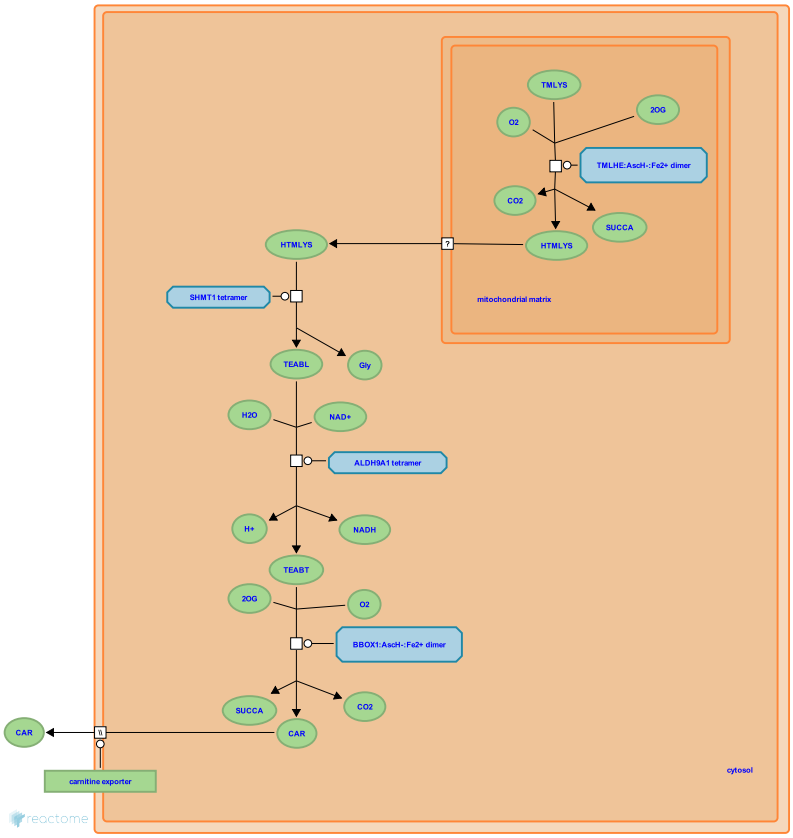
Carnitine synthesis



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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. ↗

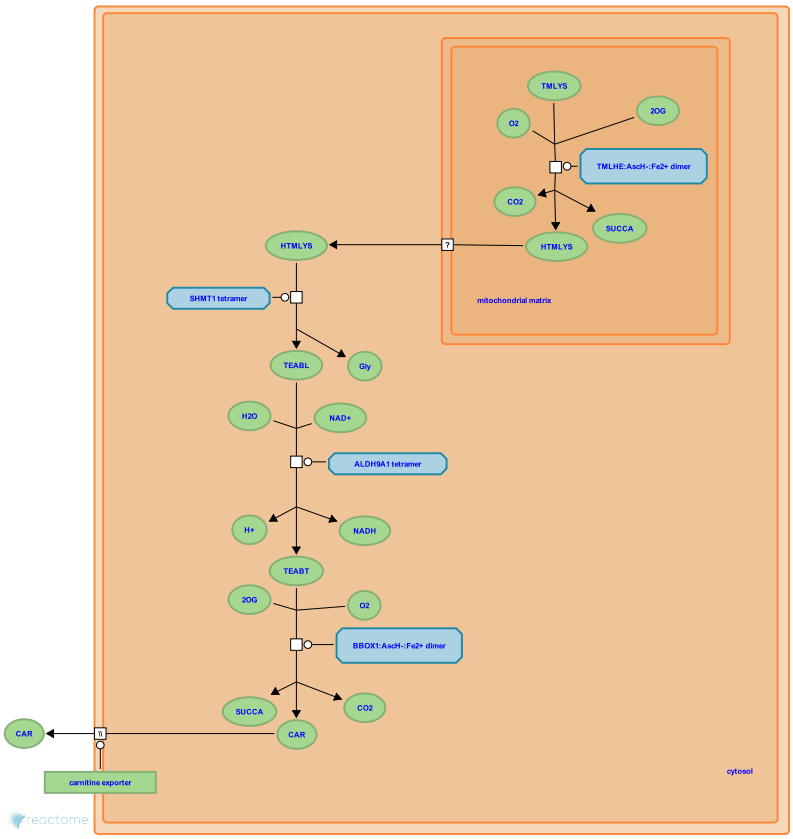
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Carnitine synthesis ↗

