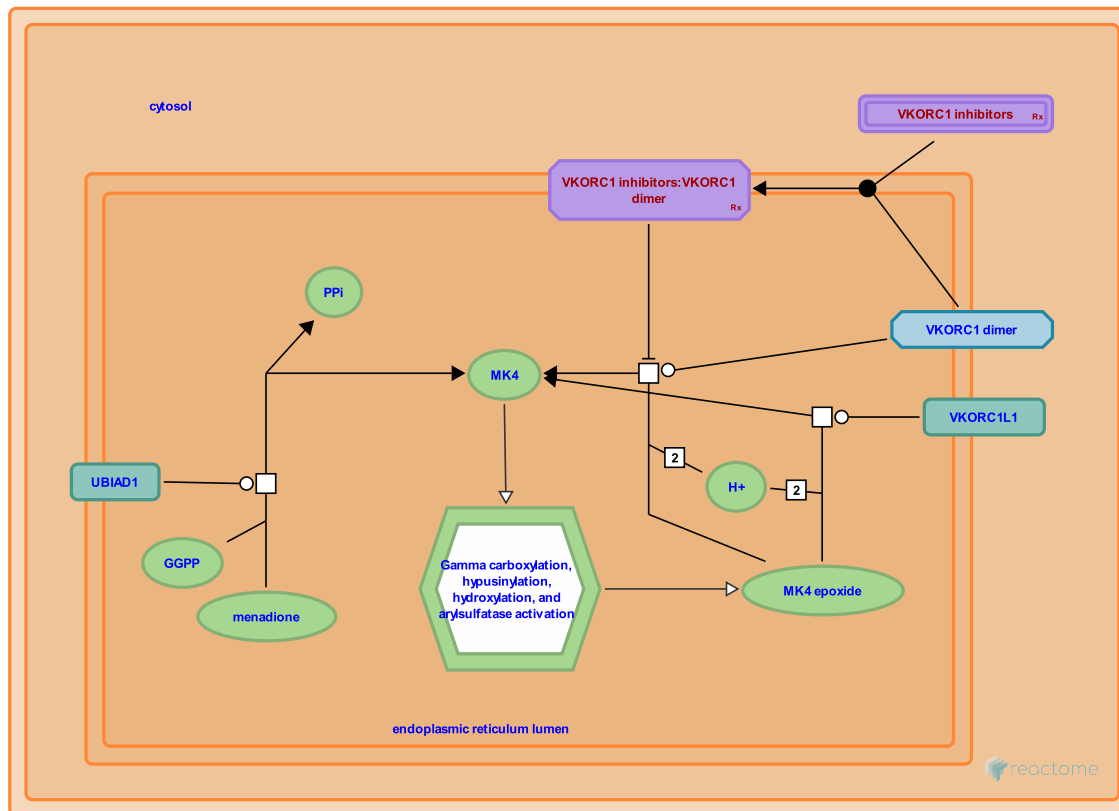


Metabolism of vitamin K



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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](https://reactome.org/textbook/).

05/05/2024

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.

