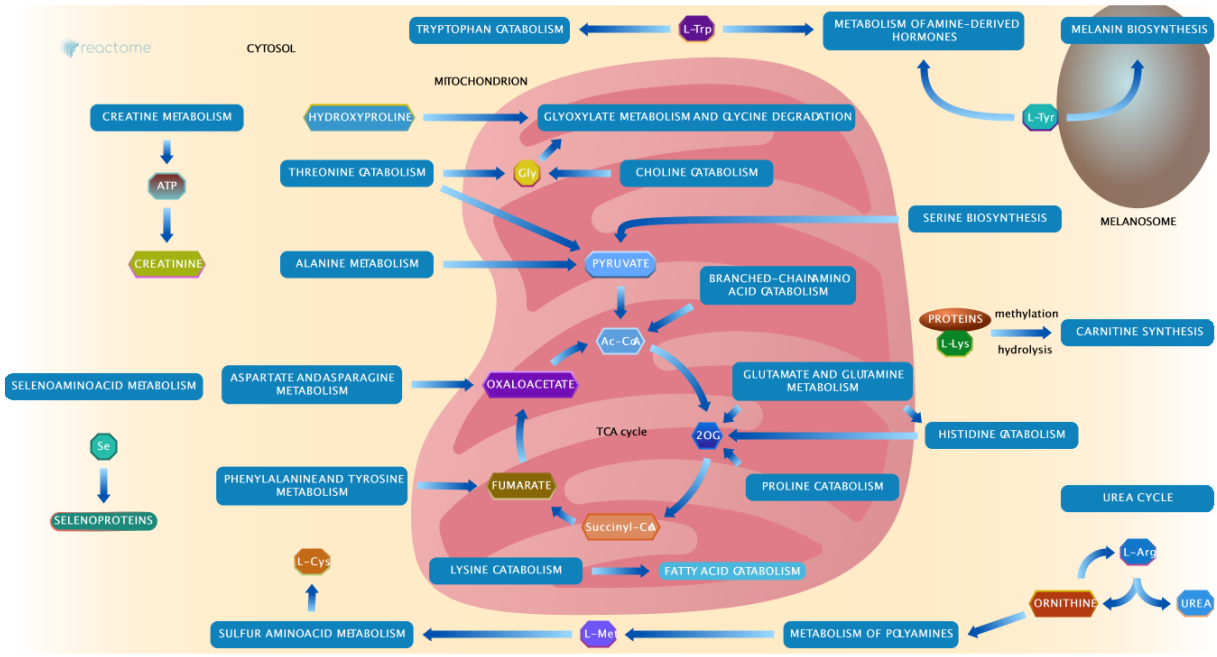
reactome

Metabolism of amino acids and derivatives



D'Eustachio, P., Gopinathrao, G., Ito, S., Jassal, B., Jupe, S., Rush, MG., Stephan, R., Williams, MG., d'Ischia, M.

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

16/08/2021

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. ↗

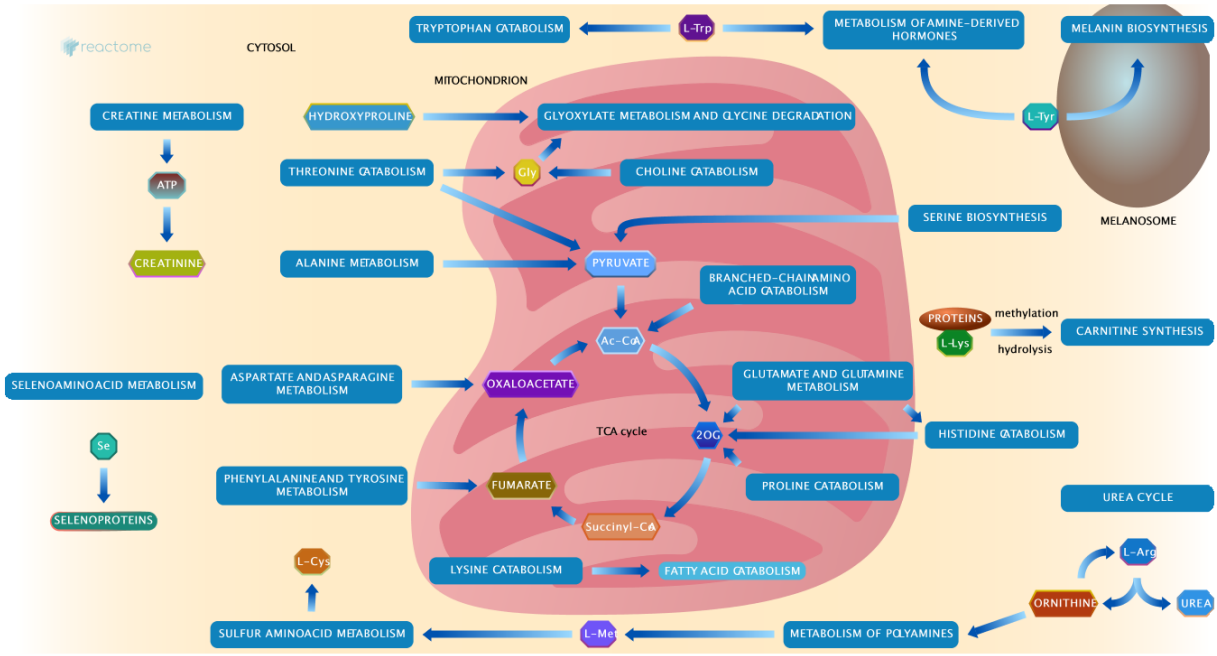
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 77

This document contains 22 pathways (see Table of Contents)

Metabolism of amino acids and derivatives ↗

Stable identifier: R-HSA-71291



Cellular metabolism of amino acids and related molecules includes the pathways for the catabolism of amino acids, the biosynthesis of the nonessential amino acids (alanine, arginine, aspartate, asparagine, cysteine, glutamate, glutamine, glycine, proline, and serine) and selenocysteine, the synthesis of urea, and the metabolism of carnitine, creatine, choline, polyamides, melanin, and amine-derived hormones. The metabolism of amino acids provides a balanced supply of amino acids for protein synthesis. In the fasting state, the catabolism of amino acids derived from breakdown of skeletal muscle protein and other sources is coupled to the processes of gluconeogenesis and ketogenesis to meet the body's energy needs in the absence of dietary energy sources. These metabolic processes also provide the nitrogen atoms for the biosynthesis of nucleotides and heme, annotated as separate metabolic processes (Felig 1975; Häussinger 1990; Owen et al. 1979).

Transport of these molecuels across lipid bilayer membranes is annotated separately as part of the module on "transmembrane transport of small molecules".

Literature references

Felig, P. (1975). Amino acid metabolism in man. *Annu. Rev. Biochem., 44*, 933-55. ↗

Owen, OE., Reichard, GA., Patel, MS., Boden, G. (1979). Energy metabolism in feasting and fasting. *Adv. Exp. Med. Biol., 111*, 169-88. ↗

Häussinger, D. (1990). Liver glutamine metabolism. *JPEN J Parenter Enteral Nutr, 14*, 56S-62S. ↗

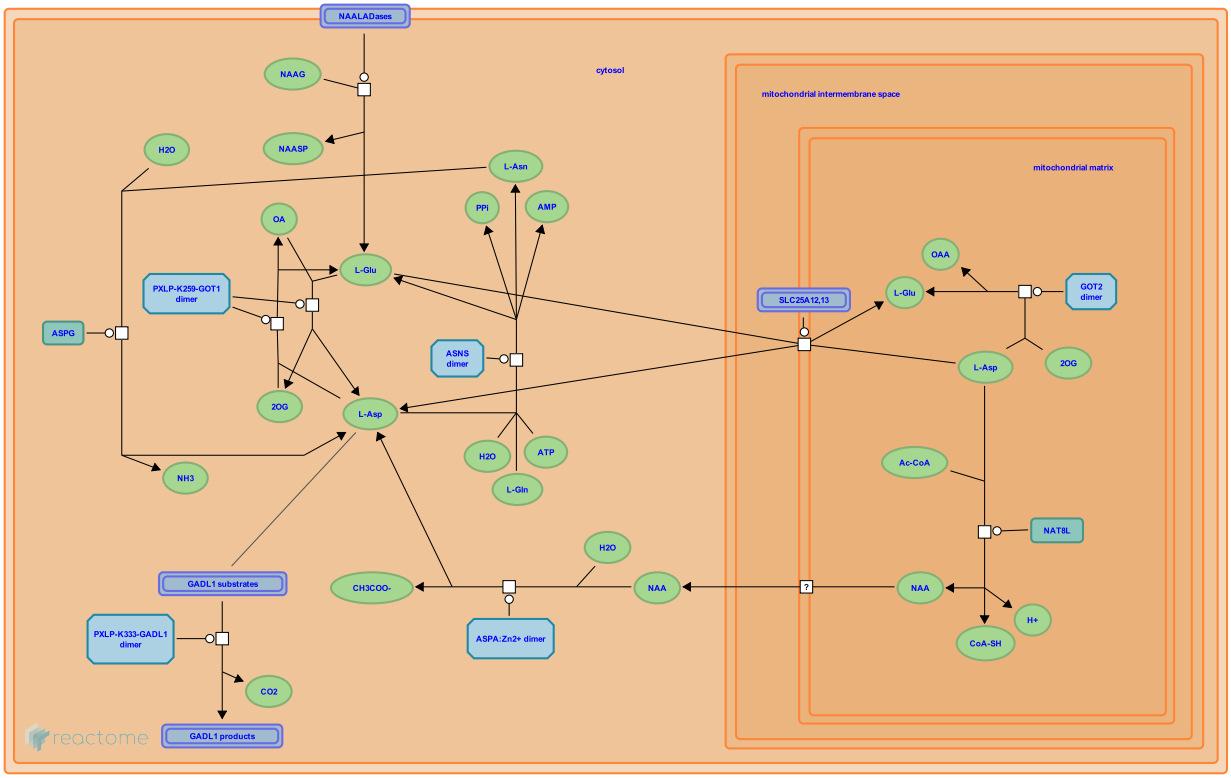
Editions

2003-11-03	Authored	D'Eustachio, P.
2010-02-18	Revised	D'Eustachio, P.
2021-05-18	Edited	D'Eustachio, P.

