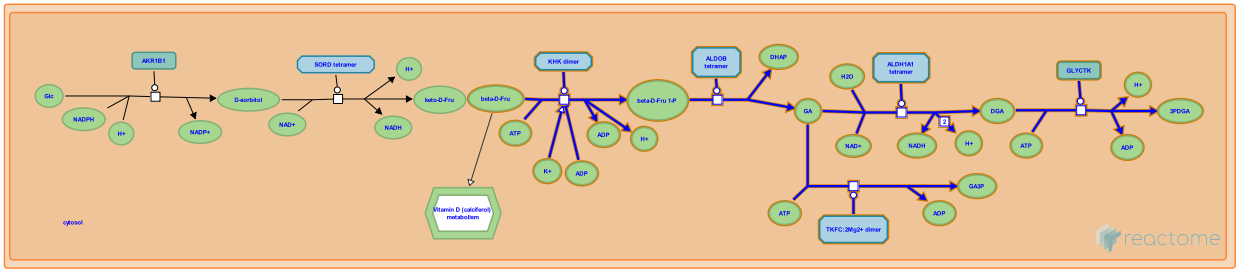
Fructose catabolism



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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. ↗

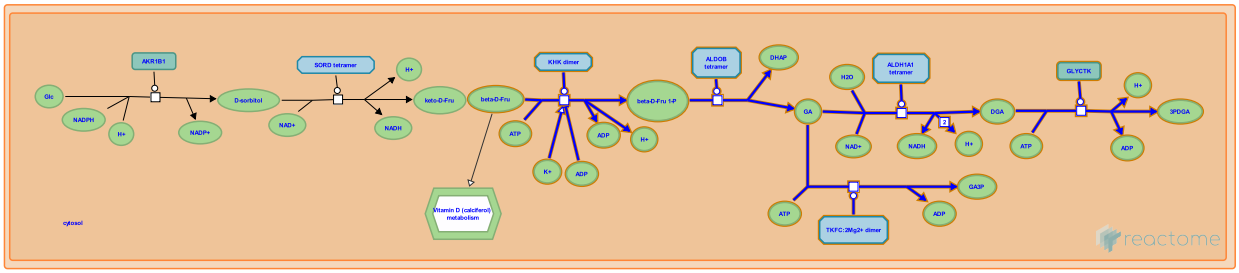
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 90

This document contains 1 pathway and 5 reactions (see Table of Contents)

Fructose catabolism ↗

Stable identifier: R-HSA-70350



Fructose occurs naturally in foods as a free monosaccharide and as a component of the disaccharide sucrose. It is also widely used as a sweetener. In the body, fructose catabolism occurs in the liver and to a lesser extent in the kidney and small intestine. In these tissues, it is converted to dihydroxyacetone phosphate and D-glyceraldehyde 3-phosphate, two intermediates in the glycolytic pathway, in a sequence of three reactions. It is phosphorylated to form fructose 1-phosphate, which is cleaved by aldolase to yield dihydroxyacetone phosphate and D-glyceraldehyde, and the latter compound is phosphorylated to yield D-glyceraldehyde 3-phosphate. Other pathways exist for the conversion of D-glyceraldehyde to intermediates of glycolysis, but these appear to play only a minor role in normal fructose metabolism (Sillero et al. 1969).

Literature references

Mayes, PA. (1993). Intermediary metabolism of fructose. *Am. J. Clin. Nutr., 58*, 754S-765S. ↗

Sillero, MA., Sillero, A., Sols, A. (1969). Enzymes involved in fructose metabolism in liver and the glyceraldehyde metabolic crossroads. *Eur. J. Biochem., 10*, 345-50. ↗

Editions

2003-06-24	Authored	D'Eustachio, P.
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2015-08-28	Authored	Ribeiro, JM., Cameselle, JC.