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Literature references

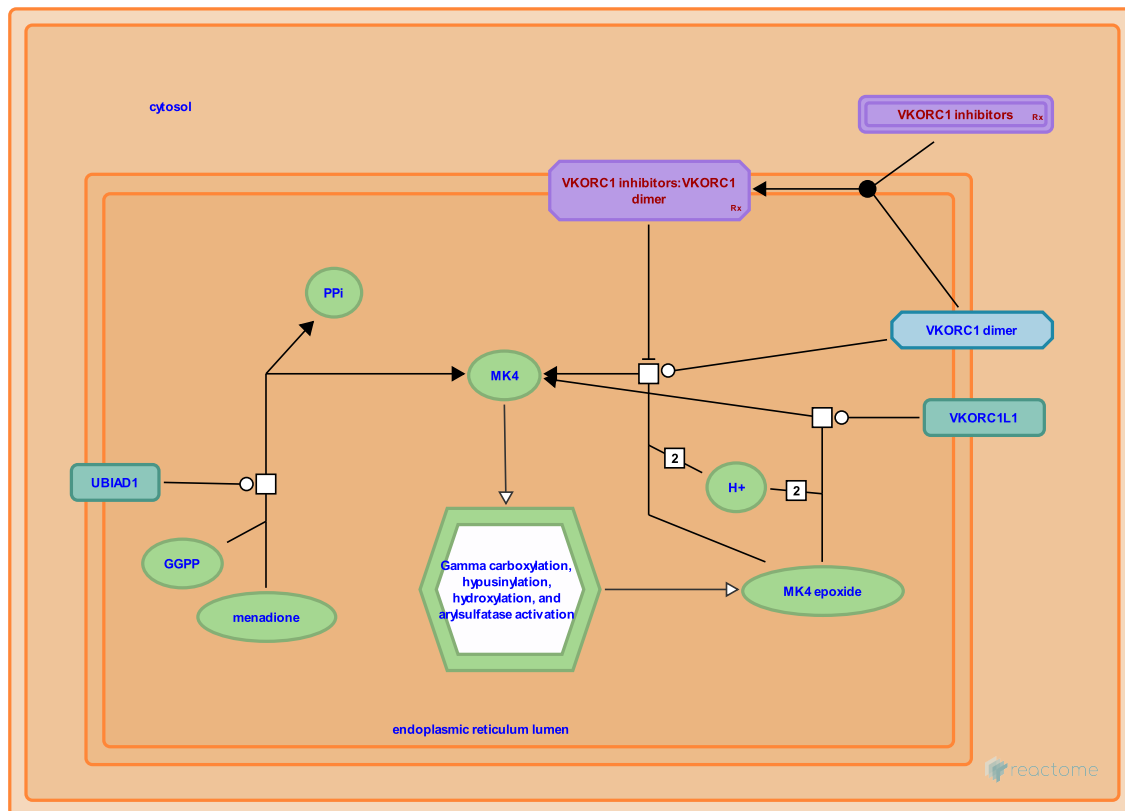
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Reactome database release: 88

This document contains 1 pathway and 4 reactions ([see Table of Contents](#))

Metabolism of vitamin K ↗

Stable identifier: R-HSA-6806664



Vitamin K is a required co-factor in a single metabolic reaction, the gamma-carboxylation of glutamate residues of proteins catalyzed by GGCX (gamma-carboxyglutamyl carboxylase). Substrates of GGCX include blood clotting factors, osteocalcin (OCN), and growth arrest-specific protein 6 (GAS6) (Brenner et al. 1998). Vitamin K is derived from green leafy vegetables as phylloquinone and is synthesized by gut flora as menaquinone-7. These molecules are taken up by intestinal enterocytes with other lipids, packaged into chylomicrons, and delivered via the lymphatic and blood circulation to tissues of the body, notably hepatocytes and osteoblasts, via processes of lipoprotein trafficking (Shearer & Newman 2014; Shearer et al. 2012) described elsewhere in Reactome.

In these tissues, menadiol (reduced vitamin K3) reacts with geranylgeranyl pyrophosphate to form MK4 (vitamin K hydroquinone), the form of the vitamin required as cofactor for gamma-carboxylation of protein glutamate residues (Hirota et al. 2013). The gamma-carboxylation reactions, annotated elsewhere in Reactome as a part of protein metabolism, convert MK4 to its epoxide form, which is inactive as a cofactor. Two related enzymes, VKORC1 and VKORCL1, can each catalyze the reduction of MK4 epoxide to active MK4. VKORC1 activity is essential for normal operation of the blood clotting cascade and for osteocalcin function (Ferron et al. 2015). A physiological function for VKORCL1 has not yet been definitively established (Hammed et al. 2013; Tie et al. 2014).