Aspartate and asparagine metabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-8963693



These reactions mediate the synthesis of aspartate and asparagine from glutamate, TCA cycle intermediates, and ammonia and and allow the utilization of carbon atoms from these amino acids for glucose synthesis under fasting conditions (Felig 1975; Owen et al. 1979).

Literature references

Felig, P. (1975). Amino acid metabolism in man. *Annu. Rev. Biochem., 44*, 933-55. ↗

Owen, OE., Reichard, GA., Patel, MS., Boden, G. (1979). Energy metabolism in feasting and fasting. *Adv. Exp. Med. Biol., 111*, 169-88. ↗

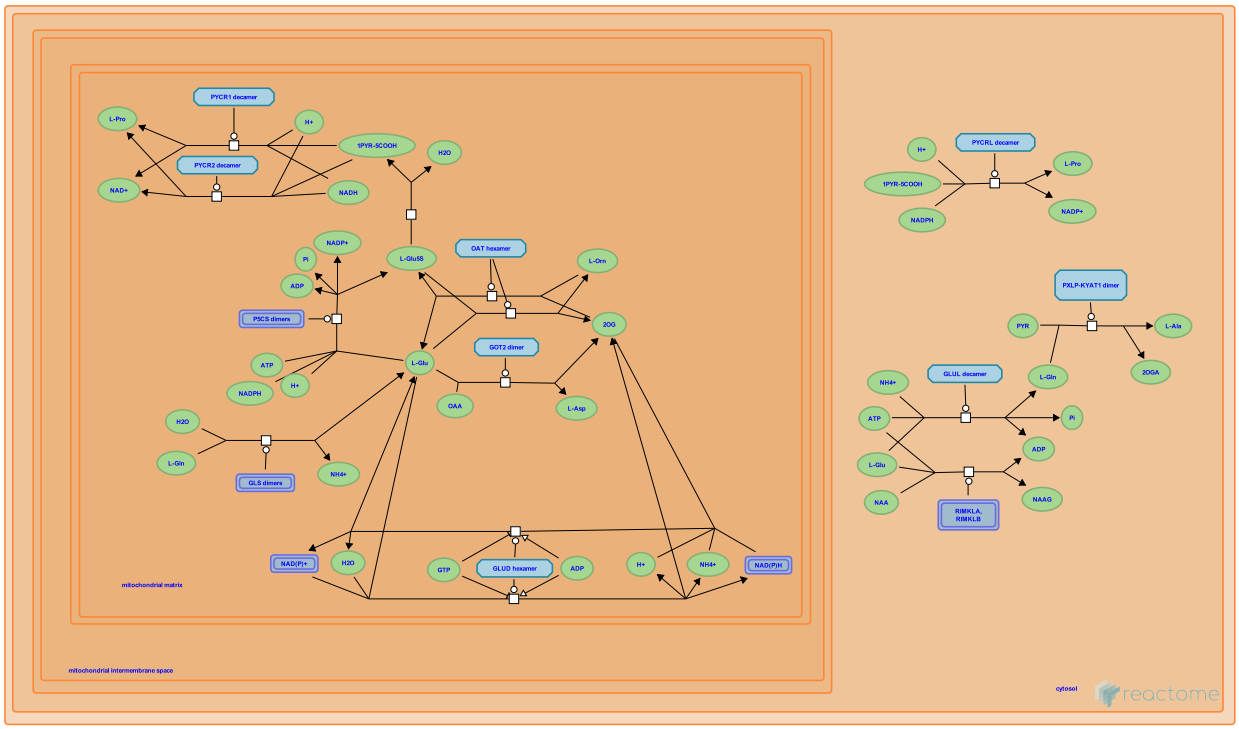
Editions

2017-02-10	Authored	Jassal, B.
2017-03-22	Edited	D'Eustachio, P.

Glutamate and glutamine metabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-8964539



These reactions mediate the synthesis of glutamate and glutamine from ammonia and TCA cycle intermediates and allow the utilization of the carbon atoms from these amino acids for glucose synthesis under fasting conditions. These reactions also provide a means to collect nitrogen, both as ammonia and as amino groups, and direct it towards urea synthesis. Transamination, the conversion of an amino acid to the corresponding alpha-keto acid coupled to the conversion of a molecule of 2-oxoglutarate (alpha-ketoglutarate) to glutamate, is the first step in the catabolism of most amino acids. Transamination reactions are freely reversible so they also provide a means to balance concentrations of various amino acids and 2-oxo (alpha-keto) acids in the cell (Felig 1975; Häussinger 1990; Owen et al. 1979).

Literature references

Felig, P. (1975). Amino acid metabolism in man. *Annu. Rev. Biochem., 44*, 933-55. ↗

Häussinger, D. (1990). Liver glutamine metabolism. *JPEN J Parenter Enteral Nutr, 14*, 56S-62S. ↗

Owen, OE., Reichard, GA., Patel, MS., Boden, G. (1979). Energy metabolism in feasting and fasting. *Adv. Exp. Med. Biol., 111*, 169-88. ↗

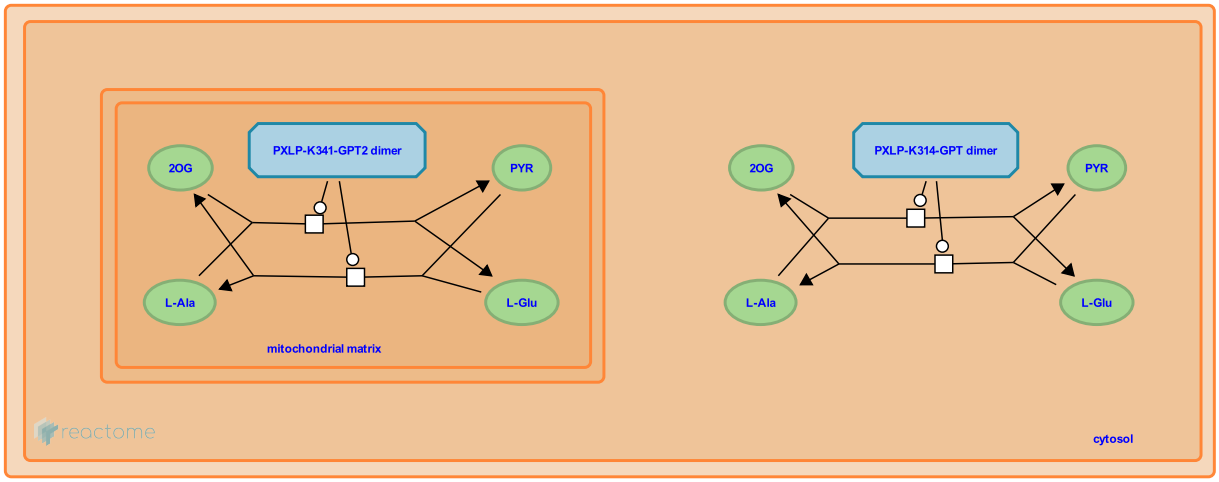
Editions

2017-02-10	Authored	Jassal, B.
2017-03-22	Edited	D'Eustachio, P.

Alanine metabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-8964540



The interconversion of alanine and pyruvate, annotated here, is a key connection among the processes of protein turnover and energy metabolism in the human body (Felig 1975; Owen et al. 1979).

Literature references

Felig, P. (1975). Amino acid metabolism in man. *Annu. Rev. Biochem., 44*, 933-55. ↗

Owen, OE., Reichard, GA., Patel, MS., Boden, G. (1979). Energy metabolism in feasting and fasting. *Adv. Exp. Med. Biol., 111*, 169-88. ↗

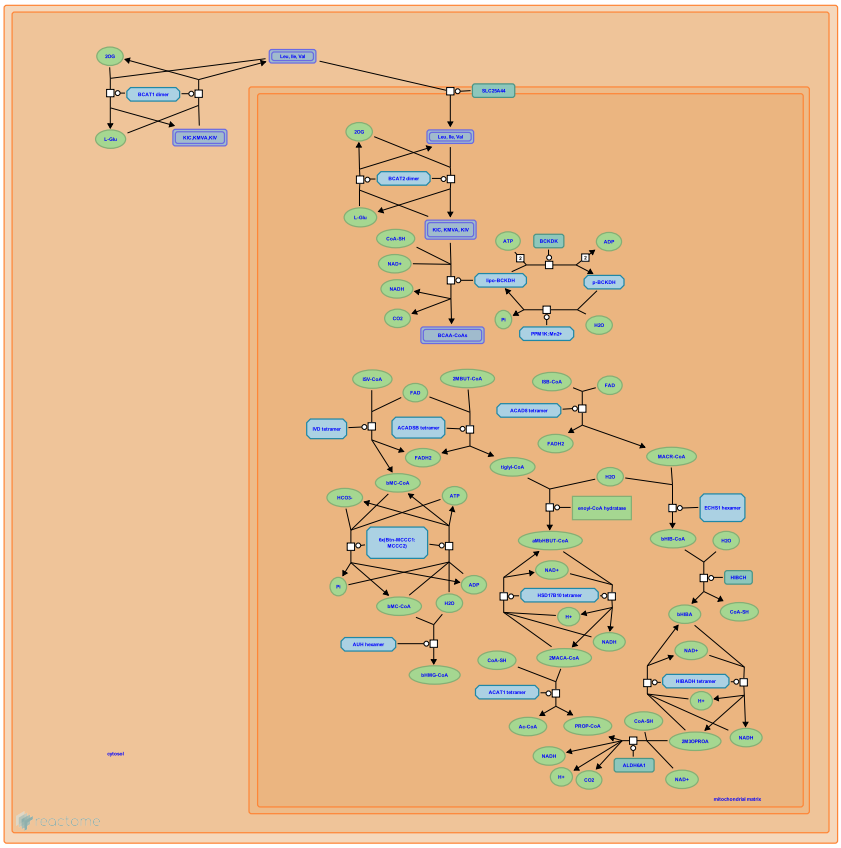
Editions

2017-02-10	Authored	Jassal, B.
2017-03-22	Edited	D'Eustachio, P.

