stimuli applied. For instance, shear stress phosphorylates Ser1177 by activating Akt and PKA; insulin activates both Akt and the AMP-activated protein kinase (AMPK); estrogen and VEGF mainly phosphorylate eNOS via Akt; whereas the bradykinin-induced phosphorylation of Ser1177 is mediated by CaMKII. When Ser1177 is phosphorylated, NO production is increased several-fold above basal levels.

The phosphorylation of a threonine residue (Thr 495), located in the CaM binding domain, is associated with a decrease in eNOS activity. When this residue is dephosphorylated, substantially more CaM binds to eNOS and elevates enzyme activity. Stimuli associated with dephosphorylation of Thr495 (e.g., bradykinin, histamine, and Ca<sup>2+</sup> ionophores) also increase Ca<sup>2+</sup> levels resulting in the phosphorylation of Ser1177.

Additional phosphorylation sites, such as Ser114 and Ser633, and tyrosine phosphorylation have all been detected, but their functional relevance remains unclear. It is speculated that the tyrosine phosphorylation of eNOS is unlikely to affect enzyme activity directly, but more likely to impact the protein-protein interactions with associated scaffolding and regulatory proteins.

## Literature references

- Duncan, JA., Michel, T., Yeh, DC., Yamashita, S. (1999). Depalmitoylation of endothelial nitric-oxide synthase by acyl-protein thioesterase 1 is potentiated by Ca<sup>2+</sup>-calmodulin. *J Biol Chem*, 274, 33148-54. ↗
- Muller-Esterl, W., Fulton, D., Oess, S., Govers, R., Icking, A. (2006). Subcellular targeting and trafficking of nitric oxide synthases. *Biochem J*, 396, 401-9. ↗
- Rabelink, TJ., Govers, R. (2001). Cellular regulation of endothelial nitric oxide synthase. *Am J Physiol Renal Physiol*, 280, F193-206. ↗
- Fleming, I., Busse, R. (2003). Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. *Am J Physiol Regul Integr Comp Physiol*, 284, R1-12. ↗

## **Editions**

2008-02-28

Reviewed

Enikolopov, G.

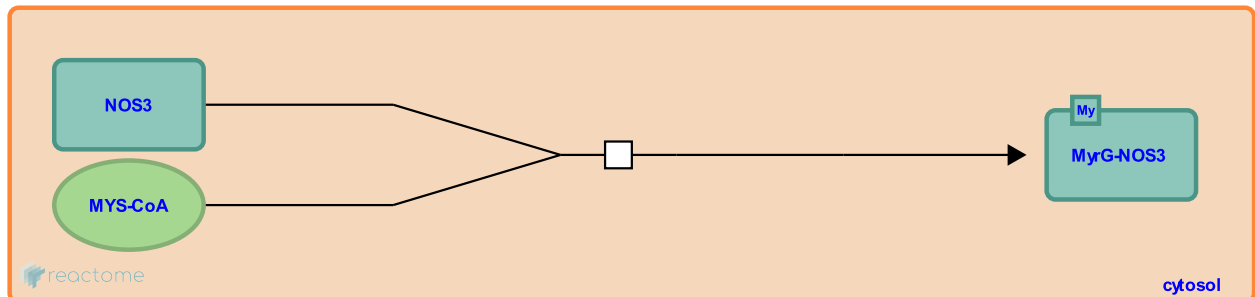
## N-myristoylation of eNOS [↗](#)

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-203611

**Type:** transition

**Compartments:** cytosol



A glycine residue (Gly2) at the N-terminus of eNOS is myristoylated, providing membrane localization.

**Followed by:** [palmitoylation of eNOS](#)

### Literature references

Liu, J., Sessa, WC. (1994). Identification of covalently bound amino-terminal myristic acid in endothelial nitric oxide synthase. *J Biol Chem*, 269, 11691-4. [↗](#)

### Editions

2007-10-19	Authored	Hemish, J.
2008-02-28	Reviewed	Enikolopov, G.

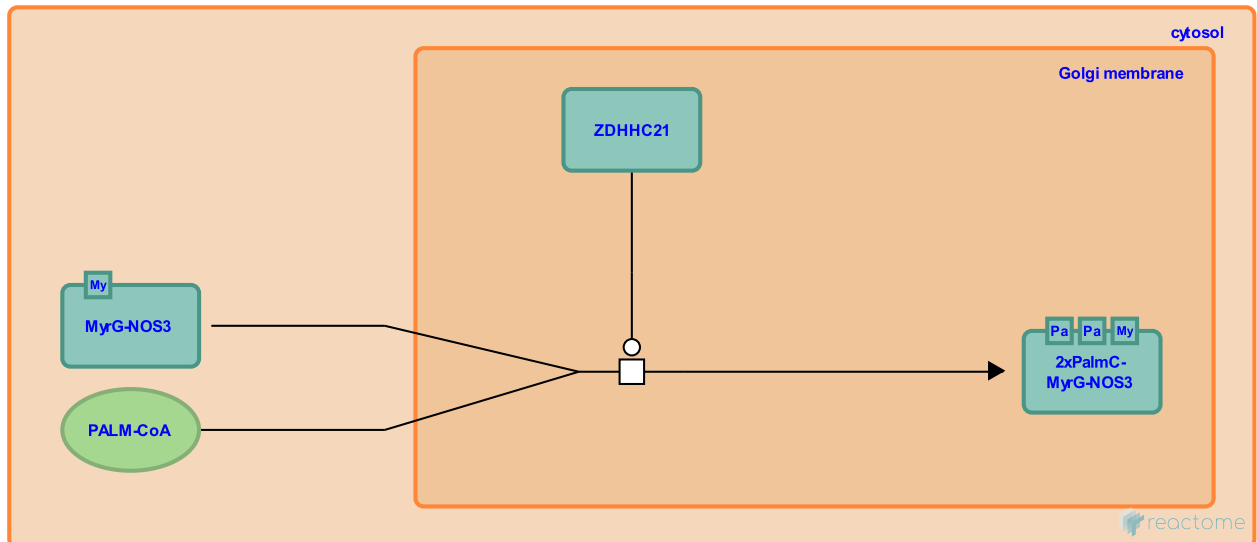
## palmitoylation of eNOS ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-203567

**Type:** transition

**Compartments:** Golgi membrane



DHHC-21 is a Golgi-localized acyl transferase that palmitoylates eNOS, which targets eNOS to plasmalemmal caveolae. Localization to this microdomain is likely to optimize eNOS activation and the extracellular release of nitric oxide.

**Preceded by:** [N-myristoylation of eNOS](#), [depalmitoylated eNOS translocates from plasma membrane](#)

**Followed by:** [eNOS translocation from Golgi to Caveolae](#)

### Literature references

Sessa, WC., Brecht, DS., Bernatchez, PN., Fernandez-Hernando, C., Fukata, M., Lin, MI. et al. (2006). Identification of Golgi-localized acyl transferases that palmitoylate and regulate endothelial nitric oxide synthase. *J Cell Biol*, 174, 369-77. ↗

Schnitzer, JE., Liu, J., Sessa, WC., Garcia-Cardena, G., Oh, P. (1996). Targeting of nitric oxide synthase to endothelial cell caveolae via palmitoylation: implications for nitric oxide signaling. *Proc Natl Acad Sci U S A*, 93, 6448-53. ↗

### Editions

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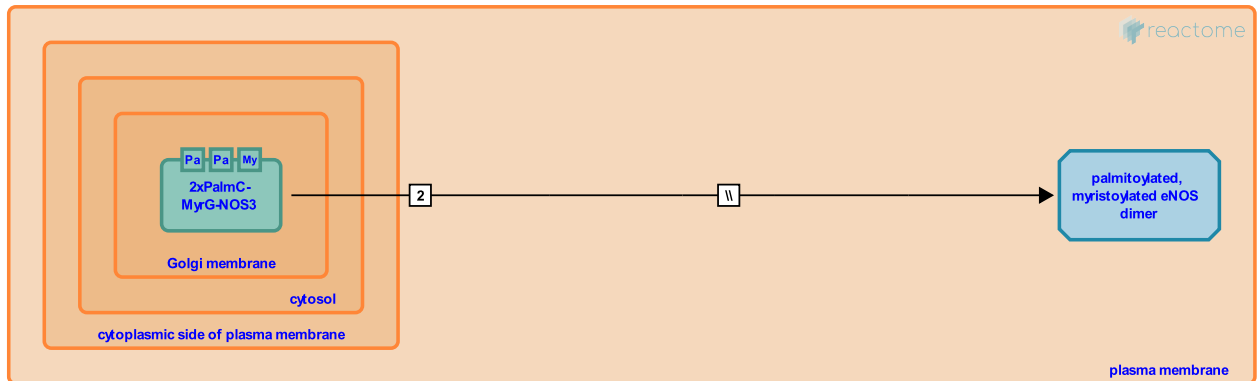
## eNOS translocation from Golgi to Caveolae ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-203700

**Type:** omitted

**Compartments:** plasma membrane, Golgi membrane, cytosol



Palmitoylated, myristoylated eNOS forms a dimer and is transported from the Golgi to the plasma membrane. Transport is thought to be mediated by intracellular vesicles, but the details remain unknown.