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Matagrín, B., Lattard, V., Prouillac, C., Spohn, G., Hammed, A., Benoit, E. (2013). VKORC1L1, an enzyme rescuing the vitamin K 2,3-epoxide reductase activity in some extrahepatic tissues during anticoagulation therapy. *J. Biol. Chem.*, 288, 28733-42. [↗](#)

Editions

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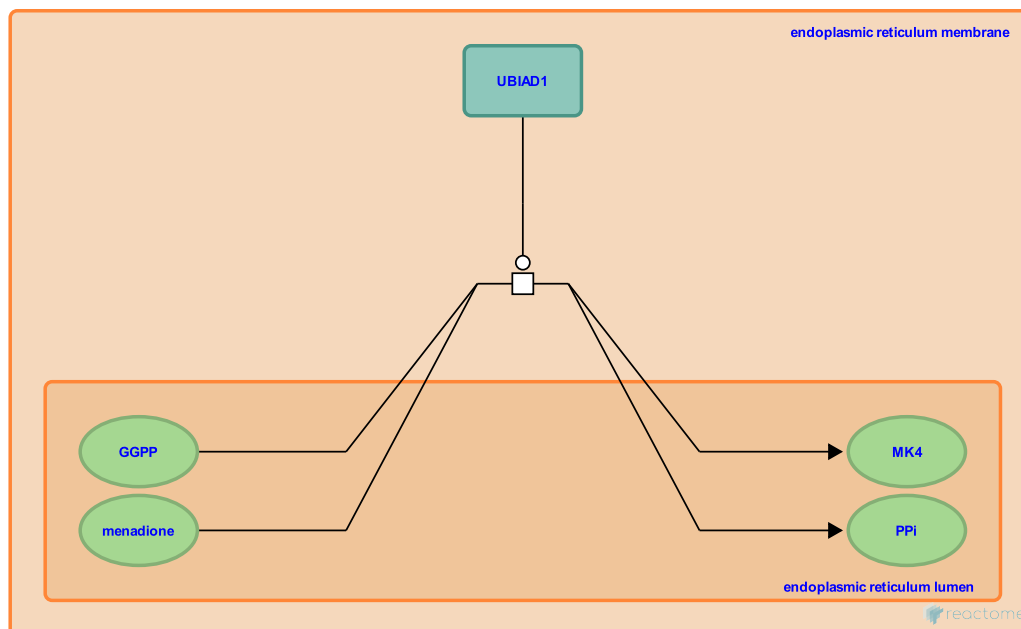
UBIAD1 prenylates menadione to form MK4 (vitamin K hydroquinone) ↗

Location: [Metabolism of vitamin K](#)

Stable identifier: R-HSA-6806674

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



UBIAD1 (UbiA prenyltransferase domain-containing protein 1) in the endoplasmic reticulum catalyzes the transfer of a geranylgeranyl group from GGPP (geranylgeranyl pyrophosphate) to menadione to form MK4 (vitamin K hydroquinone, menatetrenone) (Nakagawa et al. 2010; Hirota et al. 2013, 2015; Schumacher et al. 2015).

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- Suhara, Y., Tsugawa, N., Okano, T., Wada, A., Kamao, M., Uchino, Y. et al. (2013). Menadione (vitamin K3) is a catabolic product of oral phylloquinone (vitamin K1) in the intestine and a circulating precursor of tissue menaquinone-4 (vitamin K2) in rats. *J. Biol. Chem.*, 288, 33071-80. ↗
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Editions