Branched-chain amino acid catabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-70895



The branched-chain amino acids, leucine, isoleucine, and valine, are all essential amino acids (i.e., ones required in the diet). They are major constituents of muscle protein. The breakdown of these amino acids starts with two common steps catalyzed by enzymes that act on all three amino acids: reversible transamination by branched-chain amino acid aminotransferase, and irreversible oxidative decarboxylation by the branched-chain ketoacid dehydrogenase complex. Isovaleryl-CoA is produced from leucine by these two reactions, alpha-methylbutyryl-CoA from isoleucine, and isobutyryl-CoA from valine. These acyl-CoA's undergo dehydrogenation, catalyzed by three different but related enzymes, and the breakdown pathways then diverge. Leucine is ultimately converted to acetyl-CoA and acetoacetate; isoleucine to acetyl-CoA and succinyl-CoA; and valine to succinyl-CoA. Under fasting conditions, substantial amounts of all three amino acids are generated by protein breakdown. In muscle, the final products of leucine, isoleucine, and valine catabolism can be fully oxidized via the citric acid cycle; in liver they can be directed toward the synthesis of ketone bodies (acetoacetate and acetyl-CoA) and glucose (succinyl-CoA) (Neinast et al. 2019).

Literature references

Neinast, M., Murashige, D., Arany, Z. (2019). Branched Chain Amino Acids. *Annu. Rev. Physiol., 81*, 139-164. ↗

Editions

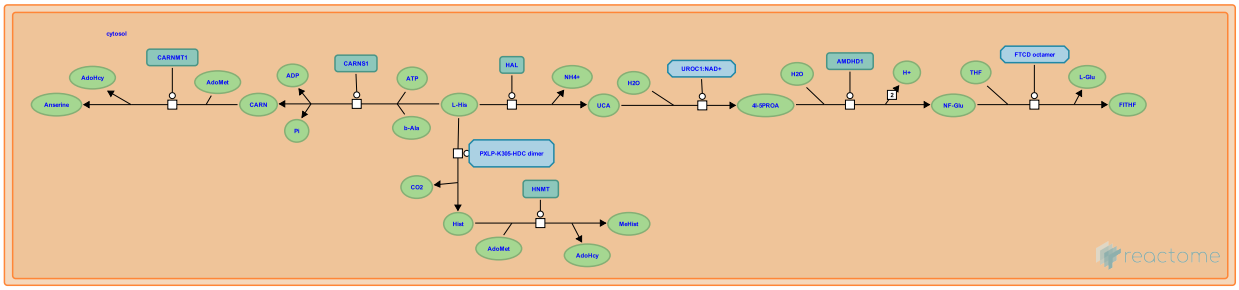
2003-06-24	Authored	D'Eustachio, P.
2010-02-18	Revised	D'Eustachio, P.
2020-01-03	Revised	D'Eustachio, P.
2021-05-18	Edited	D'Eustachio, P.

Histidine catabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-70921

Compartments: cytosol



The major pathway of histidine catabolism, annotated here, proceeds in four steps to yield glutamate and, in the process, convert one molecule of tetrahydrofolate to 5-formiminotetrahydrofolate (Morris et al. 1972). Histidine can also be decarboxylated to form histamine. Histidine can also be used to form carnosine (beta-alanyl-L-histidine), an abundant dipeptide in skeletal muscle and brain of most vertebrates.

Literature references

Morris, ML., Lee, SC., Harper, AE. (1972). Influence of differential induction of histidine catabolic enzymes on histidine degradation in vivo. *J Biol Chem, 247*, 5793-804. ↗

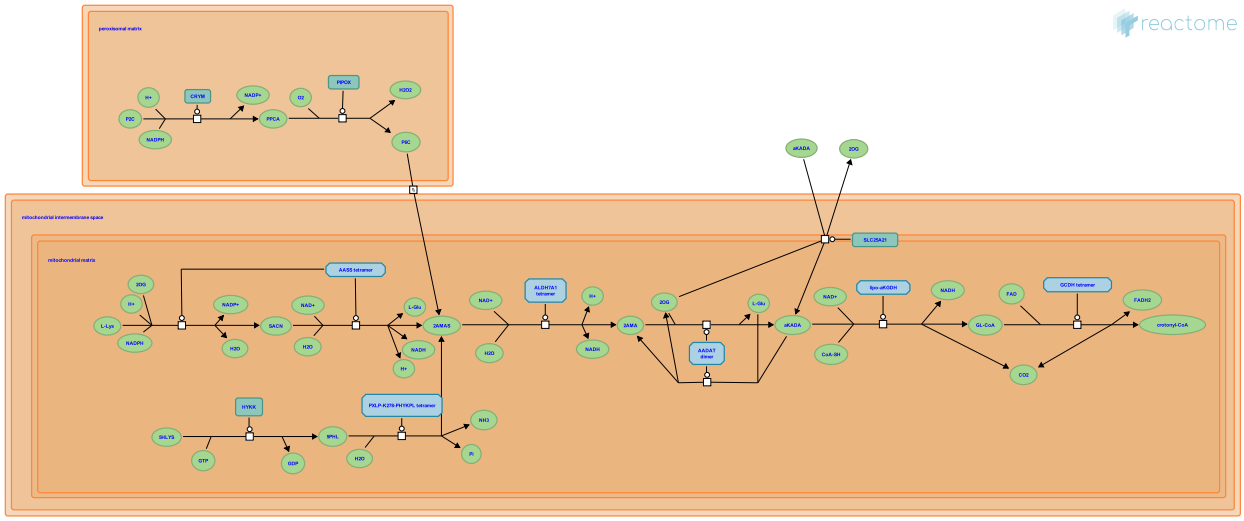
Editions

2003-06-24	Authored, Edited	D'Eustachio, P.
2010-02-18	Revised	D'Eustachio, P.

Lysine catabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-71064



In humans, most catabolism of L-lysine normally proceeds via a sequence of seven reactions which feeds into the pathway for fatty acid catabolism. In the first two reactions, catalyzed by a single enzyme complex, lysine is combined with alpha-ketoglutarate to form saccharopine, which in turn is cleaved and oxidized to yield glutamate and alpha-ketoadipic semialdehyde. The latter molecule is further oxidized to alpha-ketoadipate. Alpha-ketoadipate is oxidatively decarboxylated by the alpha-ketoglutarate dehydrogenase complex (the same enzyme complex responsible for the conversion of alpha-ketoglutarate to succinyl-CoA in the citric acid cycle), yielding glutaryl-CoA. Glutaryl-CoA is converted to crotonyl-CoA, crotonyl-CoA is converted to beta-hydroxybutyryl-CoA, and beta-hydroxybutyryl-CoA is converted to acetoacetyl-CoA. The products of lysine catabolism are thus exclusively ketogenic; i.e., under starvation conditions they can be used for the synthesis of ketone bodies, beta-hydroxybutyrate and acetoacetate, but not for the net synthesis of glucose (Cox 2001; Goodman and Freeman 2001).

Literature references

Scriver, CR., Beaudet, AL., Valle, D., Sly, WS. (2001). Errors of lysine metabolism, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1965-1970.

Scriver, CR., Beaudet, AL., Valle, D., Sly, WS. (2001). Organic acidemias due to defects in lysine oxidation: 2-ketoadipic acidemia and glutaric acidemia, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 2195-2204.

Markovitz, PJ., Chuang, DT., Cox, RP. (1984). Familial hyperlysinemias. Purification and characterization of the bifunctional aminoadipic semialdehyde synthase with lysine-ketoglutarate reductase and saccharopine dehydrogenase activities. *J Biol Chem, 259*, 11643-6. ↗

Goh, DL., Patel, A., Thomas, GH., Salomons, GS., Schor, DS., Jakobs, C. et al. (2002). Characterization of the human gene encoding alpha-aminoadipate aminotransferase (AADAT). *Mol Genet Metab, 76*, 172-80. ↗

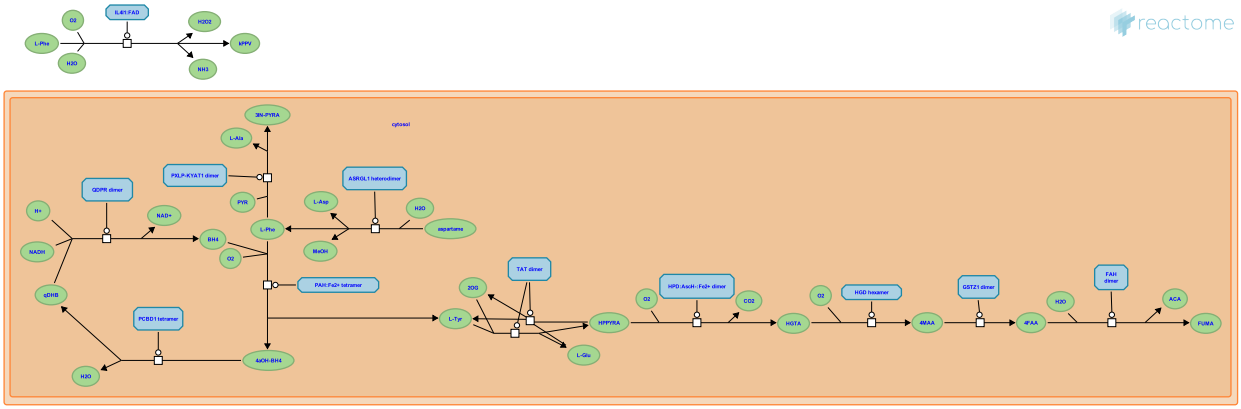
Editions

2003-06-24	Authored	D'Eustachio, P.
2010-02-18	Revised	D'Eustachio, P.
2021-05-18	Edited	D'Eustachio, P.