**Preceded by:** [palmitoylation of eNOS](#)

**Followed by:** [eNOS associates with Caveolin-1](#), [depalmitoylation of eNOS](#)

### Literature references

Rabelink, T.J., Govers, R. (2001). Cellular regulation of endothelial nitric oxide synthase. *Am J Physiol Renal Physiol*, 280, F193-206. ↗

Muller-Esterl, W., Fulton, D., Oess, S., Govers, R., Icking, A. (2006). Subcellular targeting and trafficking of nitric oxide synthases. *Biochem J*, 396, 401-9. ↗

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2008-02-28

Reviewed

Enikolopov, G.

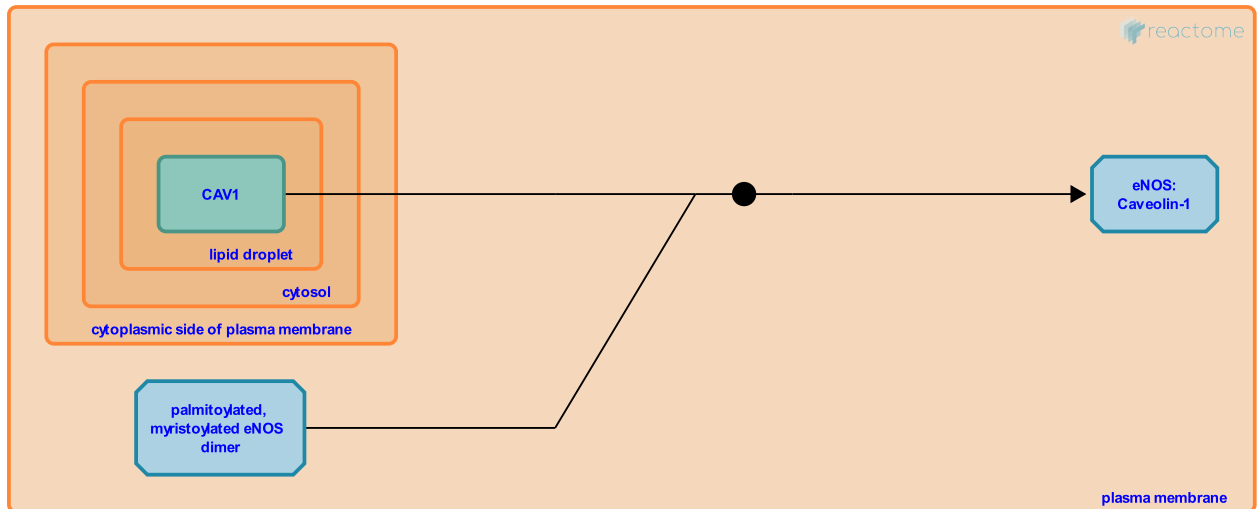
## eNOS associates with Caveolin-1 [↗](#)

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-203712

**Type:** binding

**Compartments:** plasma membrane, lipid droplet



Caveolin-1 is the primary negative regulatory protein for eNOS. Caveolin-1 binding to eNOS compromises its ability to bind Calmodulin (CaM), thereby inhibiting enzyme activity. The major binding region of caveolin-1 for eNOS is within amino acids 60-101 and to a lesser extent, amino acids 135-178.

**Preceded by:** [eNOS translocation from Golgi to Caveolae](#)

**Followed by:** [eNOS:Caveolin-1 complex binds to CaM](#)

### Literature references

- Sessa, WC., Skidd, PM., Lisanti, MP., Masters, BS., Garcia-Cardena, G., Li, S. et al. (1997). Dissecting the interaction between nitric oxide synthase (NOS) and caveolin. Functional significance of the nos caveolin binding domain in vivo. *J Biol Chem*, 272, 25437-40. [↗](#)
- Michel, T., Kobzik, L., Belhassen, L., Smith, TW., Feron, O., Kelly, RA. (1996). Endothelial nitric oxide synthase targeting to caveolae. Specific interactions with caveolin isoforms in cardiac myocytes and endothelial cells. *J Biol Chem*, 271, 22810-4. [↗](#)
- Crooks, C., Lisanti, MP., Gachhui, R., Ghosh, S., Wu, C., Stuehr, DJ. (1998). Interaction between caveolin-1 and the reductase domain of endothelial nitric-oxide synthase. Consequences for catalysis. *J Biol Chem*, 273, 22267-71. [↗](#)
- Schedl, A., Kasper, M., Verkade, P., Elger, M., Luft, FC., Menne, J. et al. (2001). Loss of caveolae, vascular dysfunction, and pulmonary defects in caveolin-1 gene-disrupted mice. *Science*, 293, 2449-52. [↗](#)

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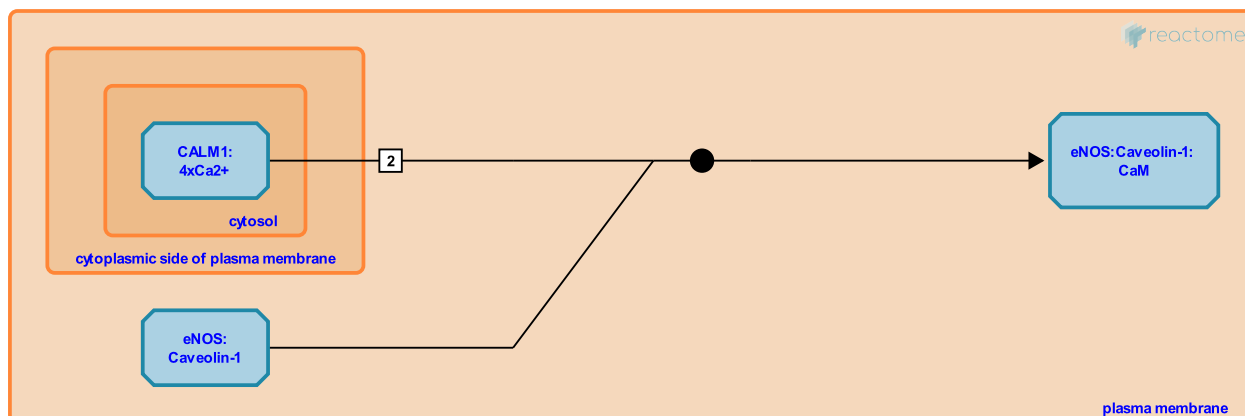
## eNOS:Caveolin-1 complex binds to CaM ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-202110

**Type:** binding

**Compartments:** plasma membrane, cytosol



Caveolin inhibition of eNOS is relieved by calmodulin, which causes dissociation of eNOS from caveolin.