Stable identifier: R-HSA-71262

Compartments: cytosol, mitochondrial matrix



Carnitine is synthesized in four steps from trimethyllysine (generated in turn by the S-adenosyl-methionine-mediated methylation of lysine residues in proteins, followed by protein hydrolysis). The enzymes that catalyze the first three steps of carnitine synthesis, converting trimethyllysine to gamma-butyrobetaine, are widely distributed in human tissues. The enzyme that catalyzes the last reaction, converting gamma-butyrobetaine to carnitine, is found only in liver and kidney cells, and at very low levels in brain tissues. Other tissues that require carnitine, such as muscle, are dependent on transport systems that mediate its export from the liver and uptake by other tissues (Bremer 1983, Kerner and Hoppel 1998).

Literature references

Bremer, J. (1983). Carnitine--metabolism and functions. *Physiol. Rev., 63*, 1420-80. ↗

Kerner, J., Hoppel, C. (1998). Genetic disorders of carnitine metabolism and their nutritional management. *Annu Rev Nutr, 18*, 179-206. ↗

Editions

2021-05-18	Edited	D'Eustachio, P.

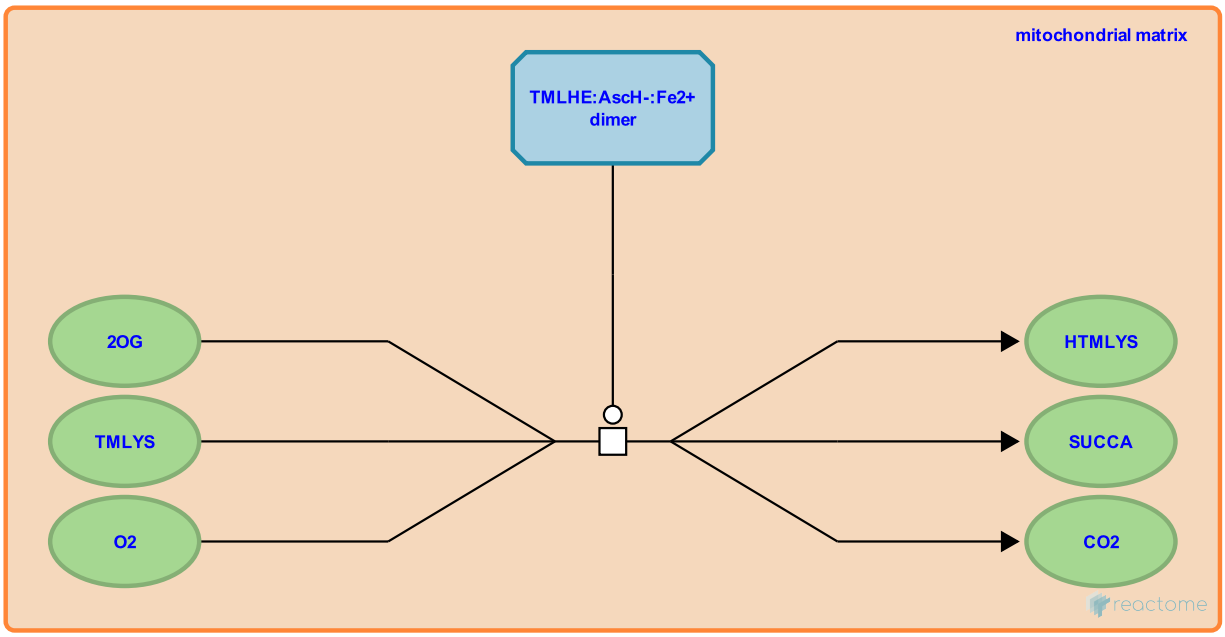
TMLHE dimer dioxygenates TMLYS and 2OG to form HTMLYS and SUCCA ↗

Location: Carnitine synthesis

Stable identifier: R-HSA-71241

Type: transition

Compartments: mitochondrial matrix



Trimethyllysine dioxygenase (TMLHE) dimer in the mitochondrial matrix catalyzes the reaction of oxygen, 2-oxoglutarate (2OG), and N6,N6,N6-trimethyl-L-lysine (TMLYS) to form CO2, 3-hydroxy-N6,N6,N6-trimethyl-L-lysine (HTMLYS), and succinate (SUCCA) (Vaz et al. 2001).