Phenylalanine and tyrosine metabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-8963691



The hydroxylation of phenylalanine, an essential amino acid, to form tyrosine is a major source of the latter amino acid in the body under normal conditions and is also the first step in phenylalanine catabolism. To continue the catabolic process, tyrosine is transaminated to 3-(4-hydroxyphenyl)pyruvate which is broken down to fumarate and acetoacetate (Blau et al. 2001; Mitchell et al. 2001).

Literature references

Scriver, CR., Beaudet, AL., Valle, D., Sly, WS. (2001). Disorders of tetrahydrobiopterin and related biogenic amines, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1725-1776.

Scriver, CR., Beaudet, AL., Valle, D., Sly, WS. (2001). Hypertyrosinemia, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1777-1805.

Editions

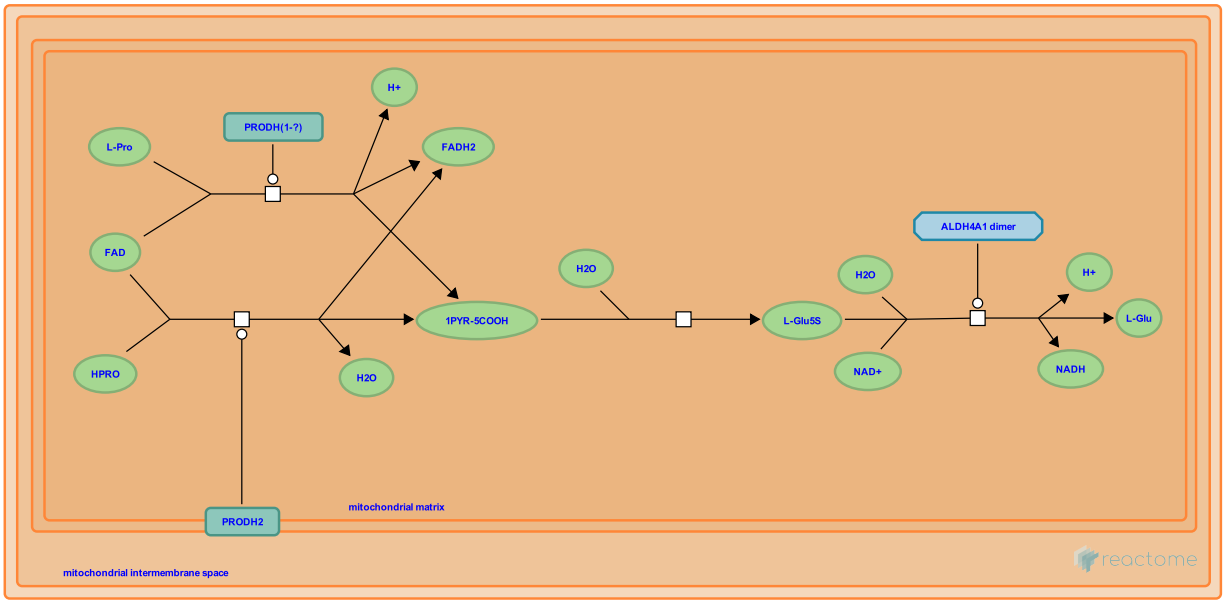
2017-02-10	Authored	Jassal, B.
2017-03-22	Edited	D'Eustachio, P.

Proline catabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-70688

Compartments: mitochondrion



Proline is catabolized in two steps to yield L-glutamate gamma-semialdehyde, which can react further with glutamate to yield ornithine and alpha-ketoglutarate (annotated as a reaction of amino acid synthesis and interconversion) or with NAD+ to yield glutamate and NADH + H+ (Phang et al. 2001).

Literature references

Scriver, CR., Beaudet, AL., Valle, D., Sly, WS. (2001). Disorders of proline and hydroxyproline metabolism, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1821-1838.

Editions

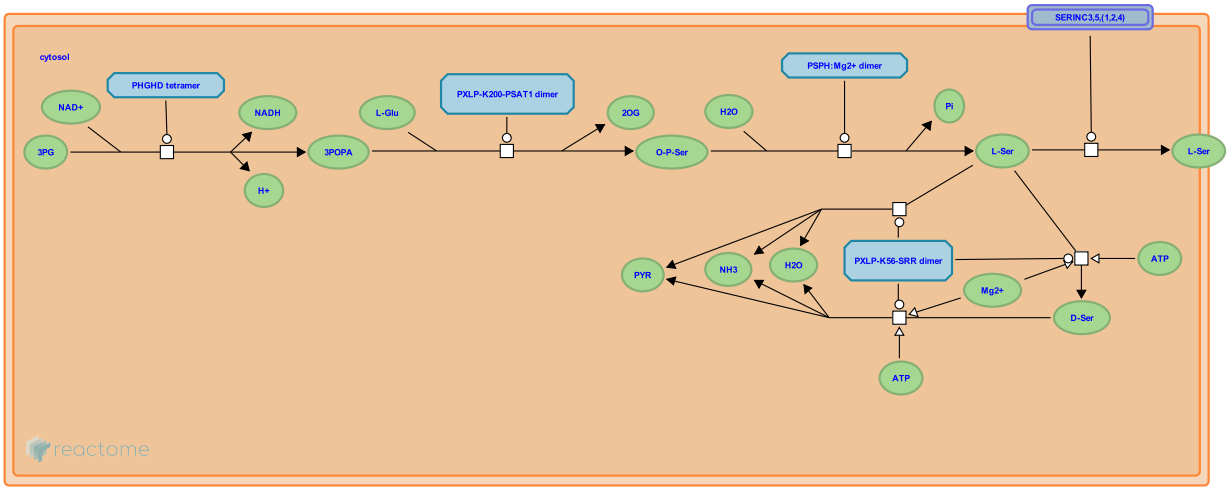
2003-06-24	Authored, Edited	D'Eustachio, P.
2010-02-18	Revised	D'Eustachio, P.

Serine biosynthesis ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-977347

Compartments: cytosol



L-Serine is needed in human brain in large amounts as precursor to important biomolecules such as nucleotides, phospholipids and the neurotransmitters glycine and D-serine. The pathway for its synthesis starts with 3-phosphoglycerate and it later needs glutamate as an amination agent. Deficiencies in the participating enzymes lead to severe neurological symptoms that are treatable with serine if treatment starts early (de Koning & Klomp 2004).

Literature references

de Koning, TJ., Klomp, LW. (2004). Serine-deficiency syndromes. *Curr Opin Neurol, 17*, 197-204. ↗

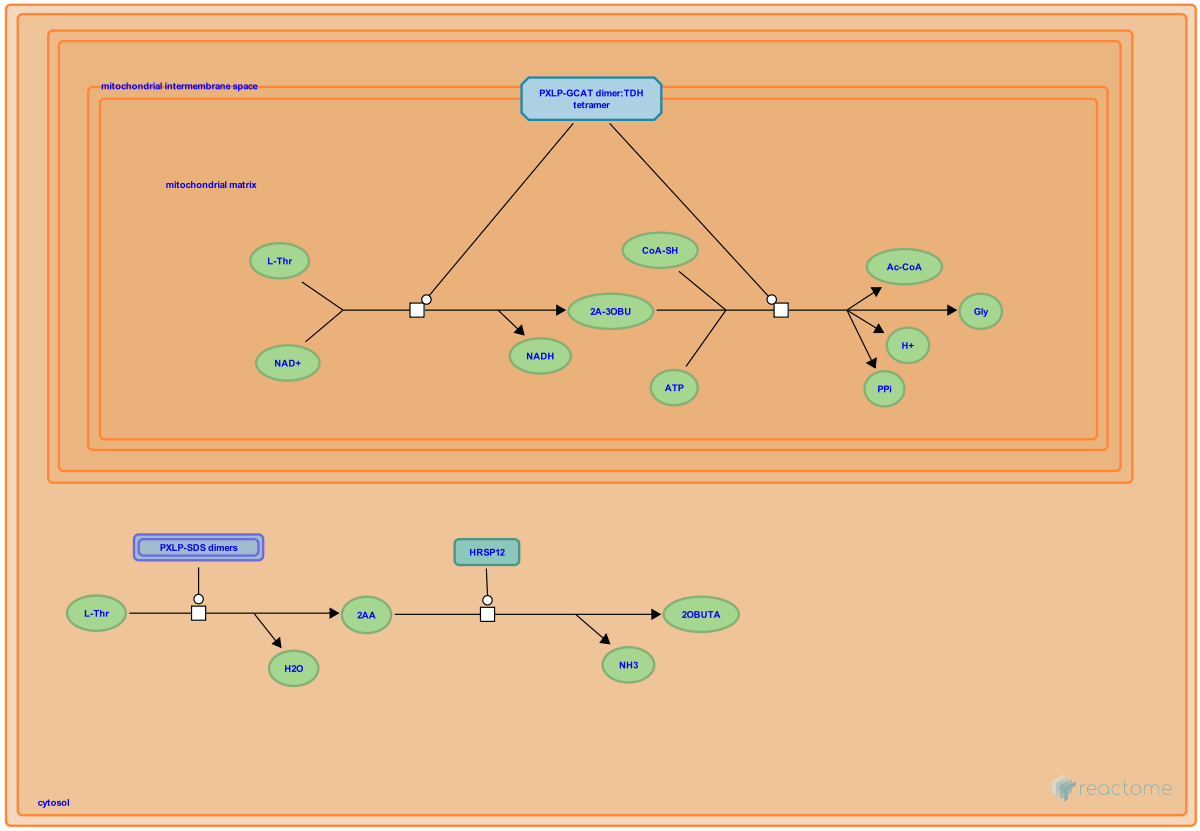
Editions

2010-10-16	Authored	Stephan, R.
2010-10-18	Edited	Jassal, B.
2011-10-26	Reviewed	D'Eustachio, P.