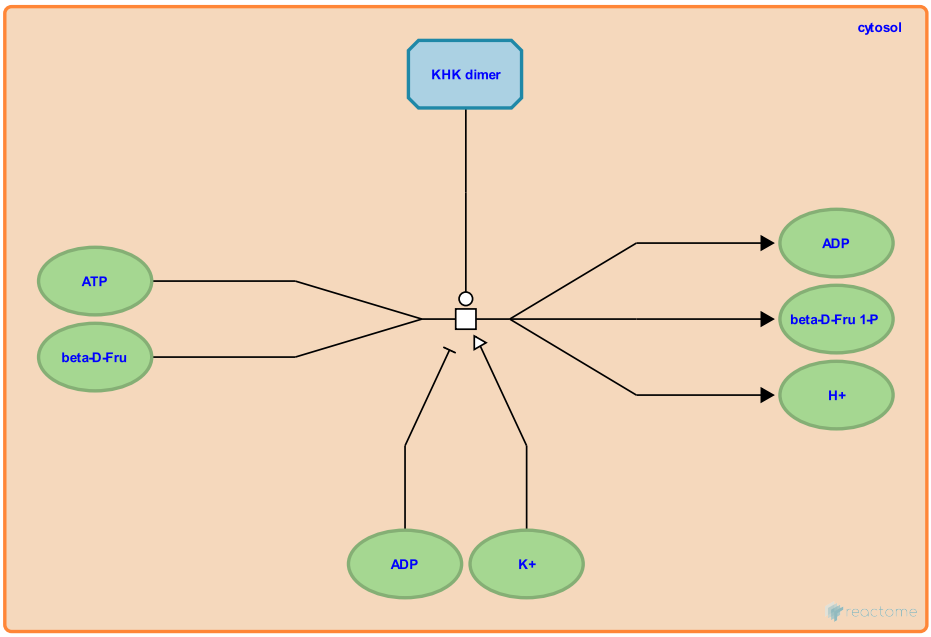
KHK dimer phosphorylates Fru to Fru 1-P ↗

Location: Fructose catabolism

Stable identifier: R-HSA-70333

Type: transition

Compartments: cytosol



Cytosolic ketohexokinase (KHK, also known as fructokinase) catalyzes the reaction of D-fructose (Fru) and ATP to form D-fructose 1-phosphate (Fru 1-P) and ADP. Two isoforms of the enzyme, A and C, are encoded by alternatively spliced forms of the gene; both form catalytically active dimers. The C isoform is predominant in liver and kidney tissues, has high affinity for fructose, and is probably responsible for the bulk of fructose phosphorylation in vivo (Asipu et al. 2003; Trinh et al. 2009). The A isoform is found in lower levels in many other tissues and may serve a role in fructose metabolism outside of liver and kidney (Funari et al. 2005). The physiological role of KHK has been established from metabolic and DNA sequencing studies of patients with essential fructosuria (Bonthron et al. 1994) and in mouse models for this disease (Diggle et al. 2010; Ishimoto et al. 2012).

Followed by: ALDOB tetramer cleaves Fru-1-P to GA and DHAP

Literature references

Maruyama, S., Diggle, CP., Ishimoto, T., Asipu, A., Kosugi, T., Bonthron, DT. et al. (2012). Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. *Proc. Natl. Acad. Sci. U.S.A., 109*, 4320-5. ↗

Hayward, BE., O'Reilly, J., Asipu, A., Bonthron, DT. (2003). Properties of normal and mutant recombinant human ketohexokinases and implications for the pathogenesis of essential fructosuria. *Diabetes, 52*, 2426-32. ↗

Trinh, CH., Phillips, SE., Asipu, A., Bonthron, DT. (2009). Structures of alternatively spliced isoforms of human ketohexokinase. *Acta Crystallogr D Biol Crystallogr, 65*, 201-11. ↗

Freeman, D., Funari, VA., Tolan, DR., Herrera, VL. (2005). Genes required for fructose metabolism are expressed in Purkinje cells in the cerebellum. *Brain Res. Mol. Brain Res., 142*, 115-22. ↗

McRae, C., Markham, AF., Hayward, BE., Crellin, D., Diggle, CP., Fisher, J. et al. (2010). Both isoforms of ketohexokinase are dispensable for normal growth and development. *Physiol. Genomics, 42*, 235-43. ↗

