Carnitine synthesis

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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.

18/11/2022
**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**


Reactome database release: 82

This document contains 1 pathway and 6 reactions (see Table of Contents)
Carnitine synthesis

Stable identifier: R-HSA-71262

Compartments: cytosol, mitochondrial matrix

Carnitine is required for the shuttling of fatty acids into the mitochondrial matrix and its deficiency is associated with metabolic diseases. It is abundant in a typical Western diet but can also be 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 & Hoppel 1998; Rebouche & Engel 1980; Vaz & Wanders 2002).

Literature references


Editions

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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) (Monfregola et al. 2005; Vaz et al. 2001).

Followed by: HTMLYS translocates from the mitochondrial matrix to the cytosol

Literature references


HTMLYS translocates from the mitochondrial matrix to the cytosol

**Location:** Carnitine synthesis

**Stable identifier:** R-HSA-8949413

**Type:** uncertain

**Compartments:** mitochondrial matrix, cytosol

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.

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

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

**Literature references**


**Editions**

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https://reactome.org
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 (3S)-3-hydroxy-N(6),N(6),N(6)-trimethyl-L-lysine(1+) (NTMLYS) to form glycine (Gly) and 4-trimethylammoniobutanal (TEABL). Ogata & Fujioka (1981) and Masuda et al. (1987) have each purified to apparent homogeneity a cytosolic enzyme that in the presence of tetrahydrofolate catalyzes the conversion of serine to glycine but that in its absence catalyzes the cleavage of L-allothreonine to glycine and an aldehyde. The native enzyme appears to be a tetramer. This rat enzyme and its human ortholog are inferred to mediate the cleavage of HTMLYS to yield TEABL and Gly in vivo (Vaz & Wanders 2002).

**Preceded by:** HTMLYS translocates from the mitochondrial matrix to the cytosol

**Followed by:** ALDH9A1 tetramer dehydrogenates TEABL to form TEABT

**Literature references**


**Editions**

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https://reactome.org
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+ (Koncitkova et al. 2019; Kurys et al. 1989; Vaz et al. 2000).

**Preceded by:** SHMT1 tetramercleaves HTMLYS to yield TEABL and Gly

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

**Literature references**


**Editions**

2022-07-19 Revised D'Eustachio, P.
**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; Tars et al. 2010; 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**


**Editions**

2022-07-19  Revised  D'Eustachio, P.

[https://reactome.org](https://reactome.org)
Unknown carnitine exporter transports CAR from the cytosol to the extracellular space

**Location:** Carnitine synthesis

**Stable identifier:** R-HSA-164967

**Type:** uncertain

**Compartments:** extracellular region, cytosol

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 that mediates this process in human tissues has not been identified, but its properties are distinct from those of SLC22A5 / OCTN2, the major transport protein responsible for carnitine uptake (Tamai et al. 1998; Wu et al. 1999). Indeed, as noted by Vaz & Wanders (2002), export of carnitine and its metabolites is probably mediated by another transport system, or possibly by passive diffusion.

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

**Literature references**


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