Threonine catabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-8849175



The degradation of L-threonine to glycine in both prokaryotes and eukaryotes takes place through a two-step biochemical pathway in mitochondria (Dale 1978). In the first step, L-threonine is oxidised to 2-amino-3-oxobutanoate. This reaction is catalysed by mitochondrial L-threonine 3-dehydrogenase tetramer (TDH tetramer). In the second step, mitochondrial 2-amino-3-ketobutyrate coenzyme A ligase (GCAT, aka KBL) catalyses the reaction between 2-amino-3-oxobutanoate and coenzyme A to form glycine and acetyl-CoA. GCAT resides on the mitochondrial inner membrane in dimeric form and requires pyridoxal 5-phosphate (PXLP) as cofactor. GCAT is thought to exist on the mitochondrial inner membrane in complex with TDH. With these two enzymes located together, it stops the rapid and spontaneous decarboxylation of 2A-3OBU to aminoacetone and carbon dioxide and instead, results in glycine formation (Tressel et al. 1986).

Literature references

Tressel, T., Thompson, R., Zieske, LR., Menendez, MI., Davis, L. (1986). Interaction between L-threonine dehydrogenase and aminoacetone synthetase and mechanism of aminoacetone production. *J. Biol. Chem., 261*, 16428-37. ↗

Dale, RA. (1978). Catabolism of threonine in mammals by coupling of L-threonine 3-dehydrogenase with 2-amino-3-oxobutyrate-CoA ligase. *Biochim. Biophys. Acta, 544*, 496-503. ↗

Editions

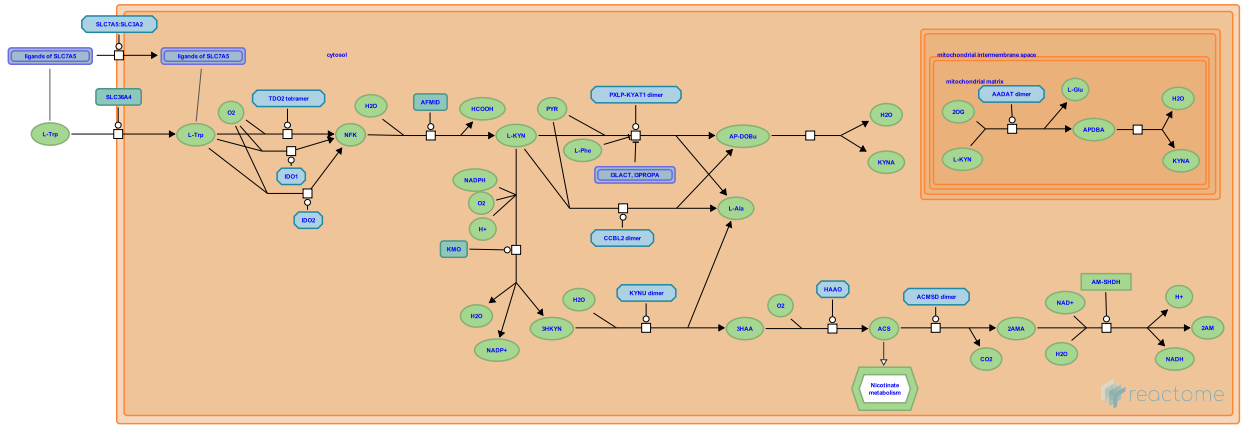
2015-12-14	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

Tryptophan catabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-71240

Compartments: cytosol



Tryptophan is catabolized in seven steps to yield aminomuconate. Intermediates in this process are also used in the synthesis of serotonin and kynurenine (Peters 1991).

Literature references

Peters, JC. (1991). Tryptophan nutrition and metabolism: an overview. *Adv Exp Med Biol, 294*, 345-58. ↗

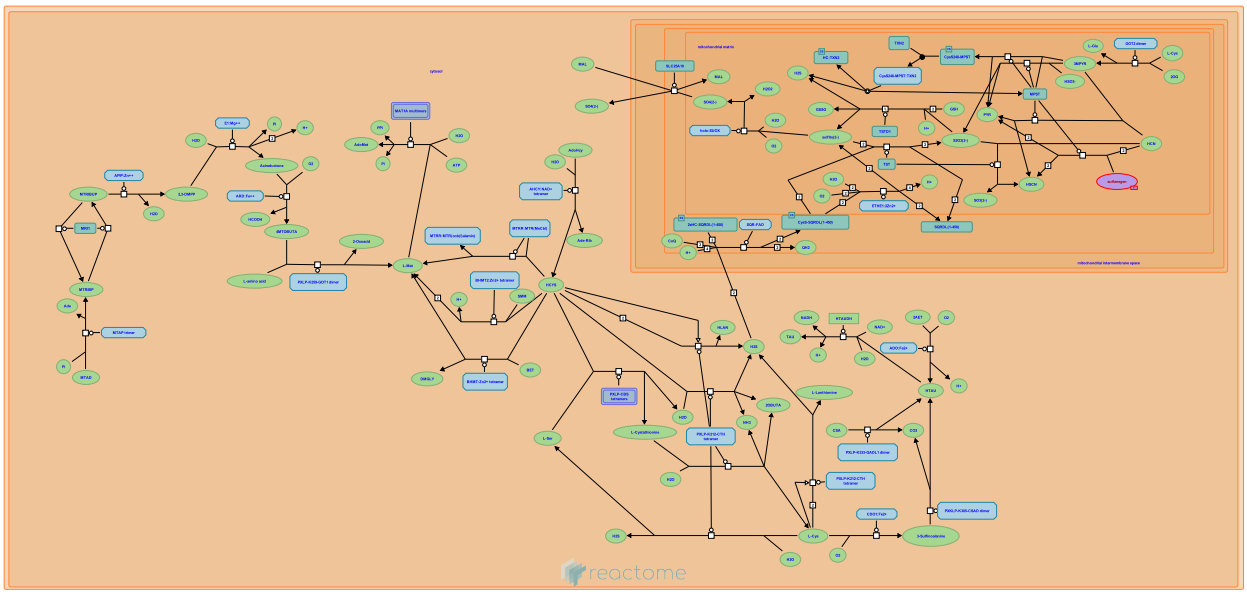
Editions

2005-07-20	Authored, Edited	D'Eustachio, P.

Sulfur amino acid metabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-1614635



The main sulfur amino acids are methionine, cysteine, homocysteine and taurine. Of these, the first two are proteinogenic.

This group of reactions contains all processes that 1) break down sulfur amino acids, 2) interconvert between them, and 3) synthesize them from solved sulfide which comes from sulfate assimilation and reduction. Only plants and microorganisms employ all processes. Humans cannot de novo synthesize any sulfur amino acid, nor convert cysteine to methionine (Brosnan & Brosnan, 2006).

Literature references

Brosnan, JT., Brosnan, ME. (2006). The sulfur-containing amino acids: an overview. *J Nutr, 136*, 1636S-1640S. ↗

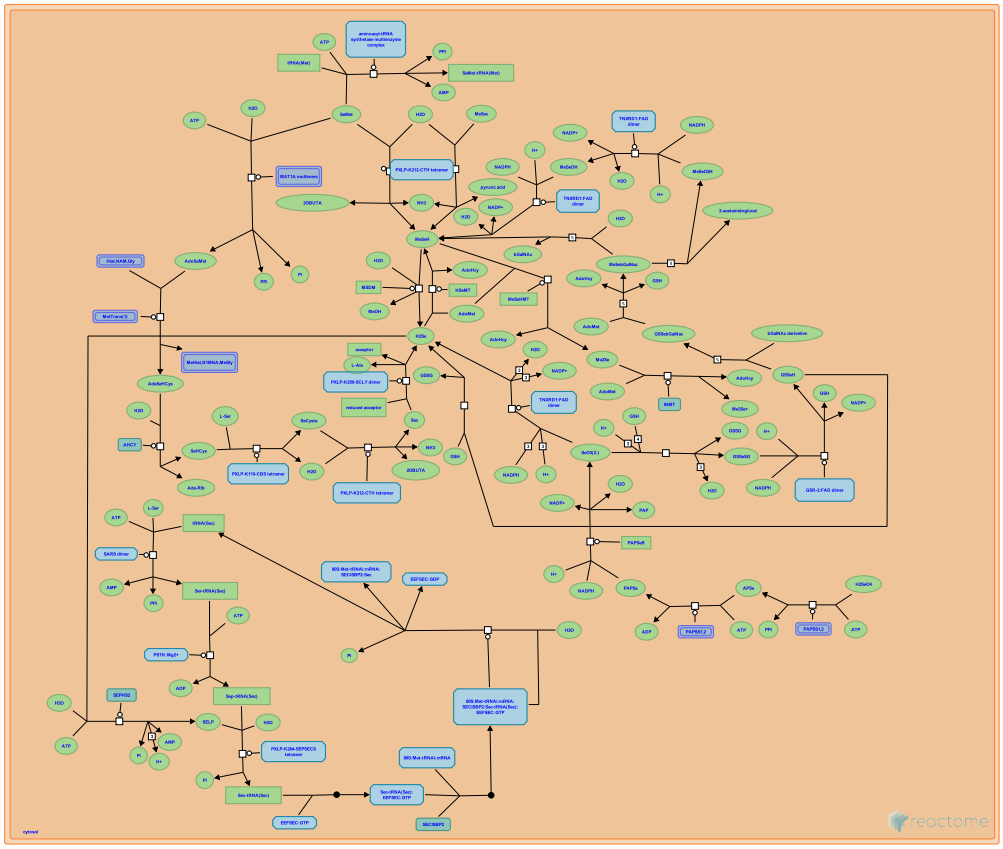
Editions

2010-10-24	Authored	Stephan, R.
2011-09-29	Edited	Jassal, B.
2011-10-13	Reviewed	D'Eustachio, P.

Selenoamino acid metabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-2408522



Selenium (Se) is a trace element essential for the normal function of the body. Selenoamino acids are defined as those amino acids where selenium has been substituted for sulphur. Selenium and sulphur share many chemical properties and so the substitution of normal amino acids with selenoamino acids has little effect on protein structure and function. Both inorganic (selenite, SeO3(2-); and selenate, SeO4(2-)) and organic (selenocysteine, Sec; and selenomethionine, SeMet) forms of selenium can be introduced in the diet where they are transformed into the intermediate selenide (Se(2-)) and then utilized for the *de novo* synthesis of Sec through a phosphorylated intermediate in a tRNA-dependent fashion. The final step of Sec formation is catalyzed by O-phosphoseryl-tRNA:selenocysteinyl-tRNA synthase (SEPSECS) that converts phosphoseryl-tRNA(Sec) to selenocysteinyl-tRNA(Sec).