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2010-01-25	Revised	D'Eustachio, P.
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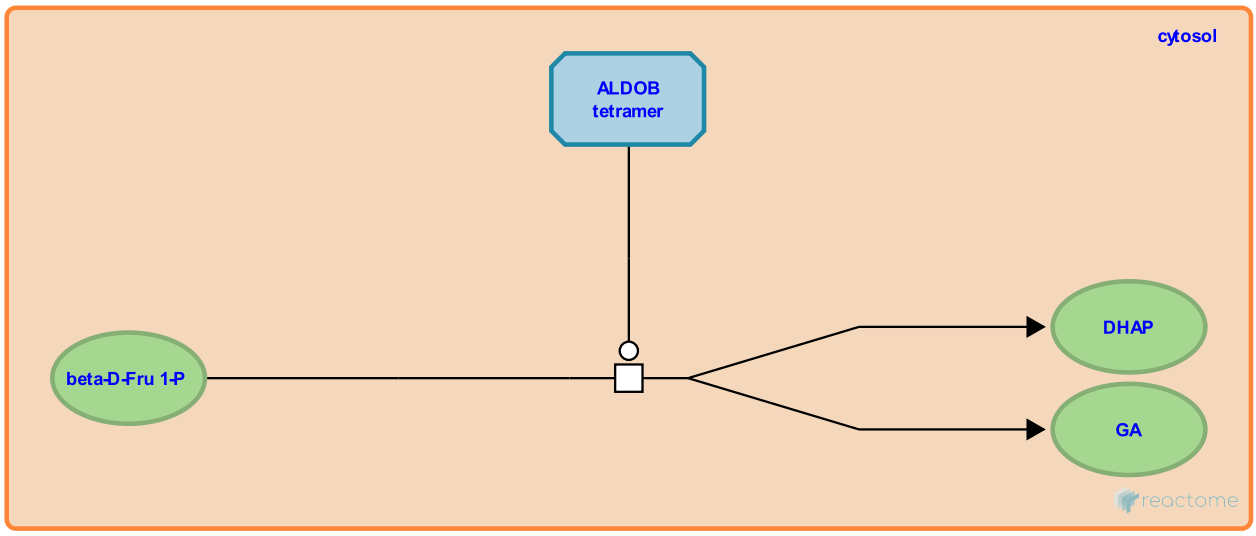
ALDOB tetramer cleaves Fru-1-P to GA and DHAP ↗

Location: Fructose catabolism

Stable identifier: R-HSA-70342

Type: transition

Compartments: cytosol



Cytosolic aldolase B (ALDOB) catalyzes the reaction of D-fructose 1-phosphate (Fru 1-P) to form dihydroxyacetone phosphate (DHAP) and D-glyceraldehyde (GA) (Hers & Kusaka 1953; Schapira 1975). The active form of the enzyme is a tetramer (Dalby et al. 2001). Deficiencies in the enzyme are associated with hereditary fructose intolerance in vivo (e.g., Tolan 1995; Ali et al. 1998).
ALDOB is the same aldolase isoform that catalyzes the reversible cleavage of fructose-1,6-bisphosphate in glycolysis. This isoform, found in liver, kidney, and intestine, is approximately equally active with fructose 1 phosphate and fructose 1,6 bisphosphate as substrates at saturating concentrations, while the muscle and brain isoforms (ALDOA and ALDOC, respectively), have little activity with fructose-1-phosphate (Lebherz & Rutter 1969; Penhoet et el. 1969).

Preceded by: KHK dimer phosphorylates Fru to Fru 1-P

Followed by: ALDH1A1 oxidises GA to DGA, DAK dimer phosphorylates D-glyceraldehyde to form D-glyceraldehyde 3-phosphate

Literature references

Tolan, DR. (1995). Molecular basis of hereditary fructose intolerance: mutations and polymorphisms in the human aldolase B gene. *Hum Mutat, 6*, 210-8. ↗

Kochman, M., Rutter, WJ., Penhoet, EE. (1969). Isolation of fructose diphosphate aldolases A, B, and C. *Biochemistry, 8*, 4391-5. ↗

Littlechild, JA., Tolan, DR., Dalby, AR. (2001). The structure of human liver fructose-1,6-bisphosphate aldolase. *Acta Crystallogr D Biol Crystallogr, 57*, 1526-33. ↗