Followed by: SHMT1 tetramer cleaves HTMLYS to yield TEABL and Gly

Literature references

Vaz, FM., Ofman, R., Westinga, K., Back, JW. (2001). Molecular and Biochemical Characterization of Rat epsilon -N-Trimethyllysine Hydroxylase, the First Enzyme of Carnitine Biosynthesis. *J Biol Chem, 276*, 33512-7. ↗

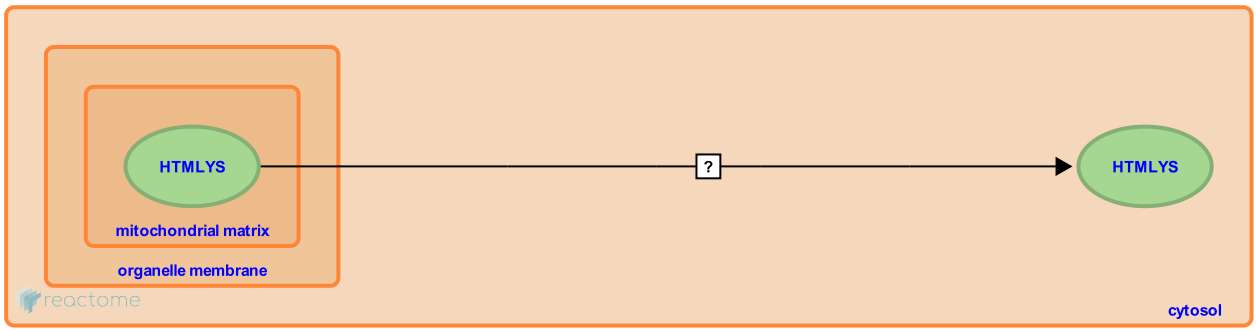
HTMLYS translocates from the mitochondrial matrix to the cytosol ↗

Location: Carnitine synthesis

Stable identifier: R-HSA-8949413

Type: uncertain

Compartments: cytosol, mitochondrial matrix



HTMLYS (3-Hydroxy-N6,N6,N6-trimethyl-L-lysine) moves from the mitochondrial matrix to the cytosol (Longo et al. 2016). The molecular mechanism for this translocation is unknown.

Literature references

Longo, N., Frigeni, M., Pasquali, M. (2016). Carnitine transport and fatty acid oxidation. *Biochim. Biophys. Acta, 1863*, 2422-35. ↗

Editions

2016-11-24	Authored, Edited	D'Eustachio, P.
2016-12-23	Reviewed	Jassal, B.

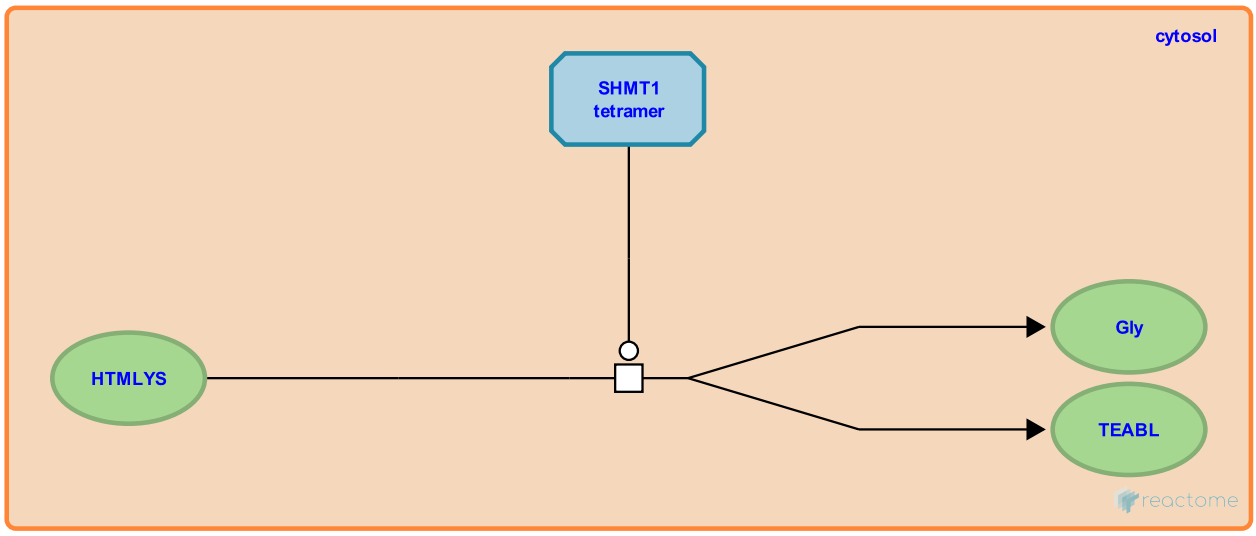
SHMT1 tetramer cleaves HTMLYS to yield TEABL and Gly ↗