**Preceded by:** [eNOS associates with Caveolin-1](#)

**Followed by:** [HSP90 binds eNOS:Caveolin-1:CaM complex](#)

### Literature references

Michel, JB., Michel, T., Sacks, D., Feron, O. (1997). Reciprocal regulation of endothelial nitric-oxide synthase by Ca<sup>2+</sup>-calmodulin and caveolin. *J Biol Chem*, 272, 15583-6. ↗

### Editions

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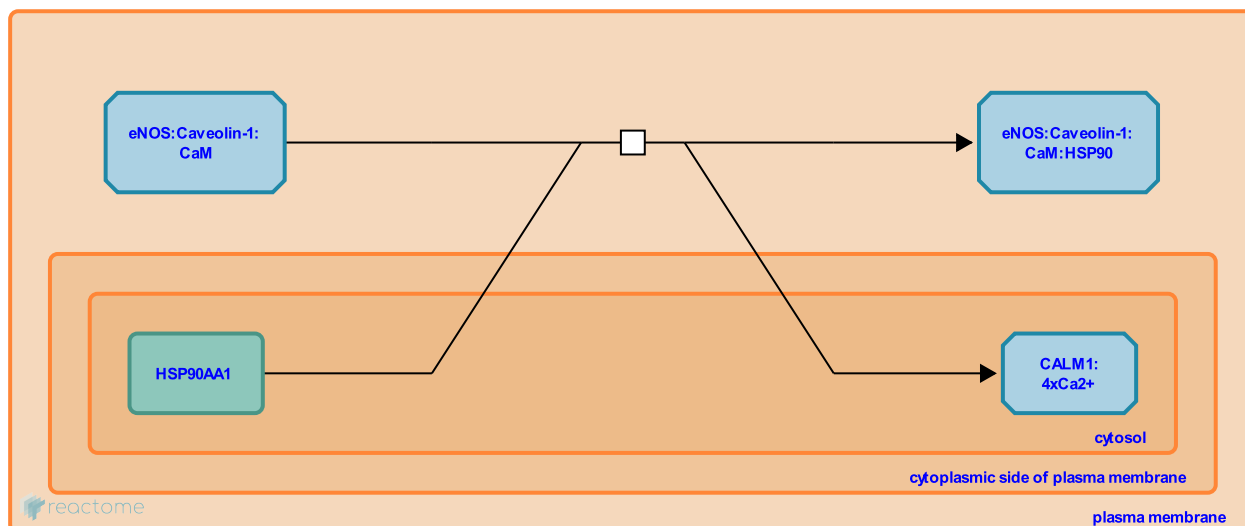
## HSP90 binds eNOS:Caveolin-1:CaM complex ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-202129

**Type:** transition

**Compartments:** plasma membrane, cytosol



HSP90 interacts with the amino terminus of eNOS (amino acids 442-600) and facilitates displacement of caveolin by calmodulin (CaM).

**Preceded by:** [eNOS:Caveolin-1 complex binds to CaM](#)

**Followed by:** [Caveolin-1 dissociates from eNOS:CaM:HSP90 complex](#)

### Literature references

Sessa, WC., Cirino, G., Garcia-Cardena, G., Sorrentino, R., Fan, R., Papapetropoulos, A. et al. (1998). Dynamic activation of endothelial nitric oxide synthase by Hsp90. *Nature*, 392, 821-4. ↗

### Editions

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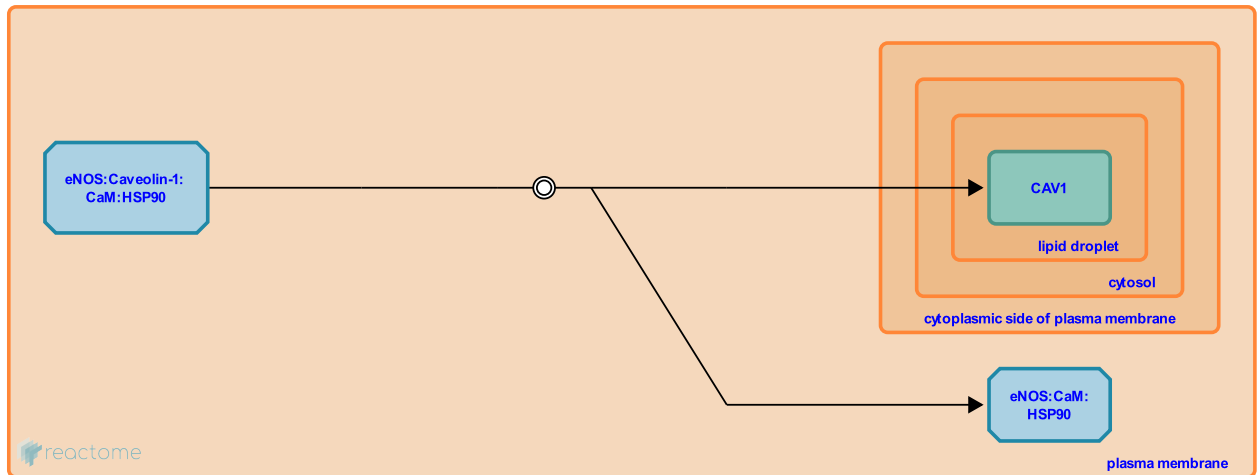
## Caveolin-1 dissociates from eNOS:CaM:HSP90 complex ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-202144

**Type:** dissociation

**Compartments:** plasma membrane



HSP90 facilitates the CaM-induced displacement of caveolin from eNOS.

**Preceded by:** [HSP90 binds eNOS:Caveolin-1:CaM complex](#)

**Followed by:** [AKT1 binds eNOS complex via HSP90](#)

### Literature references

Fontana, J., Sessa, WC., O'Connor, DS., Garcia-Cardena, G., Gratton, JP., McCabe, TJ. (2000). Reconstitution of an endothelial nitric-oxide synthase (eNOS), hsp90, and caveolin-1 complex in vitro. Evidence that hsp90 facilitates calmodulin stimulated displacement of eNOS from caveolin-1. *J Biol Chem*, 275, 22268-72. ↗

### Editions

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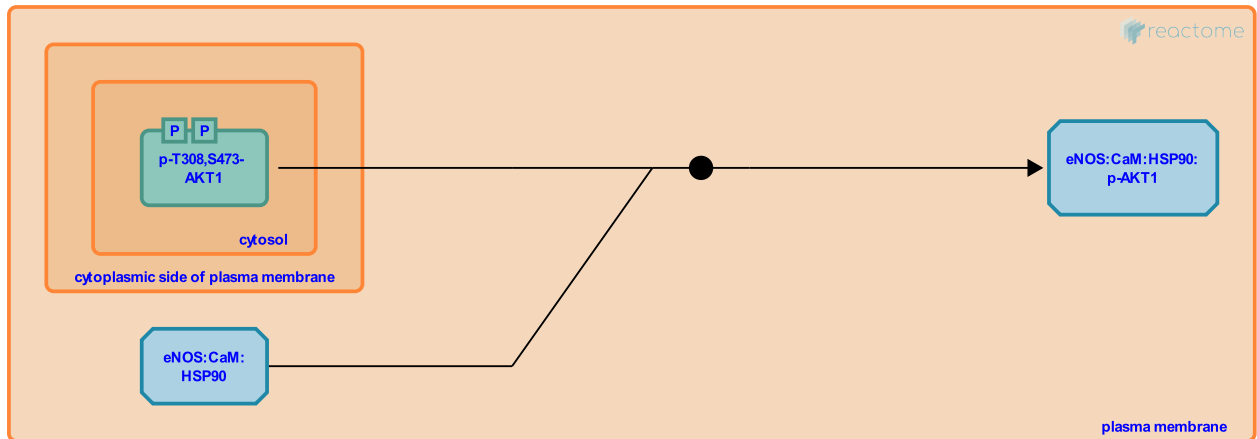
## AKT1 binds eNOS complex via HSP90 [↗](#)

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-202137

**Type:** binding

**Compartments:** plasma membrane, cytosol



AKT1 is recruited to the M domain of HSP90.