Hers, HG., Kusaka, T. (1953). [The metabolism of fructose-1-phosphate in the liver.]. *Biochim Biophys Acta, 11*, 427-37. ↗

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DAK dimer phosphorylates D-glyceraldehyde to form D-glyceraldehyde 3-phosphate

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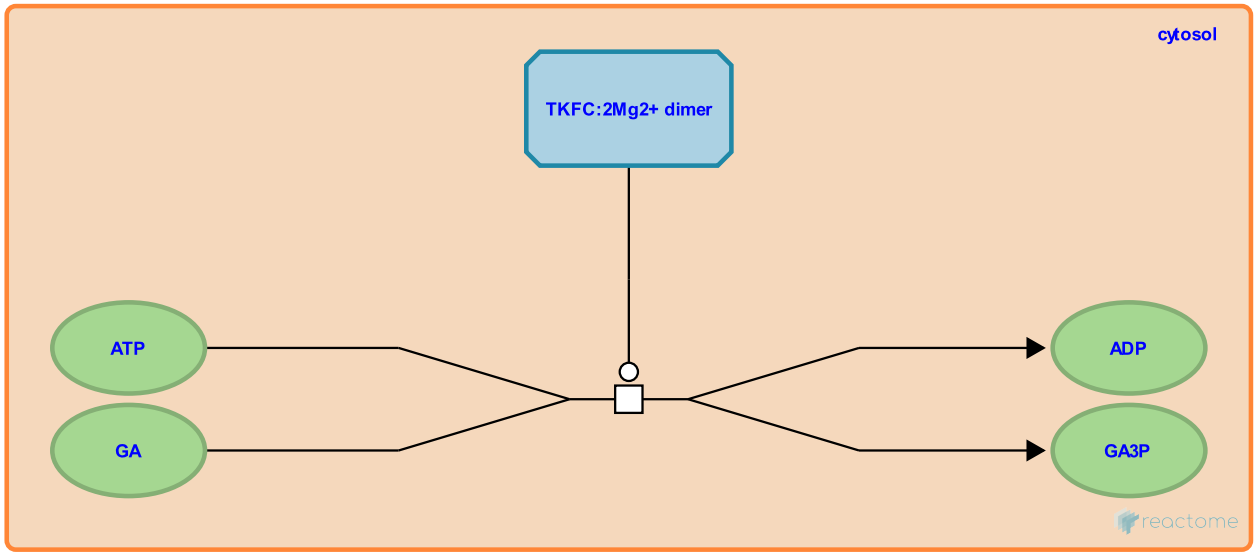
Location: Fructose catabolism

Stable identifier: R-HSA-70349

Type: transition

Compartments: cytosol



Cytosolic dihydroxyacetone kinase (DAK) catalyzes the reaction of ATP and D-glyceraldehyde (GA) to form ADP and D-glyceraldehyde 3-phosphate (GA3P). This reaction was originally characterized in studies of guinea pig liver and human erythrocytes (Hers & Kusaka 1953; Beutler & Guinto 1973). The human enzyme has been cloned and studied (Cabezas et al. 2005; Rodrigues et al. 2014). DAK/TKFC also catalyzes the phosphorylation of dihydroxyacetone (DHA) to dihydroxyacetone phosphate (DHAP), not a necessary step in fructose catabolism, but possibly functional on exogenous DHA. Triokinase activities on GA and DHA require homodimeric enzyme formed by two-domain subunits, where triose binds to one subunit and ATP to the other, each in a different domain.
DAK/TKFC is a bifunctional enzyme which, besides the ATP/Mg-dependent phosphorylation of GA and DHA, also catalyses, in presence of Mn2+, a unisubstrate reaction splitting flavin-adenine dinucleotide (FAD) into riboflavin cyclic 4',5'-phosphate (cyclic FMN) and AMP (Cabezas et al. 2005; Rodrigues et al. 2014).
In addition, DAK/TKFC protein binds to MDA5 and acts as a negative regulator of MDA5-mediated induction of IFN-alpha/beta pathways (Diao et al. 2007). Potentially related to this TKFC effect are the observations that hepatic DAK/TKFC levels correlate with outcome in chronic hepatitis C patients treated with interferon (Perdomo et al. 2012), and that a DAK/TKFC serum peptide is a predictor of disease severity in hepatitis B patients (Xu et al. 2013).