Location: Carnitine synthesis

Stable identifier: R-HSA-71249

Type: transition

Compartments: cytosol



Cytosolic serine hydroxymethyltransferase tetramer (SHMT1) catalyzes the reaction of 3-Hydroxy-N6,N6,N6-trimethyl-L-lysine (NTMLYS) to form glycine (Gly) and 4-trimethylammoniobutanal (TEABL) in vitro (Hulse et al. 1978). The possibility that an additional enzyme may catalyze this reaction in vivo has not been excluded (Bremer 1983).

Preceded by: TMLHE dimer dioxygenates TMLYS and 2OG to form HTMLYS and SUCCA

Followed by: ALDH9A1 tetramer dehydrogenates TEABL to form TEABT

Literature references

Bremer, J. (1983). Carnitine--metabolism and functions. *Physiol. Rev., 63*, 1420-80. ↗

Hulse, JD., Ellis, SR., Henderson, LM. (1978). Carnitine biosynthesis. beta-Hydroxylation of trimethyllysine by an alpha-ketoglutarate-dependent mitochondrial dioxygenase. *J Biol Chem, 253*, 1654-9. ↗

Editions

2009-05-19	Revised	D'Eustachio, P.

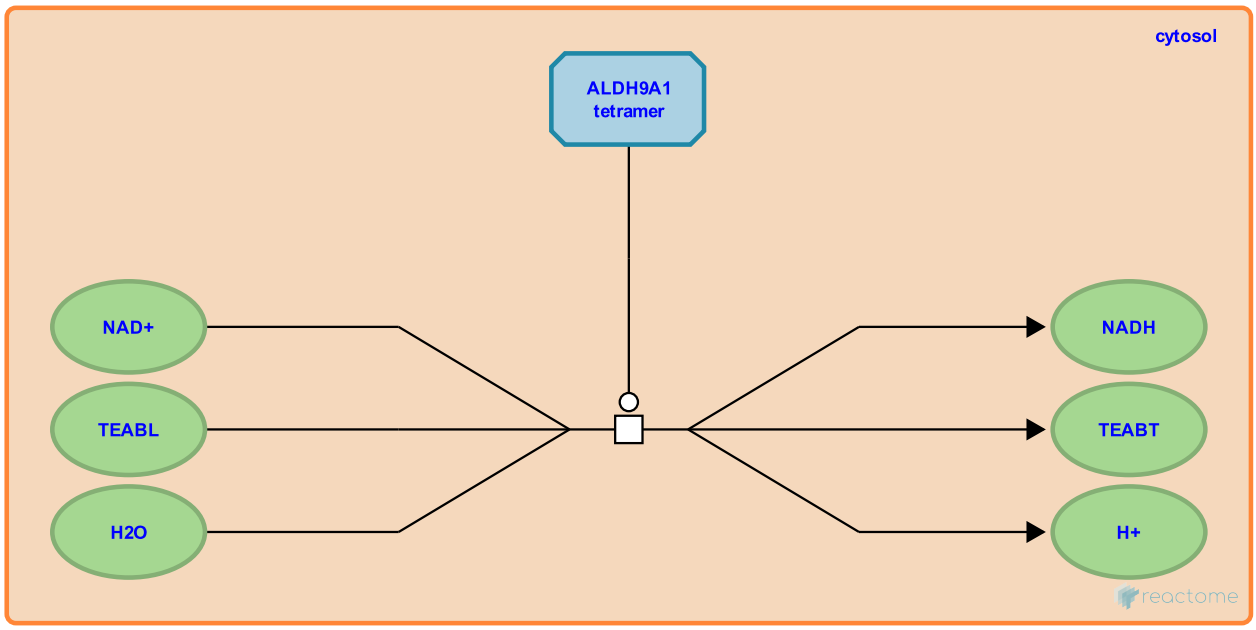
ALDH9A1 tetramer dehydrogenates TEABL to form TEABT ↗

Location: Carnitine synthesis

Stable identifier: R-HSA-71260

Type: transition

Compartments: cytosol



Cytosolic 4-trimethylaminobutyraldehyde dehydrogenase (ALDH9A1) tetramer catalyzes the reaction of NAD+ and 4-trimethylammoniobutanal (TEABL) to form 4-trimethylammoniobutanoate (TEABT) and NADH + H+ (Kurys et al. 1989; Vaz et al. 2000).