All nutritional selenium is metabolised into selenide directly or through methylselenol (MeSeH). Sec liberated from selenoproteins is transformed to Se(2-) by selenocysteine lyase (SCLY). SeMet liberated from general proteins and from free SeMet sources is transformed into Se(2-) either through MeSeH by cystathionine gamma-lyase (CTH) followed by demethylation (SeMet to CH3SeH to H2Se), or through Sec by SCLY after the trans-selenation pathway (SeMet to Sec to H2Se). MeSec is hydrolysed into MeSeH by CTH. Methylseleninic acid (MeSeO2H) is reduced to methylselenol. MeSeH is demethylated to Se(2-) for further utilization for selenoprotein synthesis or oxidised to selenite (SeO3(2-)) for excretion in the form of selenosugar. Additionally, MeSeH is further methylated to dimethylselenide (Me2Se) and trimethylselenonium (Me3Se+) for excretion.

Literature references

Fairweather-Tait, SJ., Bao, Y., Broadley, MR., Collings, R., Ford, D., Hesketh, JE. et al. (2011). Selenium in human health and disease. *Antioxid. Redox Signal., 14*, 1337-83. ↗

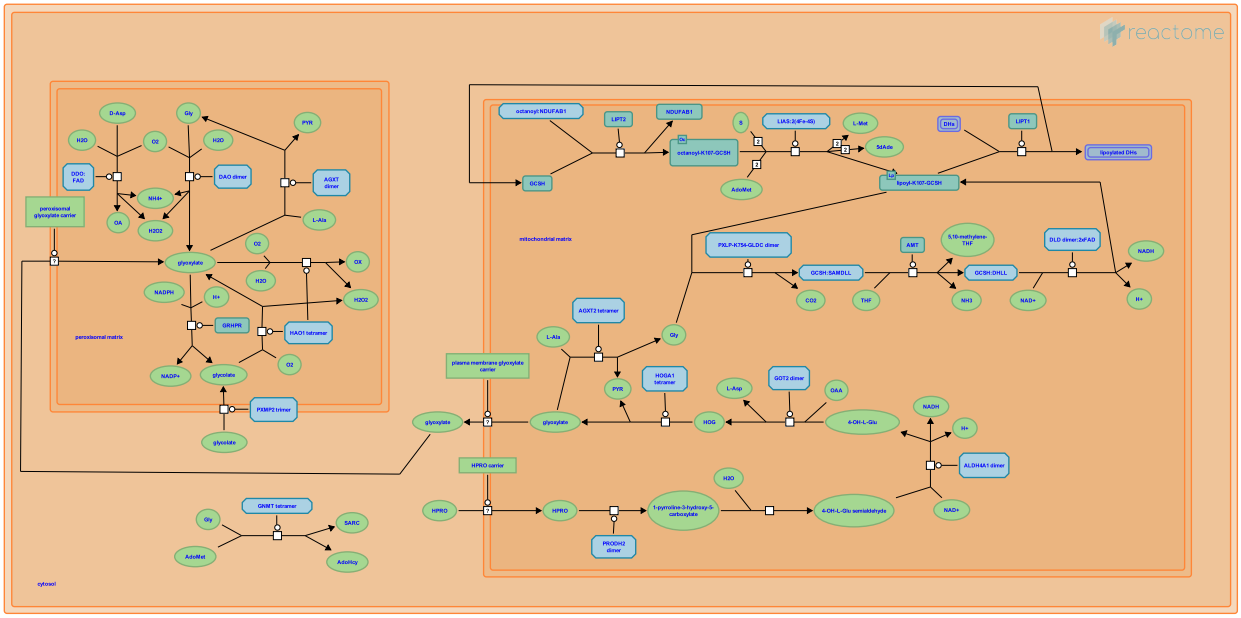
Editions

2014-05-06	Authored	Williams, MG.
2015-08-29	Edited	D'Eustachio, P.
2015-08-30	Reviewed	Rush, MG.

Glyoxylate metabolism and glycine degradation ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-389661



Glyoxylate is generated in the course of glycine and hydroxyproline catabolism and can be converted to oxalate. In humans, this process takes place in the liver. Defects in two enzymes of glyoxylate metabolism, alanine:glyoxylate aminotransferase (AGXT) and glycerate dehydrogenase/glyoxylate reductase (GRHPR), are associated with pathogenic overproduction of oxalate (Danpure 2005). The reactions that interconvert glycine, glycolate, and glyoxylate and convert glyoxylate to oxalate have been characterized in molecular detail in humans. A reaction sequence for the conversion of hydroxyproline to glyoxylate has been inferred from studies of partially purified extracts of rat and bovine liver but the enzymes involved in the corresponding human reactions have not been identified.

Literature references

Danpure, CJ. (2005). Primary hyperoxaluria: from gene defects to designer drugs?. *Nephrol Dial Transplant, 20*, 1525-9 . ↗

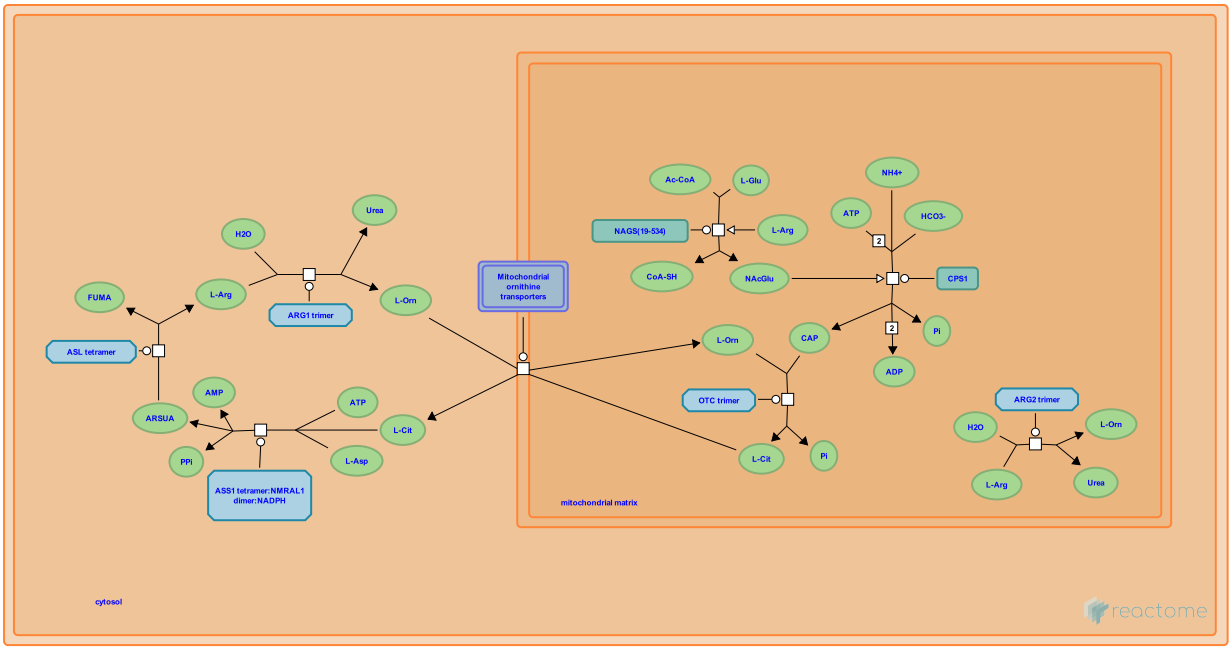
Editions

2009-01-12	Authored	D'Eustachio, P.
2009-03-03	Edited	D'Eustachio, P.
2009-03-03	Reviewed	Jassal, B.

Urea cycle ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-70635



The urea cycle yields urea, the major form in which excess nitrogen is excreted from the human body, and the amino acid arginine (Brusilow and Horwich 2001). It consists of four reactions: that of ornithine and carbamoyl phosphate to form citrulline, of citrulline and aspartate to form argininosuccinate, the cleavage of argininosuccinate to yield fumarate and arginine, and the cleavage of arginine to yield urea and re-form ornithine. The carbamoyl phosphate consumed in this cycle is synthesized in the mitochondria from bicarbonate and ammonia, and this synthesis in turn is dependent on the presence of N-acetylglutamate, which allosterically activates carbamoyl synthetase I enzyme. The synthesis of N-acetylglutamate is stimulated by high levels of arginine. Increased levels of free amino acids, indicated by elevated arginine levels, thus stimulate urea synthesis.

Two enzymes catalyze the hydrolysis of arginine to yield ornithine and urea. Cytosolic ARG1 is the canonical urea cycle enzyme. Mitochondrial ARG2 likewise catalyzes urea production from arginine and may have a substantial sparing effect in patients lacking ARG1 enzyme, so its reaction is annotated here although the role of ARG2 under normal physiological conditions remains unclear.

Literature references

Scriver, CR., Beaudet, AL., Valle, D., Sly, WS. (2001). Urea cycle enzymes, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1909-1963.