Preceded by: ALDOB tetramer cleaves Fru-1-P to GA and DHAP

Literature references

Pinto, RM., Cameselle, JC., Costas, MJ., Couto, A., Cabezas, A. (2005). Identification of human and rat FAD-AMP lyase (cyclic FMN forming) as ATP-dependent dihydroxyacetone kinases. *Biochem. Biophys. Res. Commun., 338,* 1682-9. ↗

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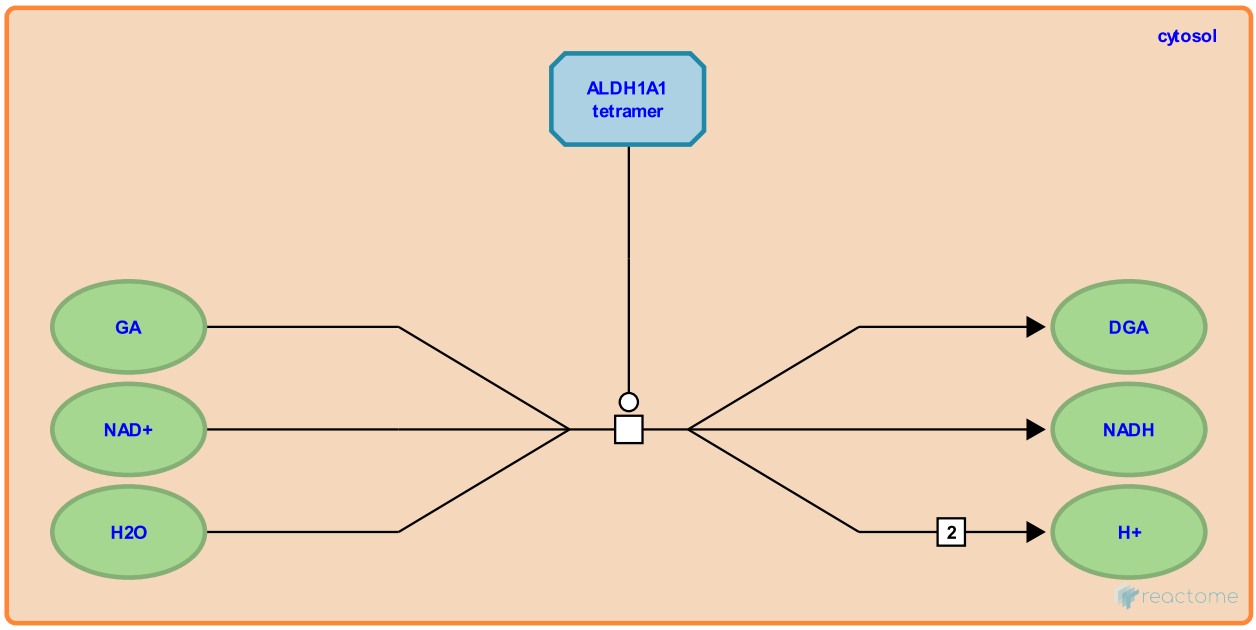
ALDH1A1 oxidises GA to DGA ↗

Location: Fructose catabolism

Stable identifier: R-HSA-6813749

Type: transition

Compartments: cytosol



Retinal dehydrogenase 1 (ALDH1A1 tetramer) is a cytosolic aldehyde dehydrogenase that can oxidise glyceraldehyde (GA) to D-glycerate (DGA) (Yoval-Sanchez et al. 2013). DGA is a metabolite in a minor pathway of fructose catabolism and serine catabolism.