Preceded by: SHMT1 tetramer cleaves HTMLYS to yield TEABL and Gly

Followed by: BBOX1:AscH-:Fe2+ dimer dioxygenates TEABT and 2OG to form CAR and SUCCA

Literature references

Kurys, G., Ambroziak, W., Pietruszko, R. (1989). Human aldehyde dehydrogenase. Purification and characterization of a third isozyme with low Km for gamma-aminobutyraldehyde. *J Biol Chem, 264*, 4715-21. ↗

Vaz, FM., Fouchier, SW., Ofman, R., Sommer, M. (2000). Molecular and biochemical characterization of rat gamma-trimethylaminobutyraldehyde dehydrogenase and evidence for the involvement of human aldehyde dehydrogenase 9 in carnitine biosynthesis. *J Biol Chem, 275*, 7390-4. ↗

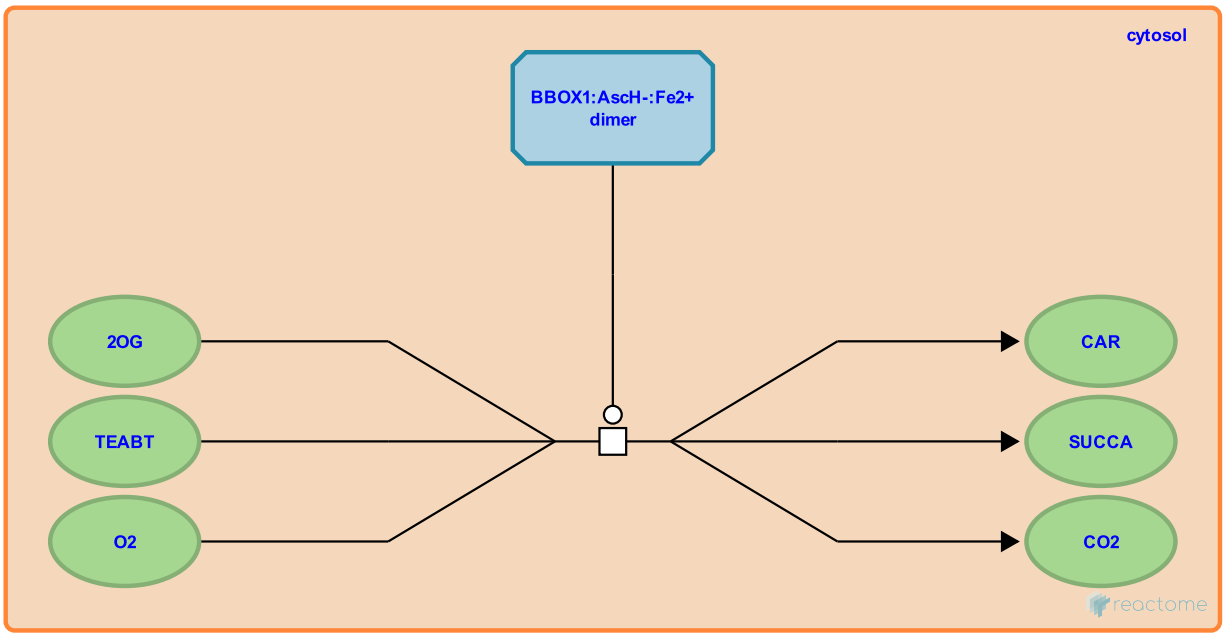
BBOX1:AscH-:Fe2+ dimer dioxygenates TEABT and 2OG to form CAR and SUCCA ↗

Location: Carnitine synthesis

Stable identifier: R-HSA-71261

Type: transition

Compartments: cytosol



Cytosolic gamma-butyrobetaine hydroxylase dimer (BBOX1), a dioxygenase, catalyzes the reaction of oxygen, 4-trimethylammoniobutanoate (TEABT), and 2-oxoglutarate (2OG)to form CO2, succinate (SUCCA), and carnitine (CAR) (Lindstedt and Nordin 1984; Vaz et al. 1998).