**Preceded by:** [dephosphorylated eNOS translocates from plasma membrane](#), [Caveolin-1 dissociates from eNOS:CaM:HSP90 complex](#)

**Followed by:** [AKT1 phosphorylates eNOS](#)

### Literature references

Fontana, J., Sessa, WC., Chen, Y., Fulton, D., Fairchild, TA., Tsuruo, T. et al. (2002). Domain mapping studies reveal that the M domain of hsp90 serves as a molecular scaffold to regulate Akt-dependent phosphorylation of endothelial nitric oxide synthase and NO release. *Circ Res*, 90, 866-73. [↗](#)

Mendelsohn, ME., Takahashi, S. (2003). Synergistic activation of endothelial nitric-oxide synthase (eNOS) by HSP90 and Akt: calcium-independent eNOS activation involves formation of an HSP90-Akt-CaM-bound eNOS complex. *J Biol Chem*, 278, 30821-7. [↗](#)

### Editions

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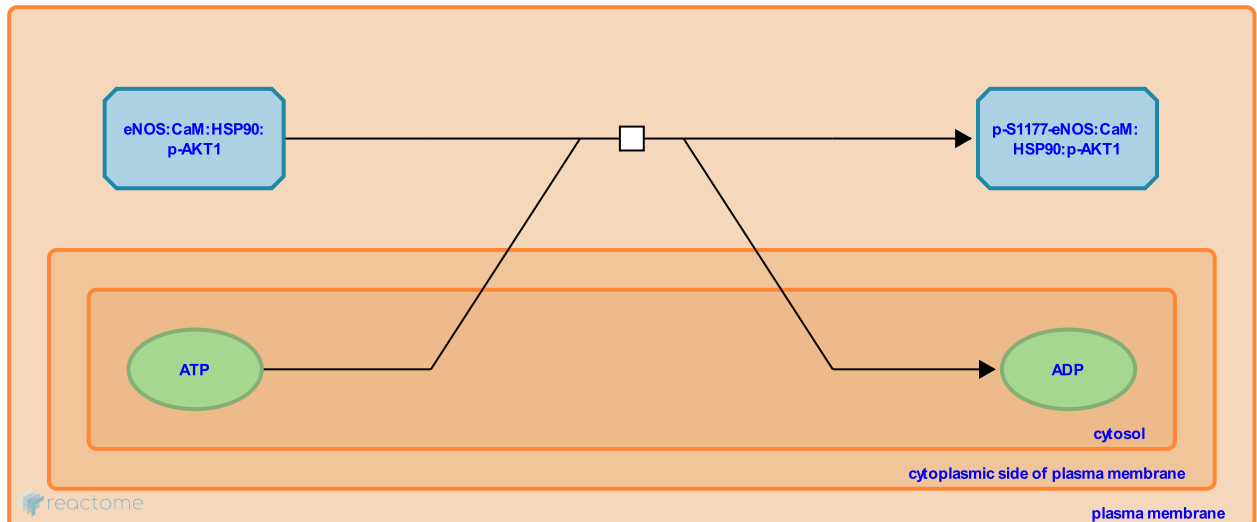
## AKT1 phosphorylates eNOS ↗

**Location:** eNOS activation

**Stable identifier:** R-HSA-202111

**Type:** transition

**Compartments:** plasma membrane, cytosol



HSP90 serves as a scaffold to promote productive interaction between AKT1 and eNOS. Due to the proximity of these proteins once complexed with HSP90, AKT1 phosphorylates eNOS at Ser1177. When Ser1177 is phosphorylated, the level of NO production is elevated two- to three-fold above basal level.

**Preceded by:** AKT1 binds eNOS complex via HSP90

**Followed by:** The cofactor BH4 is required for electron transfer in the eNOS catalytic cycle

### Literature references

- Fontana, J., Sessa, WC., Franke, TF., Walsh, K., Fulton, D., Gratton, JP. et al. (1999). Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature*, 399, 597-601. ↗
- Pearson, RB., Bozinovski, S., Rodriguez-Crespo, I., Griffiths, JE., de Montellano, PR., Kemp, BE. et al. (1999). The Akt kinase signals directly to endothelial nitric oxide synthase. *Curr Biol*, 9, 845-8. ↗
- Hermann, C., Zeiher, AM., Fleming, I., Fisslthaler, B., Busse, R., Dimmeler, S. (1999). Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature*, 399, 601-5. ↗

### Editions

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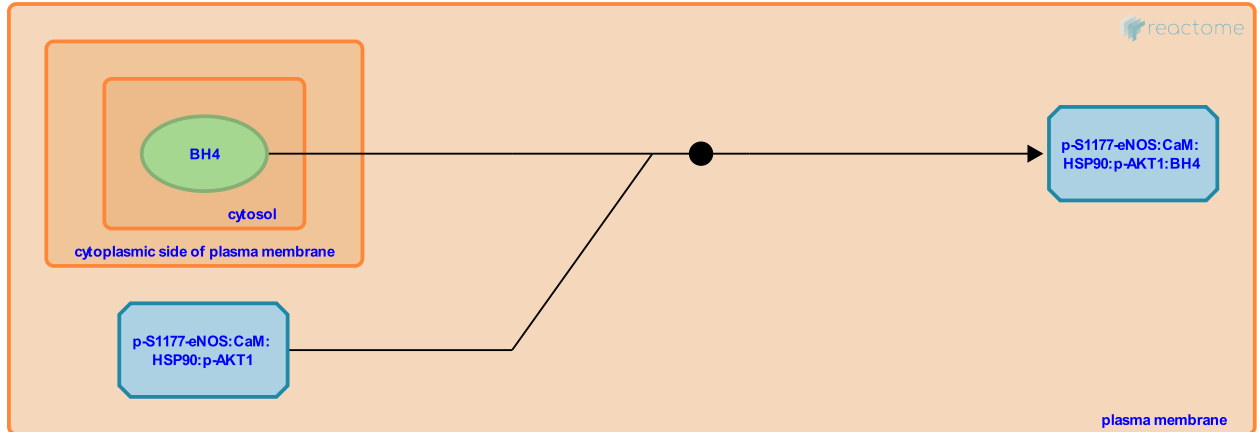
## The cofactor BH4 is required for electron transfer in the eNOS catalytic cycle ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-1497784

**Type:** binding

**Compartments:** plasma membrane, cytosol



The cofactor tetrahydrobiopterin (BH4) ensures endothelial nitric oxide synthase (eNOS) couples electron transfer to L-arginine oxidation (Berka et al. 2004). During catalysis, electrons derived from NADPH transfer to the flavins FAD and FMN in the reductase domain of eNOS and then on to the ferric heme in the oxygenase domain of eNOS. BH4 can donate an electron to intermediates in this electron transfer and is oxidised in the process, forming the BH3 radical. This radical can be reduced back to BH4 by iron, completing the cycle and forming ferrous iron again. Heme reduction enables O<sub>2</sub> binding and L-arginine oxidation to occur within the oxygenase domain (Stuehr et al. 2009).

**Preceded by:** [AKT1 phosphorylates eNOS](#)

**Followed by:** [eNOS synthesizes NO](#)

### Literature references

Berka, V., Yeh, H.C., Tsai, A.L., Kiran, F., Gao, D. (2004). Redox function of tetrahydrobiopterin and effect of L-arginine on oxygen binding in endothelial nitric oxide synthase. *Biochemistry*, 43, 13137-48. ↗

### Editions

2011-08-17	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

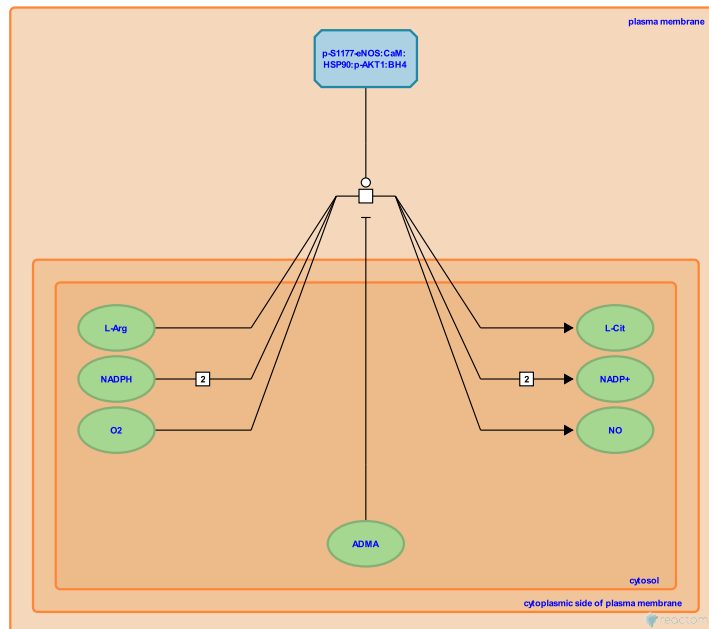
## eNOS synthesizes NO [↗](#)

**Location:** eNOS activation

**Stable identifier:** R-HSA-202127

**Type:** transition

**Compartments:** plasma membrane, cytosol



Nitric oxide (NO) is produced from L-arginine by the family of nitric oxide synthases (NOS) enzymes, forming the free radical NO and citrulline as byproduct. The cofactor tetrahydrobiopterin (BH4) is an essential requirement for the delivery of an electron to the intermediate in the catalytic cycle of NOS.

