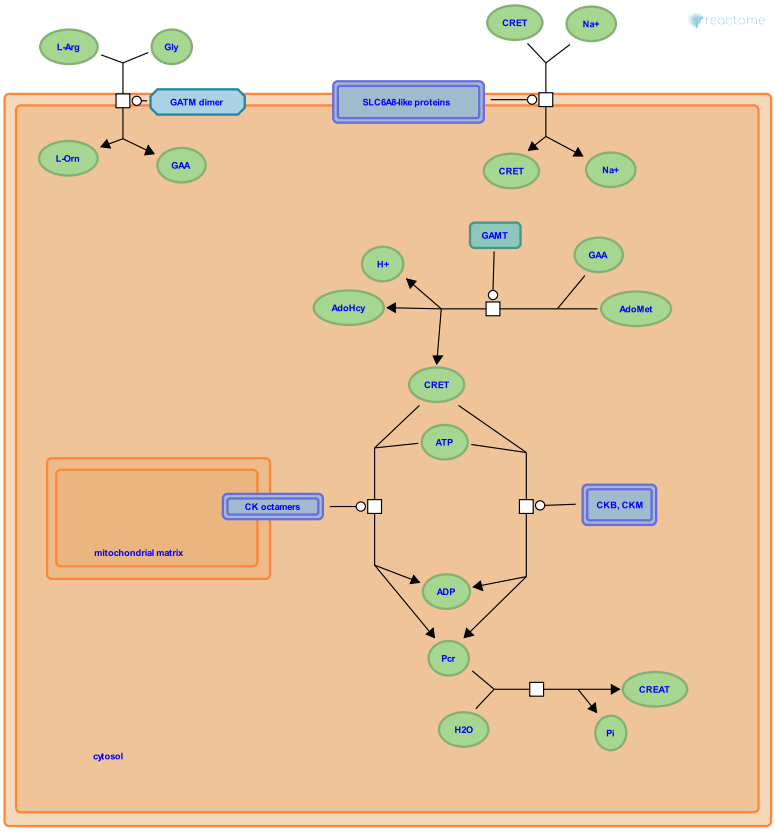
Creatine metabolism



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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. ↗

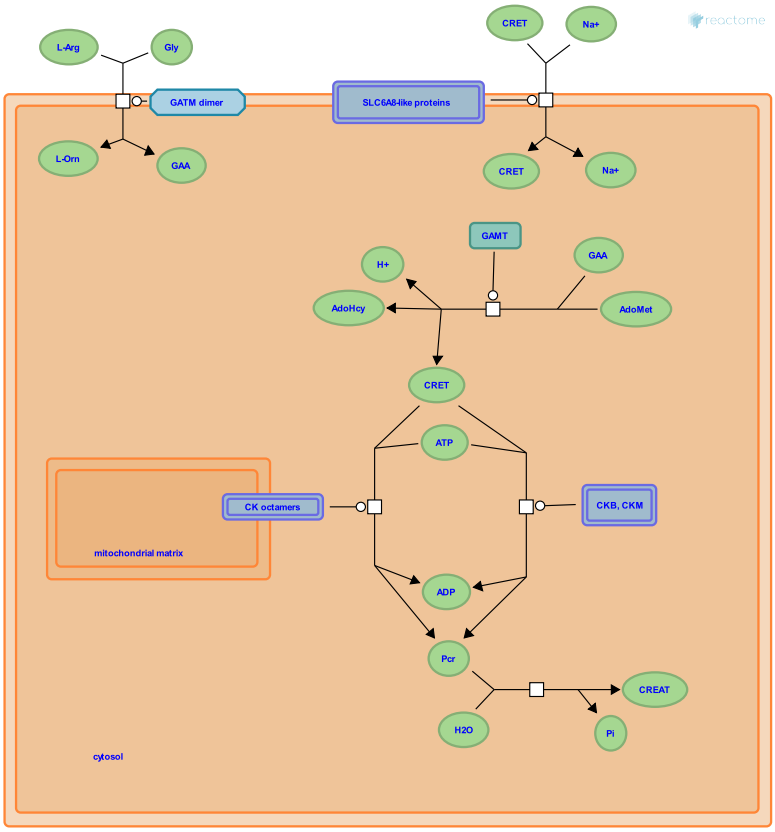
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Creatine metabolism ↗