Preceded by: ALDOB tetramer cleaves Fru-1-P to GA and DHAP

Followed by: GLYCTK phosphorylates DGA to 3PDGA

Literature references

Rodriguez-Zavala, JS., Pardo, JP., Yoval-Sánchez, B. (2013). New insights into the half-of-the-sites reactivity of human aldehyde dehydrogenase 1A1. *Proteins, 81*, 1330-9. ↗

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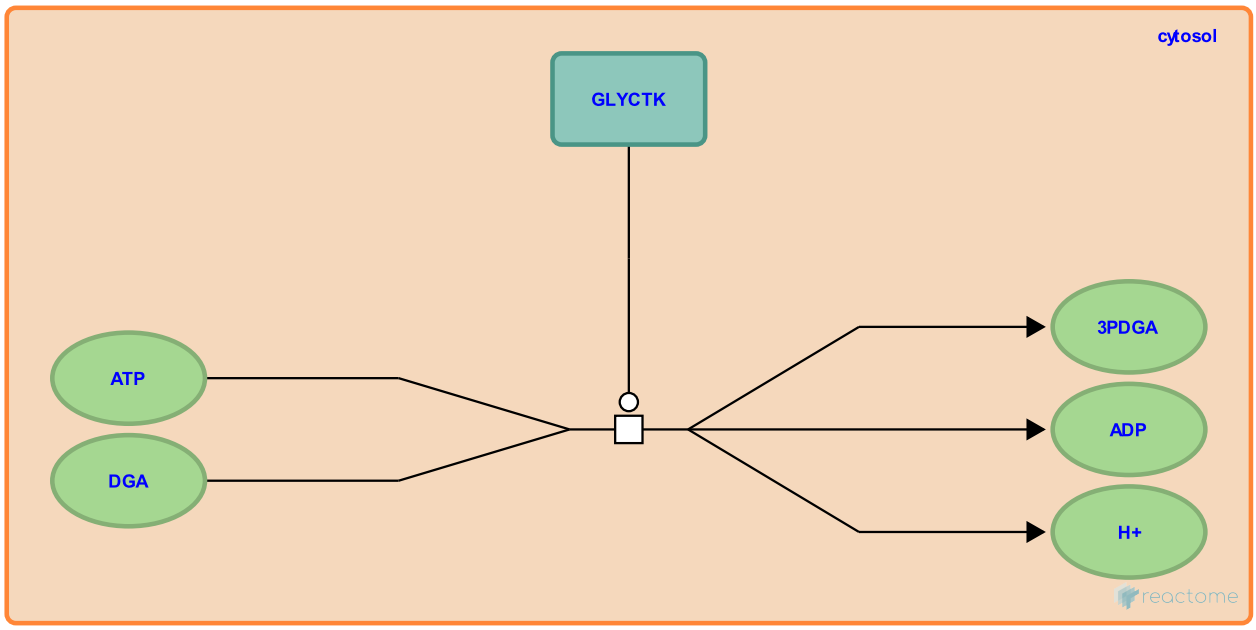
GLYCTK phosphorylates DGA to 3PDGA ↗

Location: Fructose catabolism

Stable identifier: R-HSA-6799495

Type: transition

Compartments: cytosol



D-glyceric acid (DGA) is an intermediate of serine catabolism and of a minor pathway of fructose metabolism. The only known fate of DGA is phosphorylation to 3-phospho-D-glyceric acid (3PDGA) by cytosolic glycerate kinase (GLYCTK) (Yu et al. 2006). Defects in GLYCTK can cause D-glyceric aciduria (D-GA; MIM:220120), a rare inborn error of serine and fructose metabolism where DGA is excreted in large amounts in the urine. A variable phenotype is observed, ranging from severe mental retardation and death to milder speech delays and normal development (Van Schaftingen 1989, Sass et al. 2010).

Preceded by: ALDH1A1 oxidises GA to DGA

Literature references

Sass, JO., Kapelari, K., Fischer, K., Wang, R., Scholl-Bürgi, S., Chang, R. et al. (2010). D-glyceric aciduria is caused by genetic deficiency of D-glycerate kinase (GLYCTK). *Hum. Mutat., 31*, 1280-5. ↗

Yu, L., Guo, JH., Zhao, SY., Wu, CQ., Wang, X., Hexige, S. et al. (2006). Isolation and characterization of the human D-glyceric acidemia related glycerate kinase gene GLYCTK1 and its alternatively splicing variant GLYCTK2. *DNA Seq., 17*, 1-7. ↗

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