Preceded by: ALDH9A1 tetramer dehydrogenates TEABL to form TEABT

Followed by: Unknown carnitine exporter transports CAR from the cytosol to the extracellular space

Literature references

Vaz, FM., van Gool, S., Ofman, R., Ijlst, L. (1998). Carnitine biosynthesis: identification of the cDNA encoding human gamma-butyrobetaine hydroxylase. *Biochem Biophys Res Commun, 250*, 506-10. ↗

Lindstedt, S., Nordin, I. (1984). Multiple forms of gamma-butyrobetaine hydroxylase (EC 1.14.11.1). *Biochem J, 223*, 119-27. ↗

Unknown carnitine exporter transports CAR from the cytosol to the extracellular space ↗

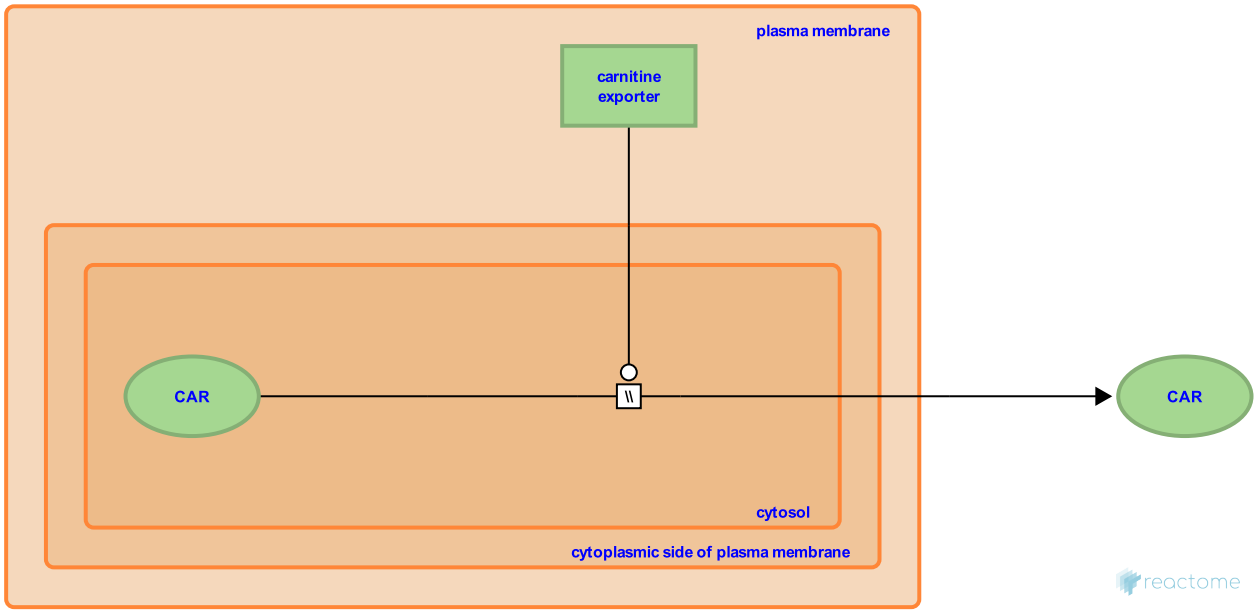
Location: Carnitine synthesis

Stable identifier: R-HSA-164967

Type: omitted

Compartments: cytosol, extracellular region

Inferred from: Unknown carnitine exporter transports CAR from the cytosol to the extracellular space (Rattus norvegicus)



Studies of carnitine (CAR) export from intact rat liver indicate that this process is mediated by a specific, saturable transporter molecule (Sandor et al. 1985). The transporter itself has not been identified, but its properties are distinct from those of OCTN2, the major transport protein responsible for carnitine uptake (Kispal et al. 1987). The existence of a human transport reaction (again without an identified transporter) is inferred from the rat one.

Preceded by: BBOX1:AscH-:Fe2+ dimer dioxygenates TEABT and 2OG to form CAR and SUCCA

Literature references

Kispal, G., Melegh, B., Alkonyi, I., Sandor, A. (1987). Enhanced uptake of carnitine by perfused rat liver following starvation. *Biochim Biophys Acta, 896*, 96-102. ↗

Sandor, A., Kispal, G., Melegh, B., Alkonyi, I. (1985). Release of carnitine from the perfused rat liver. *Biochim Biophys Acta, 835*, 83-91. ↗

Editions

2005-07-26	Authored, Edited	D'Eustachio, P.
2016-12-23	Reviewed	Jassal, B.

Table of Contents