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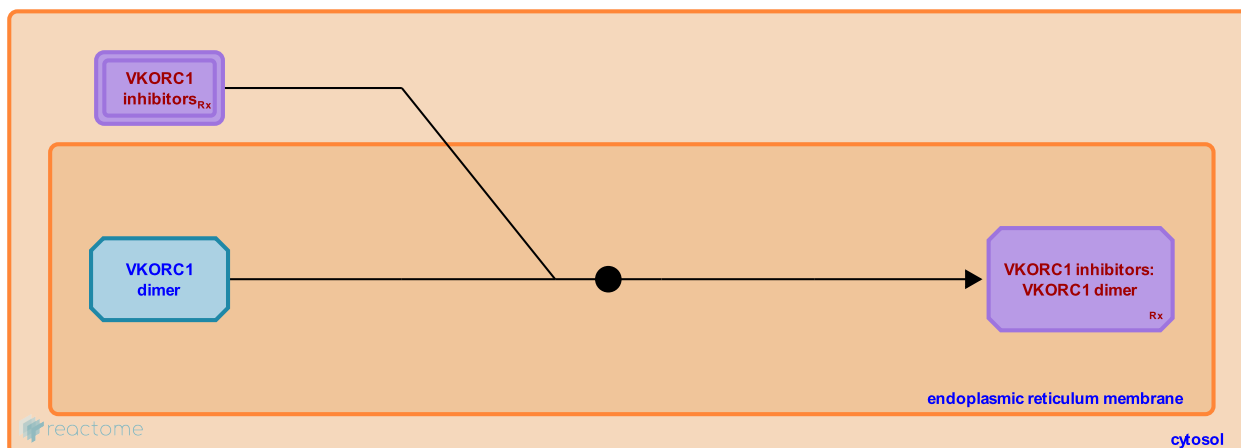
VKORC1 inhibitors binds VKORC1 dimer ↗

Location: [Metabolism of vitamin K](#)

Stable identifier: R-HSA-9026967

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol



4-Hydroxycoumarins belong to a class of vitamin K antagonist anticoagulant drug molecules derived from coumarin, a bitter-tasting but sweet-smelling natural substance made by plants. It itself doesn't affect coagulation, but is transformed in mouldy feeds or silages by a number of fungi into active dicumarol, a substance that does have anticoagulant properties. Identified in 1940, dicumarol became the prototypical drug of the 4-hydroxycoumarin anticoagulant drug class but has been superseded by warfarin since the 1950's (Norn et al. 2014). Phenindione was introduced in the early 1950s and acts similarly to warfarin, but it has been associated with hypersensitivity reactions so is now rarely used (Naisbitt et al. 2005). Other coumarin-derivatives commonly prescribed in Europe and other regions are the long-acting phenprocoumon (half-life 140 hours) and short-acting acenocoumarol (half-life 11 hours) (Gadisseeur et al. 2002). Warfarin, the more potent form of dicumarol and initially used as rat poison, was introduced as an oral anticoagulant in the 1950s and is currently the most widely used oral anticoagulant. Although the working mechanism of the 4-Hydroxycoumarin drugs is similar, there are some important differences in pharmacokinetics between them (Verhoef et al. 2014).

The reduction of vitamin K 2,3-epoxide (MK4 epoxide) by VKORC1 is essential to sustain gamma-carboxylation of vitamin K-dependent proteins such as the clotting factors II, VII, IX and X. The anticoagulant drug warfarin inhibits VKORC1 (Whitlon et al. 1978), thereby reducing clotting ability (Choonara et al. 1985, 1988), which is used as a treatment for thrombotic disorders such as deep vein thrombosis (DVT), pulmonary embolism and to prevent stroke (Ageno et al. 2012). A common side-effect of warfarin anticoagulation is bleeding which can be counteracted by vitamin K supplementation (Ageno et al. 2012). The exact mechanism by which warfarin inhibits VKORC1 remains elusive. Several recent mechanistic studies suggest competitive binding of a key residue in VKORC1 (Czogalla et al. 2017) or blockage of a dynamic electron-transfer process in VKORC1 (Shen et al. 2017). New oral anticoagulants (NOAC; rivaroxaban, dabigatran, apixaban) have become available as an alternative to warfarin anticoagulation. Unlike warfarin, they are fast-acting and don't require routine coagulation monitoring (Gomez-Outes et al. 2013).