Editions

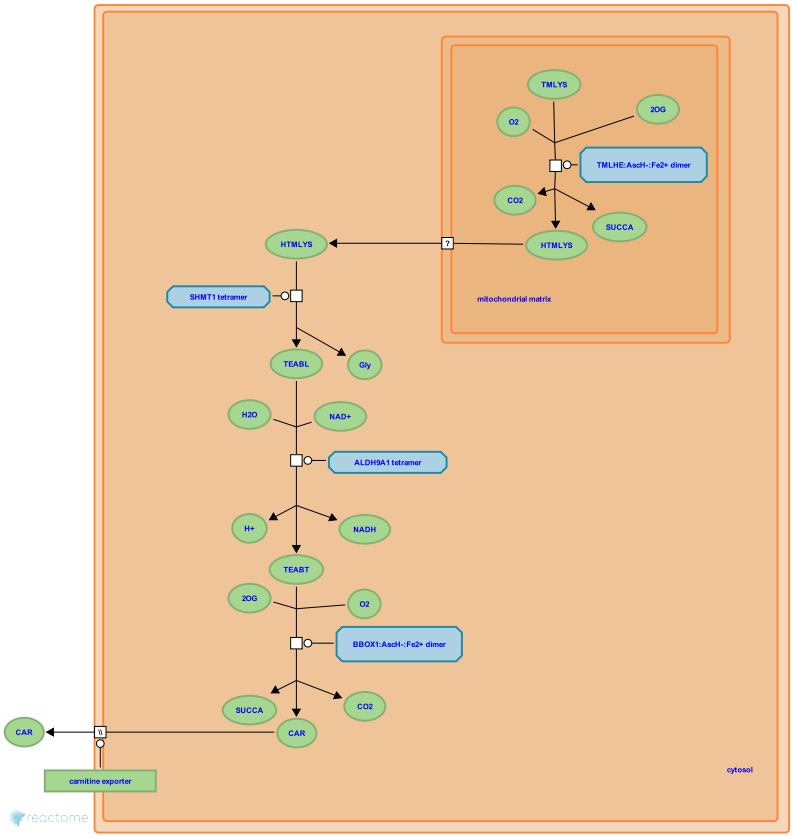
2003-06-24	Authored	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.
2021-05-18	Edited	D'Eustachio, P.

Carnitine synthesis ↗

Location: Metabolism of amino acids and derivatives

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

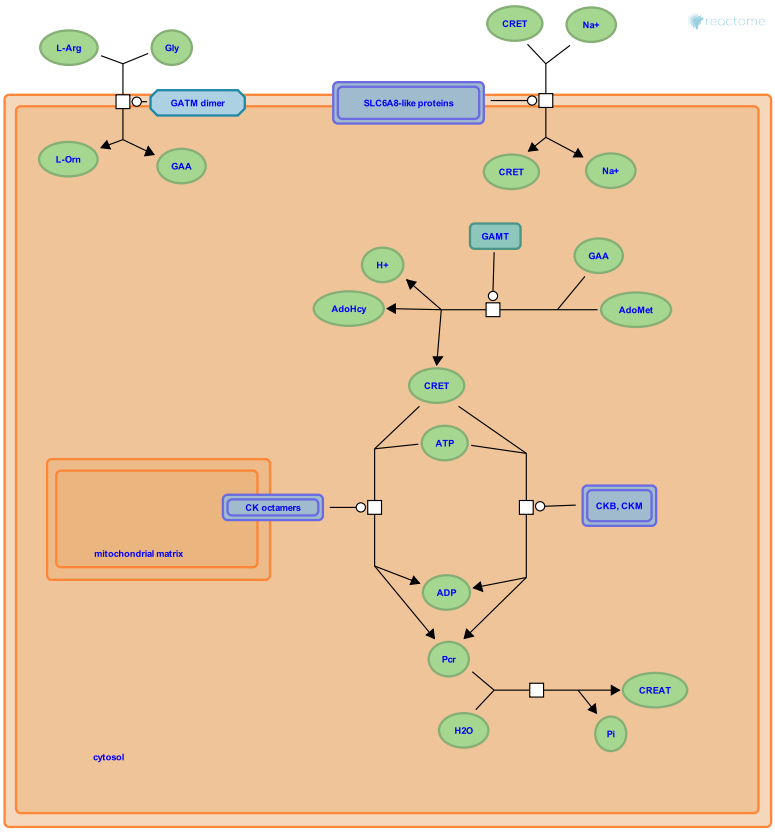
2021-05-18	Edited	D'Eustachio, P.

Creatine metabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-71288

Compartments: mitochondrial inner membrane, mitochondrial intermembrane space, cytosol, plasma membrane



In humans, creatine is synthesized primarily in the liver and kidney, from glycine, arginine, and S-adenosylmethionine, in a sequence of two reactions. From the liver, creatine is exported to tissues such as skeletal muscle and brain, where it undergoes phosphorylation and serves as a short-term energy store. The mechanism by which creatine leaves producer tissues is unclear, but its uptake by consumer tissues is mediated by the SLC6A8 transporter.

Once formed, phosphocreatine undergoes a slow spontaneous reaction to form creatinine, which is excreted from the body.

Literature references

Wyss, M., Kaddurah-Daouk, R. (2000). Creatine and creatinine metabolism. *Physiol Rev, 80*, 1107-213. ↗

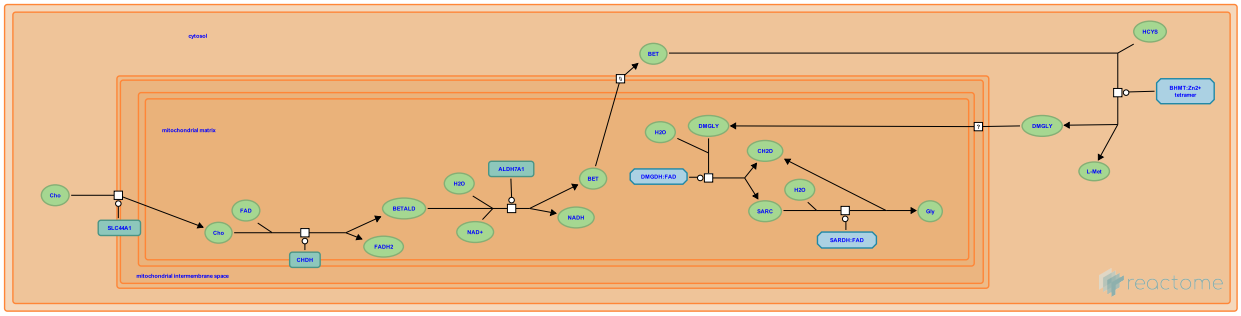
Editions

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

Choline catabolism ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-6798163



Choline is an essential water-soluble nutrient in humans, serving as a precursor of phospholipids and the neurotransmitter acetylcholine. It is often associated with B vitamins based on its chemical structure but it isn't an official B vitamin. Its oxidation to betaine provides a link to folate-dependent, one-carbon metabolism where betaine is a methyl donor in the methionine cycle. Betaine is further metabolised to dimethylglycine which is cleared by the kidney (Ueland 2011, Hollenbeck 2012).

Literature references

Ueland, PM. (2011). Choline and betaine in health and disease. *J. Inherit. Metab. Dis., 34*, 3-15. ↗

Hollenbeck, CB. (2012). An introduction to the nutrition and metabolism of choline. *Cent Nerv Syst Agents Med Chem, 12*, 100-13. ↗

Editions

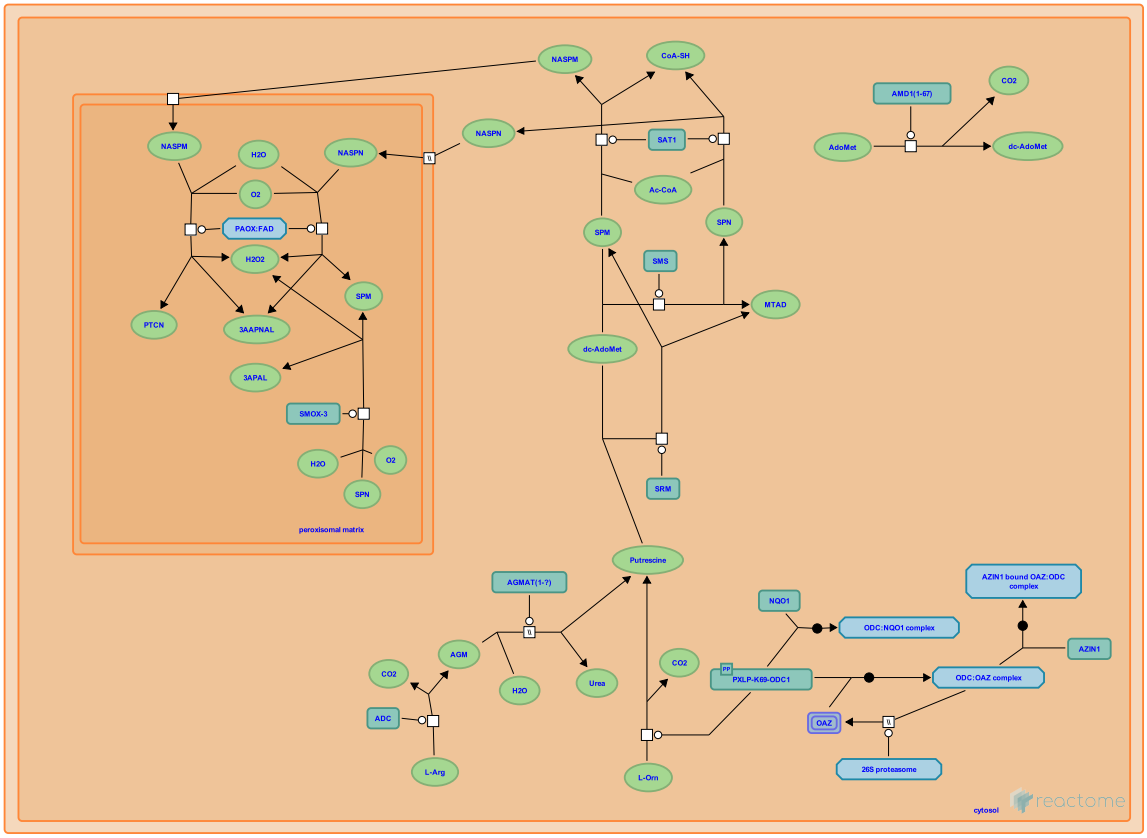
2015-09-17	Authored, Edited	Jassal, B.
2016-01-11	Reviewed	D'Eustachio, P.