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

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

Editions

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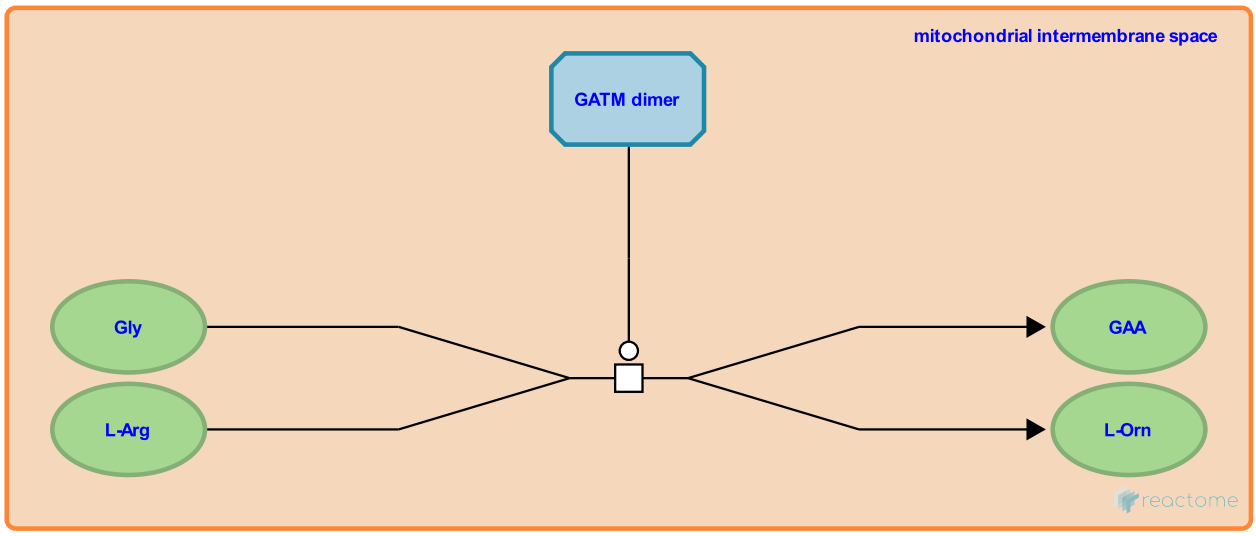
arginine + glycine => ornithine + guanidoacetate ↗

Location: Creatine metabolism

Stable identifier: R-HSA-71275

Type: transition

Compartments: mitochondrial intermembrane space



Glycine amindinotransferase, localized to the mitochondrial intermembrane space, catalyzes the reaction of arginine and glycine to form guanidinoacetate and ornithine. The active form of the enzyme is a dimer (Humm et al. 1997 {EMBO J]; Humm et al 1997 [Biochem J]). Its function in vivo has been confirmed by molecular and biochemical studies of patients deficient in the enzyme (Item et al. 2001).

Followed by: guanidinoacetate + S-adenosylmethionine => creatine + S-adenosylhomocysteine

Literature references

Huber, R., Humm, A., Fritsche, E., Gohl, M., Mann, K. (1997). Recombinant expression and isolation of human L-arginine:glycine amidinotransferase and identification of its active-site cysteine residue. *Biochem J, 322,* 771-6. ↗

Steinbacher, S., Huber, R., Humm, A., Fritsche, E. (1997). Crystal structure and mechanism of human L-arginine:glycine amidinotransferase: a mitochondrial enzyme involved in creatine biosynthesis. *EMBO J, 16,* 3373-85. ↗

Cioni, G., Stockler-Ipsiroglu, S., Stromberger, C., Bianchi, MC., Item, CB., Tosetti, M. et al. (2001). Arginine:glycine amidinotransferase deficiency: the third inborn error of creatine metabolism in humans. *Am J Hum Genet, 69,* 1127-33. ↗

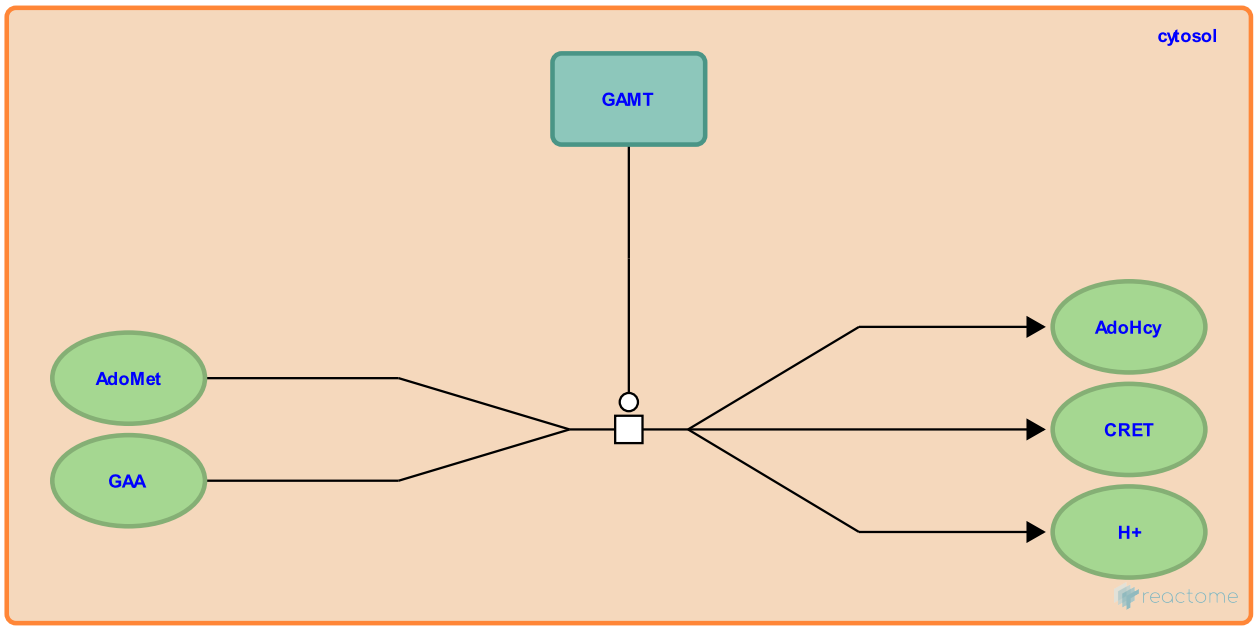
guanidinoacetate + S-adenosylmethionine => creatine + S-adenosylhomocysteine ↗