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Maitland-van der Zee, AH., de Boer, A., van Schie, RM., Daly, AK., Redekop, WK., Verhoef, TI. (2014). Pharmacogenetic-guided dosing of coumarin anticoagulants: algorithms for warfarin, acenocoumarol and phenprocoumon. *Br J Clin Pharmacol*, 77, 626-41. [↗](#)

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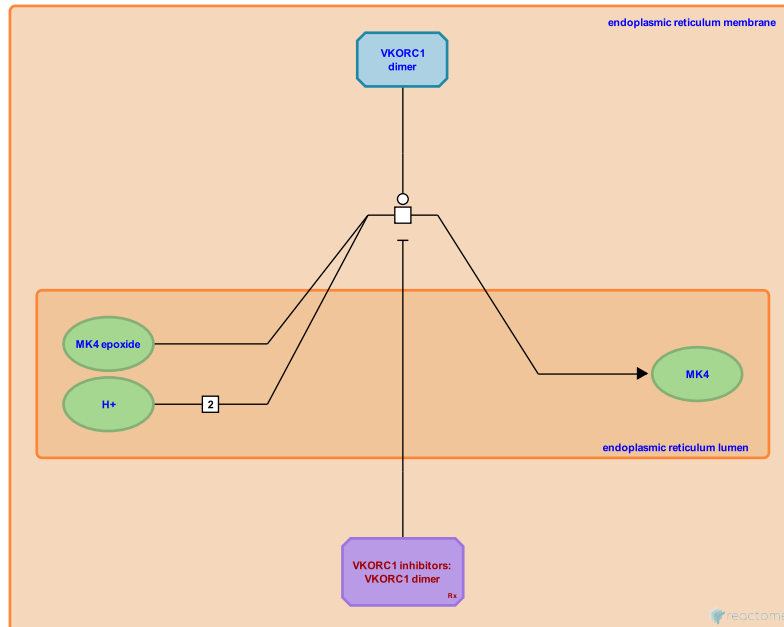
VKORC1 reduces vitamin K epoxide to MK4 (vitamin K hydroquinone) ↗

Location: Metabolism of vitamin K

Stable identifier: R-HSA-159790

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen, cytosol



4-Hydroxycoumarins belong to a class of vitamin K antagonist anticoagulant drug molecules derived from coumarin, a bitter-tasting but sweet-smelling natural substance made by plants. It itself doesn't affect coagulation, but is transformed in mouldy feeds or silages by a number of fungi into active dicumarol, a substance that does have anticoagulant properties. Identified in 1940, dicumarol became the prototypical drug of the 4-hydroxycoumarin anticoagulant drug class but has been superseded by warfarin since the 1950's (Norn et al. 2014). Phenindione was introduced in the early 1950s and acts similarly to warfarin, but it has been associated with hypersensitivity reactions so is now rarely used (Naisbitt et al. 2005). Other coumarin-derivatives commonly prescribed in Europe and other regions are long-acting phenprocoumon (half-life 140 hours) and short-acting acenocoumarol (half-life 11 hours) (Gadisseur et al. 2002). Warfarin, the more potent form of dicumarol and initially used as rat poison, was introduced as an oral anticoagulant in the 1950s and is currently the most widely used oral anticoagulant. Although the working mechanism of the 4-Hydroxycoumarin drugs is similar, there are some important differences in pharmacokinetics between them (Verhoef et al. 2014).