Metabolism of polyamines ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-351202

Compartments: cytosol, peroxisomal matrix



Polyamines is a family of molecules (i.e. putrescine, spermine, spermidine) derived from ornithine according to a decarboxylation/condensative process. More recently, it has been demonstrated that arginine can be metabolised according to the same pathway leading to agmatine formation. Polyamines are essential for the growth, the maintenance and the function of normal cells. The complexity of their metabolism and the fact that polyamines homeostasis is tightly regulated support the idea that polyamines are essential to cell survival. Multiple abnormalities in the control of polyamines metabolism might be implicated in several pathological processes (Moinard et al., 2005). Legend for the following figure:

Literature references

Hillary, RA., Pegg, AE. (2003). Decarboxylases involved in polyamine biosynthesis and their inactivation by nitric oxide. *Biochim Biophys Acta, 1647*, 161-6. ↗

Moinard, C., Cynober, L., de Bandt, JP. (2005). Polyamines: metabolism and implications in human diseases. *Clin Nutr, 24*, 184-97. ↗

Urdiales, JL., Medina, MA., Sánchez-Jiménez, F. (2001). Polyamine metabolism revisited. *Eur J Gastroenterol Hepatol, 13*, 1015-9. ↗

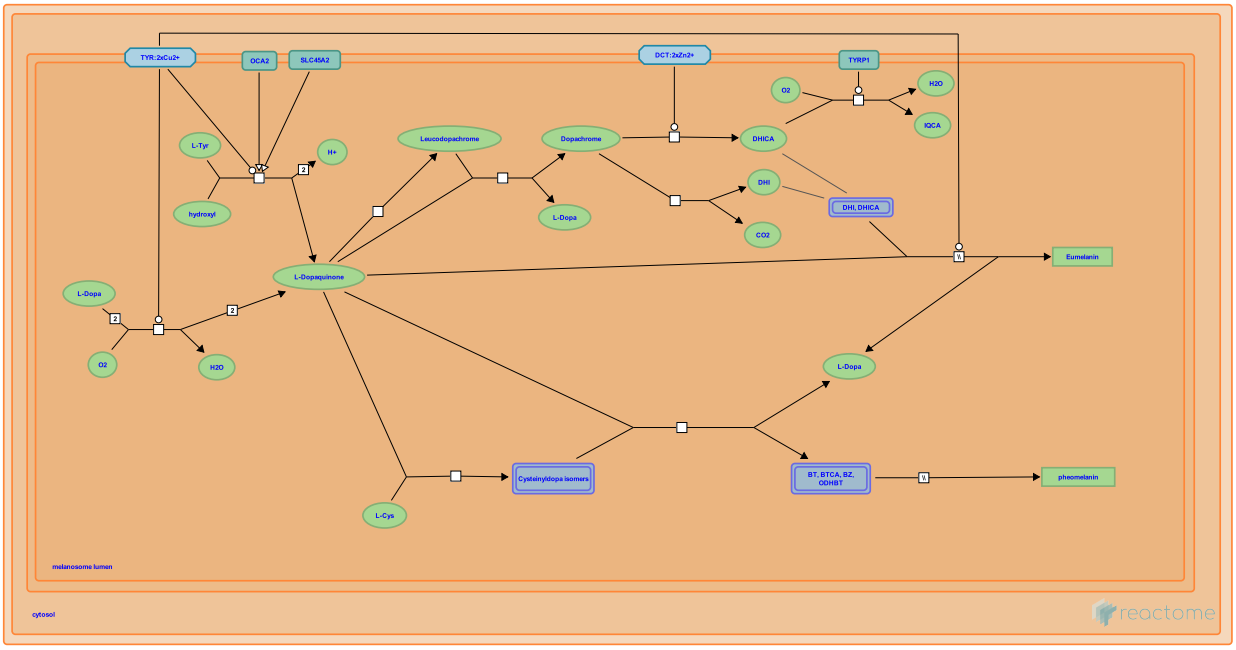
Editions

2008-05-21	Authored	Gopinathrao, G.
2008-06-12	Reviewed	D'Eustachio, P.
2017-03-22	Edited	D'Eustachio, P.

Melanin biosynthesis ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-5662702



Melanin biosynthesis takes place in specialized cells called melanocytes, within membrane-bound organelles referred to as melanosomes. Melanosomes are transferred via dendrites to surrounding keratinocytes. Keratinocytes and melanocytes are collectively known as 'the epidermal melanin unit'. Each melanocyte is in contact with approximately 40 keratinocytes in the basal and suprabasal layers (Cichorek et al. 2013). Melanocytes are distributed in the epidermis, hair follicles, the inner ear and the eye (Yamaguchi et al. 2007, Tolleson 2005).

Melanocytes in mammals and birds produce two chemically distinct types of melanin, black to brown eumelanin and yellow to reddish-brown pheomelanin (Ito & Wakamatsu 2008, Simon et al. 2009, d'Ischia et al. 2013). These differ in their responses to UV radiation; eumelanin has the ability to convert absorbed light energy into heat energy (Meredith & Riesz 2004) and to detoxify reactive oxygen species (ROS) (Bustamante et al. 1993), while pheomelanin is a phototoxic pro-oxidant (Samokhvalov 2005). Most natural melanin pigments contain eumelanin and pheomelanin (Ito & Wakamatsu 2003) and are termed 'mixed' melanins. Neuromelanins are mixed melanin-like pigments which are mainly found in neurons of the substantia nigra and locus coeruleus (Fedorow et al. 2005). Synthesis of NM may prevent the accumulation of toxic catechol derivatives (Zecca et al. 2003). NM can sequester a variety of potentially damaging molecules such as beta-carbolines, heavy metal ions and 1-methyl-4-phenylpyridinium (MPP+) (D'Amato et al. 1986), a drug which causes Parkinson's Disease-like symptoms. Models suggest that mixed melanogenesis occurs in three stages (Ito et al. 2000). The initial stage of melanin biosynthesis is the production of cysteinyldopas, which continues while sufficient cysteine is available. The second stage is the oxidation of cysteinyldopas to produce pheomelanin, which continues while cysteinyldopa concentration is sufficiently high. The last stage is the production of eumelanin, which begins when cysteinyldopas and cysteine are depleted. The ratio of eumelanin to pheomelanin is determined by tyrosinase activity and the availability of tyrosine and cysteine (Land et al. 2003).

Literature references

Ito, S., Wakamatsu, K. (2008). Chemistry of mixed melanogenesis--pivotal roles of dopaquinone. *Photochem. Photobiol., 84*, 582-92.

d'Ischia, M., Wakamatsu, K., Napolitano, A., Briganti, S., Garcia-Borron, JC., Kovacs, D. et al. (2013). Melanins and melanogenesis: methods, standards, protocols. *Pigment Cell Melanoma Res, 26*, 616-33.

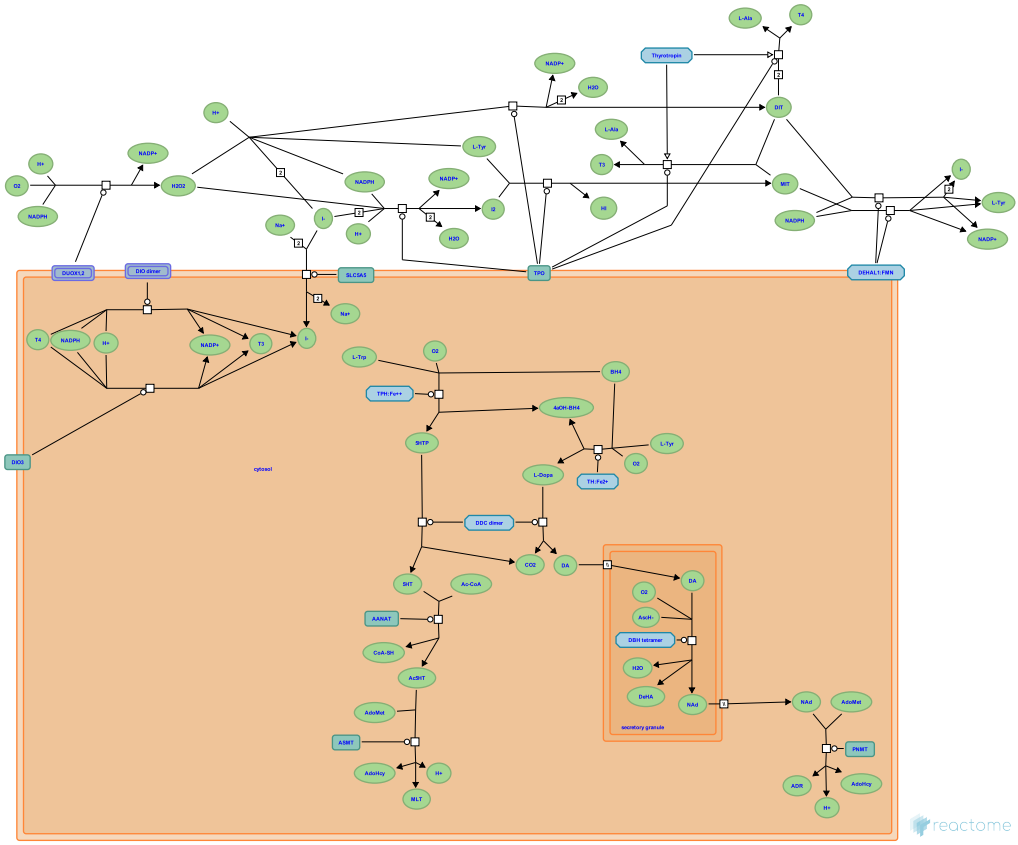
Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

Metabolism of amine-derived hormones ↗

Location: Metabolism of amino acids and derivatives

Stable identifier: R-HSA-209776



Catecholamines and thyroxine are synthesized from tyrosine, and serotonin and melatonin from tryptophan.

Literature references

Flatmark, T. (2000). Catecholamine biosynthesis and physiological regulation in neuroendocrine cells. *Acta Physiol Scand, 168*, 1-17. ↗

Köhrle, J., Brabant, G., Hesch, RD. (1987). Metabolism of the thyroid hormones. *Horm Res, 26*, 58-78. ↗

Ruddick, JP., Evans, AK., Nutt, DJ., Lightman, SL., Rook, GA., Lowry, CA. (2006). Tryptophan metabolism in the central nervous system: medical implications. *Expert Rev Mol Med, 8*, 1-27. ↗

Editions

2008-01-08	Edited	Jassal, B.
2008-05-28	Reviewed	D'Eustachio, P.
2008-10-01	Authored	Jassal, B.

Table of Contents