**Preceded by:** [The cofactor BH4 is required for electron transfer in the eNOS catalytic cycle](#)

### Literature references

- Misra, MK., Tuteja, N., Chandra, M., Tuteja, R. (2004). Nitric Oxide as a Unique Bioactive Signaling Messenger in Physiology and Pathophysiology. *J Biomed Biotechnol*, 2004, 227-237. [↗](#)
- Snyder, SH., Brecht, DS. (1994). Nitric oxide: a physiologic messenger molecule. *Annu Rev Biochem*, 63, 175-95. [↗](#)
- Schmidt, K., Werner, ER., Mayer, B., Klatt, P. (1996). Determination of nitric oxide synthase cofactors: heme, FAD, FMN, and tetrahydrobiopterin. *Methods Enzymol*, 268, 358-65. [↗](#)
- Sessa, WC., Schmidt, K., Volker, C., Gorren, AC., Werner, ER., List, BM. et al. (1997). Characterization of bovine endothelial nitric oxide synthase as a homodimer with down-regulated uncoupled NADPH oxidase activity: tetrahydrobiopterin binding kinetics and role of haem in dimerization. *Biochem J*, 323, 159-65. [↗](#)

### Editions

2007-10-19	Authored	Hemish, J.
2008-02-28	Reviewed	Enikolopov, G.

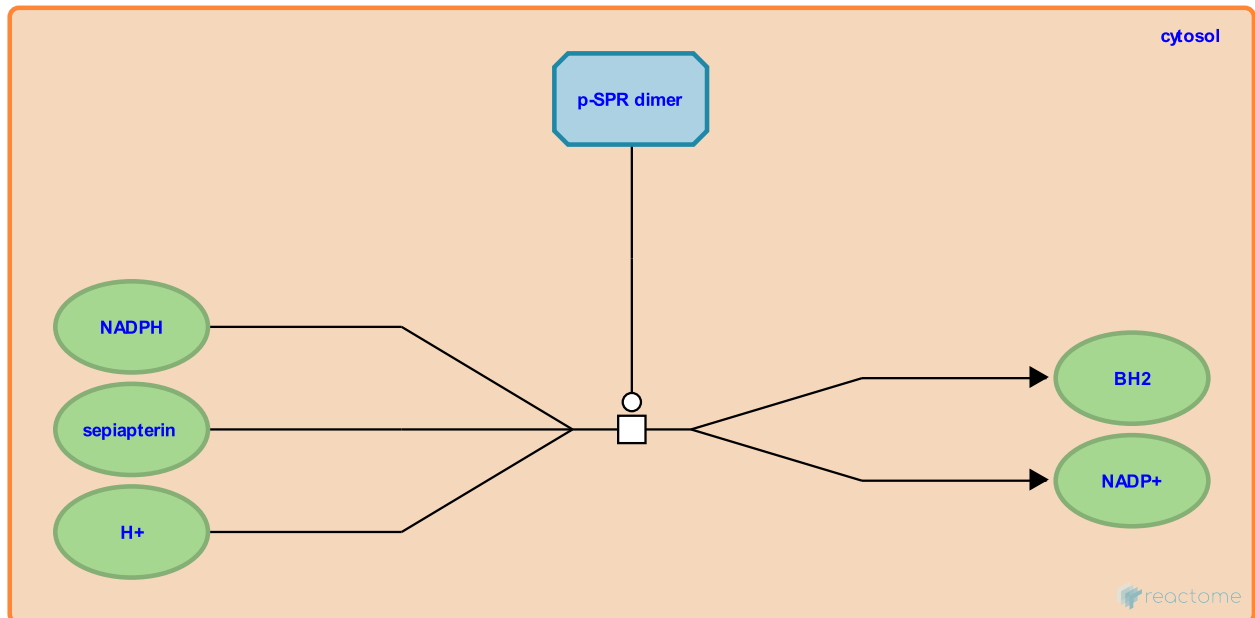
## Salvage - Sepiapterin is reduced to BH2 [↗](#)

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-1497869

**Type:** transition

**Compartments:** cytosol



In the first of two salvage steps to maintain BH4 levels in the cell, sepiapterin is taken up by the cell and reduced by sepiapterin reductase (SRP) to form BH2 (Sawabe et al. 2008).

**Followed by:** [BH2 binding can lead to eNOS uncoupling](#)

### Literature references

Matsuoka, H., Sugawara, Y., Harada, Y., Sawabe, K., Hasegawa, H., Yamamoto, K. et al. (2008). Cellular uptake of sepiapterin and push-pull accumulation of tetrahydrobiopterin. *Mol Genet Metab*, 94, 410-6. [↗](#)

### Editions

2011-08-17	Authored, Edited	Jassal, B.
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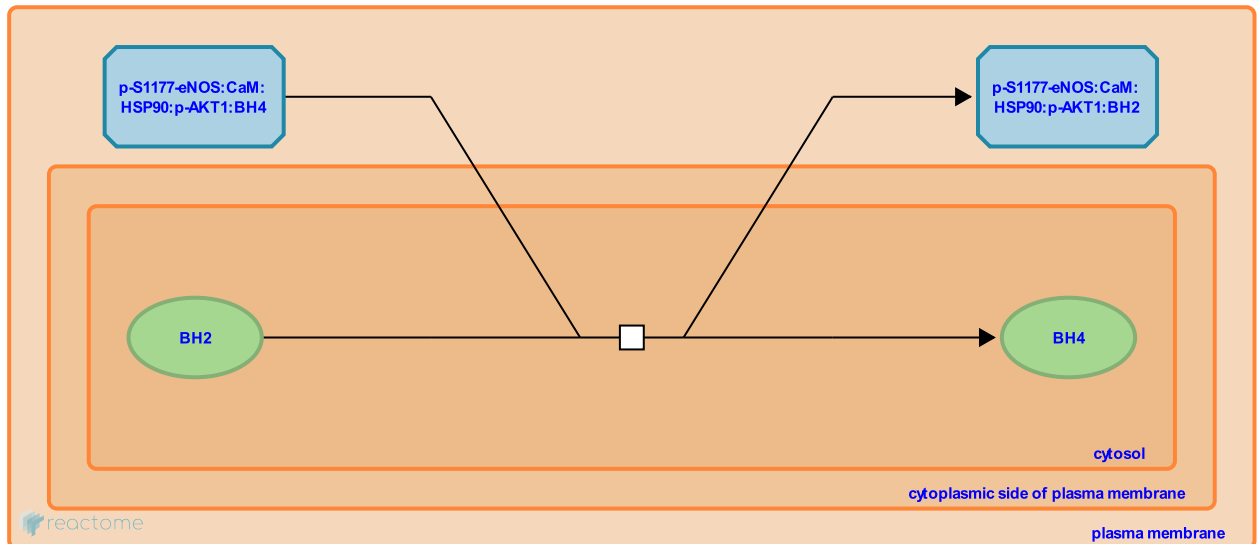
## BH2 binding can lead to eNOS uncoupling ↗

**Location:** eNOS activation

**Stable identifier:** R-HSA-1497796

**Type:** transition

**Compartments:** cytosol



The oxidation product of BH4, 7,8-dihydrobiopterin (BH2), can compete with BH4 for binding to eNOS. This can lead to the uncoupling of eNOS and can result in the formation of reactive oxygen species (Vasquez-Vivar et al. 2002).

