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


Reactome database release: 76

This document contains 1 pathway and 6 reactions (see Table of Contents)
The first reaction in this pathway converts phenylalanine to tyrosine, coupled to the conversion of tetrahydrobiopterin to 4a-hydroxytetrahydrobiopterin, catalyzed by phenylalanine hydroxylase. Deficiencies in this enzyme are responsible for the commonest form of phenylketonuria (PKU) in humans. This reaction functions both as the first step in the pathway by which the body disposes of excess phenylalanine, and as a source of the amino acid tyrosine. The next two reactions are responsible for the regeneration of tetrahydrobiopterin from 4a-hydroxytetrahydrobiopterin (Blau et al. 2001).

**Literature references**


**Editions**

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<td>2010-02-18</td>
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ASRGL1 hydrolyses aspartame to L-Asp, L-Phe

Location: Phenylalanine metabolism

Stable identifier: R-HSA-5696365

Type: transition

Compartments: cytosol

The human isoaspartyl peptidase/L-asparaginase (ASRGL1) is an N-terminal nucleophile (Ntn) hydrolase superfamily member that catalyses the hydrolysis of l-asparagine and beta-aspartyl-dipeptides and their methyl esters such as aspartame (beta-L-Asp-L-Phe methyl ester) (Cantor et al. 2009, Li et al. 2012, Nomme et al. 2014). ASRGL1 is a cytosolic enzyme that is active as a heterodimer of alpha and beta chains, formed by autocleavage between Gly167 and Thr168 (Nomme et al. 2012). ASRGL1 is expressed in brain, kidney, testis and the gastrointestinal tract. Aspartame is an artificial sweetener used as a sugar substitute in some drinks. Sufferers of phenylketonuria (PKU) are advised to avoid aspartame as one of its breakdown products, phenylalanine, could contribute to the excess pool of phenylalanine that PKU sufferers cannot metabolise from the body.

Literature references


Editions

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phenylalanine + pyruvate $\Rightarrow$ 3-(indol-3-yl)pyruvate + alanine

**Location:** Phenylalanine metabolism

**Stable identifier:** R-HSA-893593

**Type:** transition

**Compartments:** cytosol

CCBL1 (KAT 1) catalyzes the reaction of phenylalanine and pyruvate to form 3-(indol-3-yl)pyruvate and alanine. The active form of CCBL1 is a homodimer with one molecule of pyridoxal phosphate bound to each monomer (Baran et al. 1994; Han et al. 2009; Rossi et al. 2004). The enzyme's cytosolic localization is inferred from that of recombinant protein overexpressed in transfected cells (Perry et al. 1995).

**Literature references**


**Editions**

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PAH:Fe2+ tetramer hydroxylates L-Phe to L-Tyr

Location: Phenylalanine metabolism

Stable identifier: R-HSA-71118

Type: transition

Compartments: cytosol

Inactivating mutations of cytosolic phenylalanine hydroxylase (PAH) block the normal reaction of phenylalanine, molecular oxygen and tetrahydrobiopterin to form tyrosine, water, and 4 alpha-hydroxy-tetrahydrobiopterin. Excess phenylalanine accumulates as a result, driving the formation of abnormally high levels of phenylpyruvate, and phenyllactate (Guldberg et al. 1996; Mitchell et al. 2011) in reactions not annotated here.

**Preceded by:** q-dihydrobiopterin + NADH + H+ => tetrahydrobiopterin + NAD+

**Followed by:** 4a-hydroxytetrahydrobiopterin => q-dihydrobiopterin + H2O

**Literature references**


**Editions**

2003-06-24 Authored, Edited D'Eustachio, P.
4a-hydroxytetrahydrobiopterin => q-dihydrobiopterin + H2O

Location: Phenylalanine metabolism

Stable identifier: R-HSA-71146

Type: transition

Compartments: cytosol

Cytosolic pterin-4-alpha-carbinolamine dehydratase (PCDB1) catalyzes the reaction of 4a-hydroxytetrahydrobiopterin to form q-dihydrobiopterin and water (Hauer et al. 1993. The active enzyme is a homotetramer (Ficner et al. 1995); mutations in the PCDB1 gene are associated with mild hyperphenylalanemia in vivo (Citron et al. 1993).

Preceded by: PAH:Fe2+ tetramer hydroxylates L-Phe to L-Tyr

Followed by: q-dihydrobiopterin + NADH + H+ => tetrahydrobiopterin + NAD+

Literature references


Editions

2003-06-24 Author, Edited by D'Eustachio, P.
q-dihydrobiopterin + NADH + H+ ⇄ tetrahydrobiopterin + NAD+

**Location:** Phenylalanine metabolism

**Stable identifier:** R-HSA-71130

**Type:** transition

**Compartments:** cytosol

Cytosolic dihydropteridine reductase (QDPR) catalyzes the reaction of q-dihydrobiopterin with NADH + H+to form tetrahydrobiopterin and NAD+. The enzyme is a homodimer (Lockyer et al. 1987; Su et al. 1993).

**Preceded by:** 4a-hydroxytetrahydrobiopterin ⇒ q-dihydrobiopterin + H2O

**Followed by:** PAH:Fe2+ tetramer hydroxylates L-Phe to L-Tyr

**Literature references**


**Editions**

2003-06-24 Authored, Edited D'Eustachio, P.
Extracellular L-amino-acid oxidase (IL4I1) catalyzes the reaction of phenylalanine, water, and molecular oxygen to form keto-phenylpyruvate, ammonia, and hydrogen peroxide. IL4I1, inferred to form a complex with FAD, has L-amino acid oxidase activity and with a strong preference for phenylalanine. The enzyme, found both in lysosomes and secreted into the extracellular space, is produced in the body by myeloid and dendritic cells (Boulland et al. 2007).

**Literature references**

Phenylalanine metabolism

- ASRGL1 hydrolyses aspartame to L-Asp, L-Phe
- phenylalanine + pyruvate => 3-(indol-3-yl)pyruvate + alanine
- PAH:Fe2+ tetramer hydroxylates L-Phe to L-Tyr
- 4a-hydroxytetrahydrobiopterin => q-dihydrobiopterin + H2O
- q-dihydrobiopterin + NADH + H+ => tetrahydrobiopterin + NAD+
- IL4I1:FAD oxidises L-Phe to kPPV