The reduction of vitamin K 2,3-epoxide (MK4 epoxide) by VKORC1 is essential to sustain gamma-carboxylation of vitamin K-dependent proteins such as the clotting factors II, VII, IX and X. The anticoagulant drug warfarin inhibits VKORC1 (Whitlon et al. 1978), thereby reducing clotting ability (Choonara et al. 1985, 1988), which is used as a treatment for thrombotic disorders such as deep vein thrombosis (DVT), pulmonary embolism and to prevent stroke (Ageno et al. 2012). A common side-effect of warfarin anticoagulation is bleeding which can be counteracted by vitamin K supplementation (Ageno et al. 2012). The exact mechanism by which warfarin inhibits VKORC1 remains elusive. Several recent mechanistic studies suggest competitive binding of a key residue in VKORC1 (Czogalla et al. 2017) or blockage of a dynamic electron-transfer process in VKORC1 (Shen et al. 2017). New oral anticoagulants (NOAC; rivaroxaban, dabigatran, apixaban) have become available as an alternative to warfarin anticoagulation. Unlike warfarin, they are fast-acting and don't require routine coagulation monitoring (Gomez-Outes et al. 2013). The regeneration of reduced vitamin K (vitamin K hydroquinone) from vitamin K epoxide is catalyzed by vitamin K epoxide reductase (VKORC1) (Sadler 2004). Two important features of this reaction remain unclear. First, dithiothreitol functions efficiently as a reductant *in vitro* (Wallin & Martin 1985), but the *in vivo* reductant remains unknown. Second, while people homozygous for mutations in VKORC1 protein lack epoxide reductase activity (Rost et al. 2004) and cultured insect cells transfected with the cloned human VKORC1 gene express vitamin K epoxide reductase activity (Li et al. 2004), the possibility that the active form of the enzyme is a complex with other proteins cannot be formally excluded.

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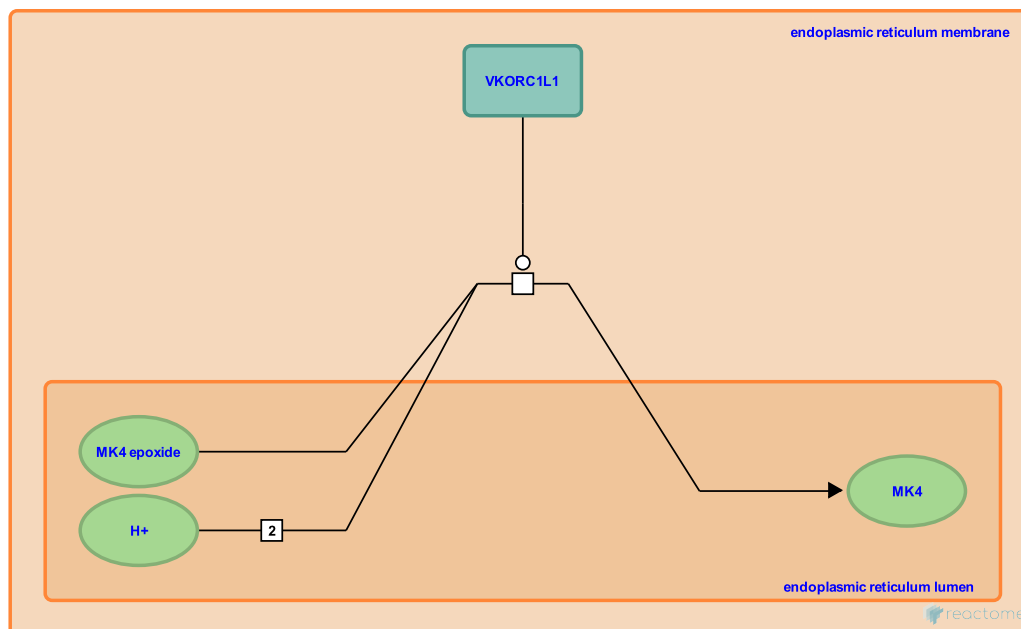
VKORC1L1 reduces vitamin K epoxide to MK4 (vitamin K hydroquinone) ↗

Location: [Metabolism of vitamin K](#)

Stable identifier: R-HSA-6806647

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



VKORC1L1 (Vitamin K epoxide reductase complex subunit 1-like protein 1) in the endoplasmic reticulum catalyzes the reduction of MK4 epoxide to MK4, the active form of vitamin K. A physiological role for this reaction has not been established (Hammed et al. 2013; Tie et al. 2014; Westhofen et al. 2011).

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