**Preceded by:** Salvage - Sepiapterin is reduced to BH2

**Followed by:** Uncoupled eNOS favours the formation of superoxide

### Literature references

Kalyanaraman, B., Joseph, J., Whitsett, J., Vásquez-Vivar, J., Martasek, P. (2002). The ratio between tetrahydrobiopterin and oxidized tetrahydrobiopterin analogues controls superoxide release from endothelial nitric oxide synthase: an EPR spin trapping study. *Biochem J*, 362, 733-9. ↗

### Editions

2011-08-17	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

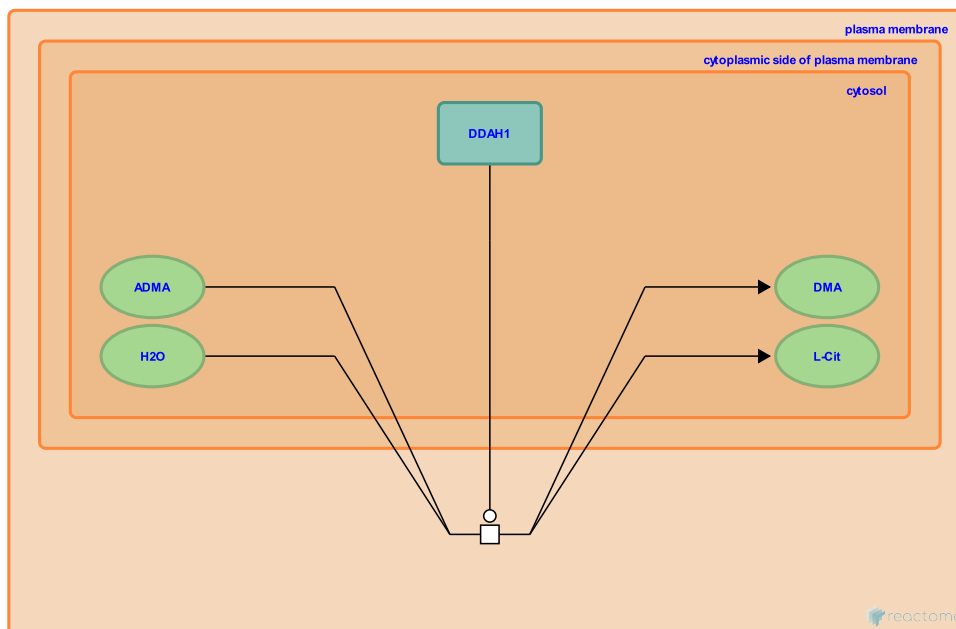
## DDAH1,2 hydrolyses ADMA to DMA and L-Cit [↗](#)

**Location:** eNOS activation

**Stable identifier:** R-HSA-5693373

**Type:** transition

**Compartments:** plasma membrane, cytosol



N(G),N(G)-dimethylarginine dimethylaminohydrolase 1 (DDAH1) plays a role in the regulation of nitric oxide generation by catalyzing the hydrolysis an endogenous inhibitor of nitric oxide synthase (NOS), N(omega),N(omega)-dimethyl-L-arginine (ADMA) to dimethylamine (DMA) and L-citrulline (L-Cit) (Forbes et al. 2008, Wang et al. 2009). DDAH2, an isoform of DDAH1 previously thought to catalyze this reaction (Cillero-Pastor et al. 2012) has recently been shown to have no detectable catalytic activity against ADMA under conditions in which DDAH1 is active (Ragavan et al. 2023).

### Literature references

- Rubets, E., Jarzebska, N., Suzuki-Yamamoto, T., Chen, Y., Bernhardt, N., Bianconi, E. et al. (2023). A multicentric consortium study demonstrates that dimethylarginine dimethylaminohydrolase 2 is not a dimethylarginine dimethylaminohydrolase. *Nat Commun*, 14, 3392. [↗](#)
- Oreiro, N., Ruiz-Romero, C., Mateos, J., Blanco, FJ., Cillero-Pastor, B., Fernández-López, C. (2012). Dimethylarginine dimethylaminohydrolase 2, a newly identified mitochondrial protein modulating nitric oxide synthesis in normal human chondrocytes. *Arthritis Rheum.*, 64, 204-12. [↗](#)
- Monzingo, AF., Robertus, JD., Wang, Y., Fast, W., Schaller, TH., Hu, S. (2009). Developing dual and specific inhibitors of dimethylarginine dimethylaminohydrolase-1 and nitric oxide synthase: toward a targeted polypharmacology to control nitric oxide. *Biochemistry*, 48, 8624-35. [↗](#)
- Green-Church, KB., Forbes, SP., Guzman, JE., Parinandi, N., Druhan, LJ., Cardounel, AJ. et al. (2008). Mechanism of 4-HNE mediated inhibition of hDDAH-1: implications in no regulation. *Biochemistry*, 47, 1819-26. [↗](#)

### Editions

2015-05-15	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

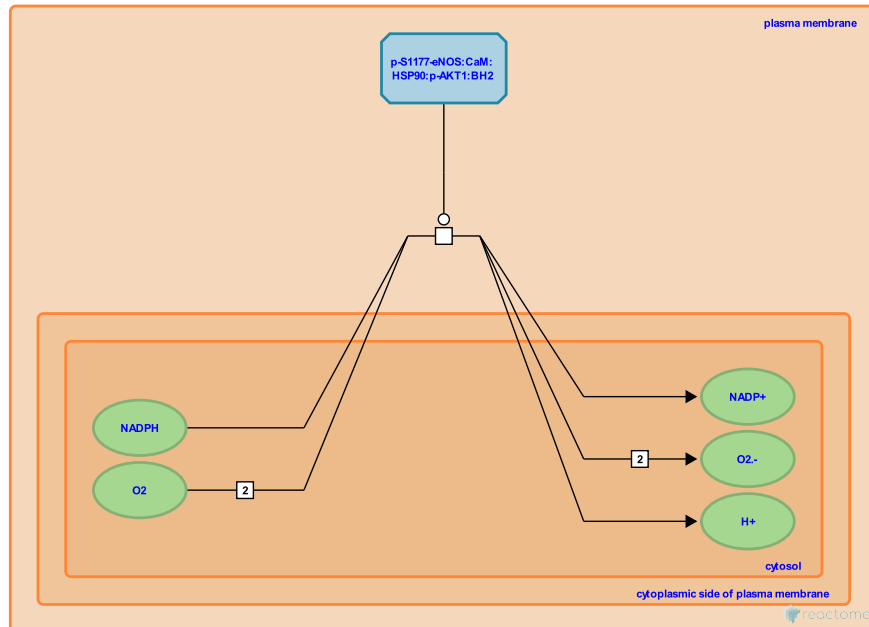
## Uncoupled eNOS favours the formation of superoxide ↗

**Location:** eNOS activation

**Stable identifier:** R-HSA-1497810

**Type:** transition

**Compartments:** plasma membrane, cytosol



BH2 may compete with BH4 to bind eNOS, uncoupling eNOS leading to the formation of superoxide rather than nitric oxide. BH2, the oxidised form of BH4, cannot contribute electrons to heme in the reductase domain of eNOS, thereby uncoupling it from arginine oxidation and producing superoxide from oxygen instead (Vasquez-Vivar et al. 2002).

**Preceded by:** BH2 binding can lead to eNOS uncoupling

**Followed by:** Superoxide reacts rapidly with NO to form peroxynitrite (ONOO-)

### Literature references

Kalyanaraman, B., Joseph, J., Whitsett, J., Vásquez-Vivar, J., Martasek, P. (2002). The ratio between tetrahydrobiopterin and oxidized tetrahydrobiopterin analogues controls superoxide release from endothelial nitric oxide synthase: an EPR spin trapping study. *Biochem J*, 362, 733-9. ↗

### Editions

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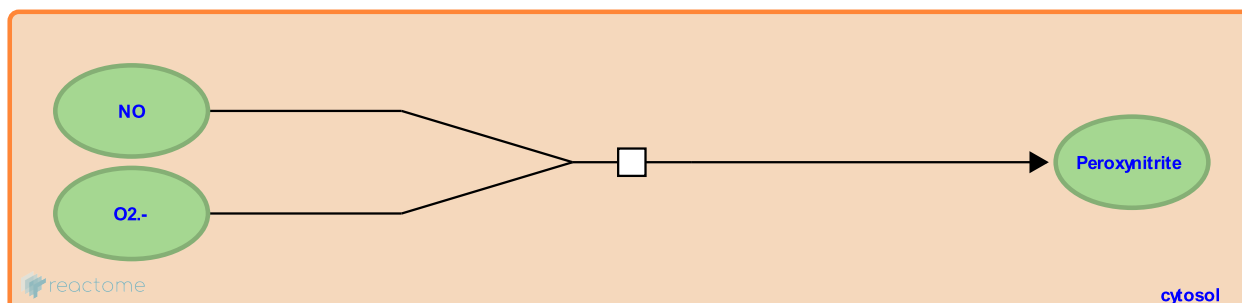
## Superoxide reacts rapidly with NO to form peroxynitrite (ONOO-) ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-1497878

**Type:** transition

**Compartments:** cytosol



Superoxide (O<sub>2</sub><sup>-</sup>) formed from an uncoupled eNOS action, together with nitric oxide (NO) formed from a coupled eNOS action, readily react together to form peroxynitrite (ONOO-) (Jour'd'heuil et al. 2001, Reiter et al. 2000).

**Preceded by:** [Uncoupled eNOS favours the formation of superoxide](#)

### Literature references

Teng, RJ., Beckman, JS., Reiter, CD. (2000). Superoxide reacts with nitric oxide to nitrate tyrosine at physiological pH via peroxynitrite. *J Biol Chem*, 275, 32460-6. ↗

Grisham, MB., Musah, RA., Jour'd'heuil, D., Wink, DA., Kutchukian, PS., Jour'd'heuil, FL. (2001). Reaction of superoxide and nitric oxide with peroxynitrite. Implications for peroxynitrite-mediated oxidation reactions in vivo. *J Biol Chem*, 276, 28799-805. ↗

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2011-08-17	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

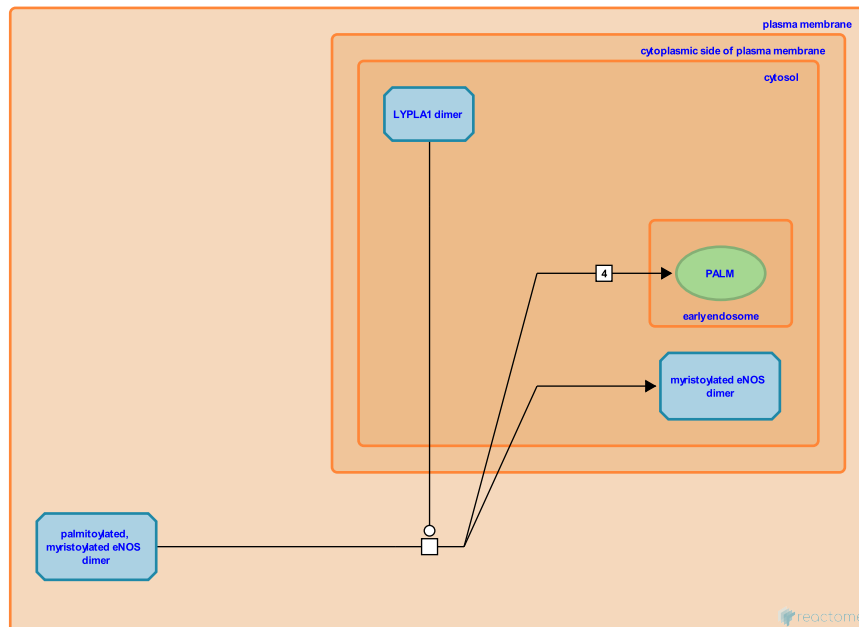
## depalmitoylation of eNOS ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-203613

**Type:** transition

**Compartments:** plasma membrane, cytosol



Increases in intracellular calcium and calmodulin stimulate depalmitoylation of eNOS by acyl protein thioesterase 1, which displaces eNOS from the membrane. This might be a mechanism to downregulate NO production following intense stimuli.

**Preceded by:** [eNOS translocation from Golgi to Caveolae](#)

**Followed by:** [depalmitoylated eNOS translocates from plasma membrane](#)

### Editions

2007-10-19

Authored

Hemish, J.

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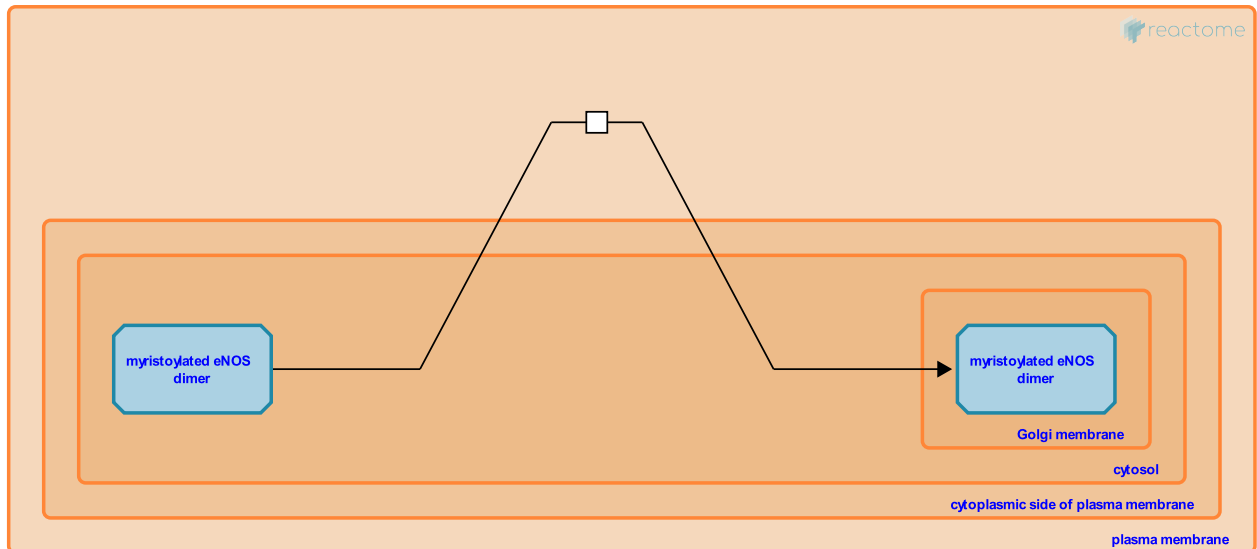
## depalmitoylated eNOS translocates from plasma membrane ↗

**Location:** [eNOS activation](#)

**Stable identifier:** R-HSA-202132

**Type:** transition

**Compartments:** plasma membrane, Golgi membrane



Once depalmitoylated, it's proposed that eNOS is displaced from the plasma membrane and redistributed to other intracellular membranes, including the Golgi, where re-palmitoylation occurs. The mechanism of transport from the plasma membrane is still unknown.

**Preceded by:** [depalmitoylation of eNOS](#)

**Followed by:** [AKT1 binds eNOS complex via HSP90](#), [palmitoylation of eNOS](#)

### Literature references

Michel, T. (1999). Targeting and translocation of endothelial nitric oxide synthase. *Braz J Med Biol Res*, 32, 1361-6. ↗

### Editions

2007-10-19	Authored	Hemish, J.
2008-02-28	Reviewed	Enikolopov, G.

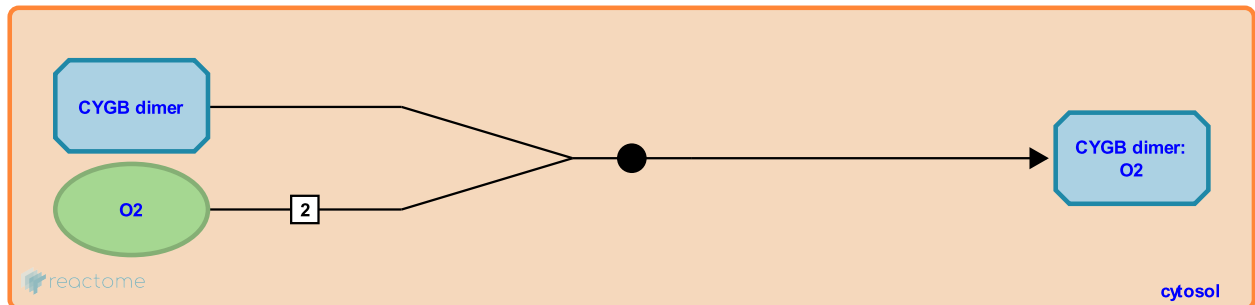
## CYGB binds O2 ↗

**Location:** eNOS activation

**Stable identifier:** R-HSA-5340214

**Type:** binding

**Compartments:** cytosol



Vertebrates possess multiple respiratory globins that differ in structure, function, and tissue distribution. Three different globins have been described so far: hemoglobin facilitates oxygen transport in blood, myoglobin mediates oxygen transport and storage in the muscle and neuroglobin has a yet unidentified function in nerve cells. A fourth globin has been identified in mouse, human and zebrafish. It is ubiquitously expressed in human tissue and therefore called cytoglobin (CYGB) (Burmester et al. 2002, Trent & Hargrove 2002). Unlike the specific expression patterns of Hb and Mb, CYGB is found in vascular smooth muscle, fibroblasts and cardiomyocytes. CYGB functions as a homodimer (Hamdane et al. 2003) and is localised to the cytosol of these cells where its O2 loading and unloading ability within a narrow O2 tension range makes it an ideal protein for O2 storage, especially during hypoxia (Fago et al. 2004).

**Followed by:** CYGB dioxygenates NO

## Literature references

- Hankeln, T., Burmester, T., Pesce, A., Hamdane, D., Bolognesi, M., Kiger, L. et al. (2003). The redox state of the cell regulates the ligand binding affinity of human neuroglobin and cytoglobin. *J. Biol. Chem.*, 278, 51713-21. ↗
- Hargrove, MS., Trent, JT. (2002). A ubiquitously expressed human hexacoordinate hemoglobin. *J. Biol. Chem.*, 277, 19538-45. ↗
- Gilany, K., Hundahl, C., Dewilde, S., Moens, L., Fago, A., Weber, RE. (2004). Allosteric regulation and temperature dependence of oxygen binding in human neuroglobin and cytoglobin. Molecular mechanisms and physiological significance. *J. Biol. Chem.*, 279, 44417-26. ↗
- Hankeln, T., Burmester, T., Ebner, B., Weich, B. (2002). Cytoglobin: a novel globin type ubiquitously expressed in vertebrate tissues. *Mol. Biol. Evol.*, 19, 416-21. ↗

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2014-03-12	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.
2017-05-11	Reviewed	Burmester, T.

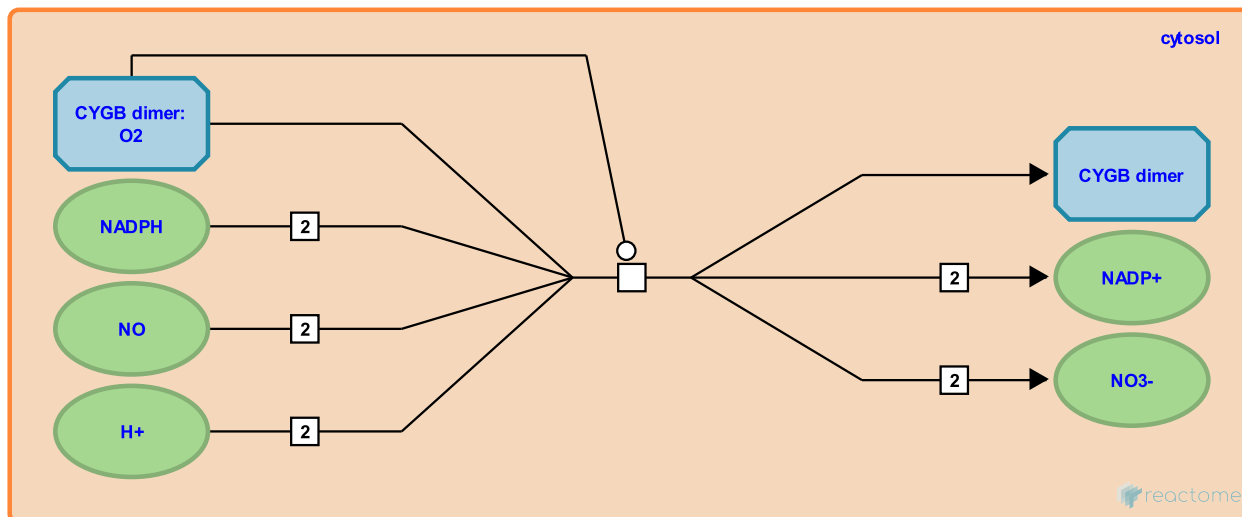
## CYGB dioxygenates NO ↗

**Location:** eNOS activation

**Stable identifier:** R-HSA-5340226

**Type:** transition

**Compartments:** cytosol



Vertebrates possess multiple respiratory globins that differ in structure, function, and tissue distribution. Three different globins have been described so far: haemoglobin facilitates oxygen transport in blood, myoglobin mediates oxygen transport and storage in the muscle and neuroglobin has a yet unidentified function in nerve cells. A fourth globin has been identified in mouse, human and zebrafish. It is ubiquitously expressed in human tissue and therefore called cytoglobin (CYGB) (Trent & Hargrove 2002). Unlike the specific expression patterns of Hb and Mb, CYGB is found in vascular smooth muscle, fibroblasts and cardiomyocytes. CYGB functions as a homodimer (Hamdane et al. 2003) and is localised to the cytosol. As well as oxygen binding capability, CYGB possesses nitric oxide dioxygenase activity (Halligan et al. 2009), a common feature amongst the globin family (Smagghe et al. 2008). CYGB consumes NO through the dioxygenase pathway, which regulates cell respiration and proliferation (Smagghe et al. 2008). O<sub>2</sub> binds to the ferric form of CYGB (CYGB-Fe<sup>2+</sup>:O<sub>2</sub>). During NO dioxygenation, CYGB is reduced to the ferrous form (CYGB-Fe<sup>3+</sup>) (Gardner 2005).

**Preceded by:** CYGB binds O<sub>2</sub>

### Literature references

- Jourd'heuil, FL., Halligan, KE., Jourd'heuil, D. (2009). Cytoglobin is expressed in the vasculature and regulates cell respiration and proliferation via nitric oxide dioxygenation. *J. Biol. Chem.*, 284, 8539-47. ↗
- Hankeln, T., Burmester, T., Pesce, A., Hamdane, D., Bolognesi, M., Kiger, L. et al. (2003). The redox state of the cell regulates the ligand binding affinity of human neuroglobin and cytoglobin. *J. Biol. Chem.*, 278, 51713-21. ↗
- Hargrove, MS., Trent, JT. (2002). A ubiquitously expressed human hexacoordinate hemoglobin. *J. Biol. Chem.*, 277, 19538-45. ↗
- Hargrove, MS., Trent JT, 3rd., Smagghe, BJ. (2008). NO dioxygenase activity in hemoglobins is ubiquitous in vitro, but limited by reduction in vivo. *PLoS One*, 3, e2039. ↗
- Gardner, PR. (2005). Nitric oxide dioxygenase function and mechanism of flavohemoglobin, hemoglobin, myoglobin and their associated reductases. *J. Inorg. Biochem.*, 99, 247-66. ↗

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2014-03-12	Authored, Edited	Jassal, B.
2015-02-11	Reviewed	D'Eustachio, P.



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