Location: Creatine metabolism

Stable identifier: R-HSA-71286

Type: transition

Compartments: cytosol



Cytosolic guanidinoacetate methyltransferase catalyzes the reaction of S-adenosylmethionine and guanidinoacetate to form S-adenosylhomocysteine and creatine (Stockler et al. 1996).

Preceded by: arginine + glycine => ornithine + guanidoacetate

Followed by: creatine + ATP => phosphocreatine + ADP [CKB,CKM], creatine + ATP => phosphocreatine + ADP [CK octamer]

Literature references

Isbrandt, D., Stockler, S., von Figura, K., Hanefeld, F., Schmidt, B. (1996). Guanidinoacetate methyltransferase deficiency: the first inborn error of creatine metabolism in man. *Am J Hum Genet, 58*, 914-22. ↗

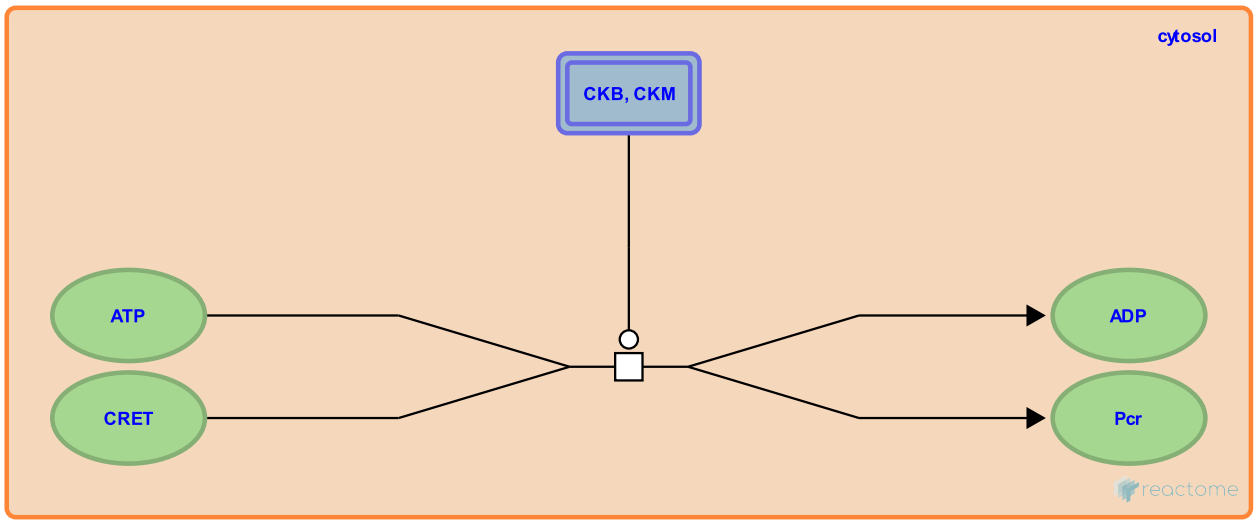
creatine + ATP => phosphocreatine + ADP [CKB,CKM] ↗

Location: Creatine metabolism

Stable identifier: R-HSA-200318

Type: transition

Compartments: cytosol



Cytosolic creatine kinase catalyzes the reaction of creatine and ATP to form phosphocreatine and ADP. The active form of the enzyme is a dimer. Monomers of the cytosolic enzyme occur in two isoforms, B and M, so called because of their abundance in brain and muscle respectively. The enzyme is widely expressed in the body and many tissues express both isoforms. Both homo- (BB, MM) and heterodimers (BM) are catalytically active.

Preceded by: Creatine transport across the plasma membrane, guanidinoacetate + S-adenosylmethionine => creatine + S-adenosylhomocysteine

Followed by: phosphocreatine + H2O => creatinine + orthophosphate

Literature references

Flynn, AJ., Naor, MM., McLeish, MJ., Jensen, JH., Cui, G., Wang, PF. et al. (2006). Exploring the role of the active site cysteine in human muscle creatine kinase. *Biochemistry, 45*, 11464-72. ↗

Editions

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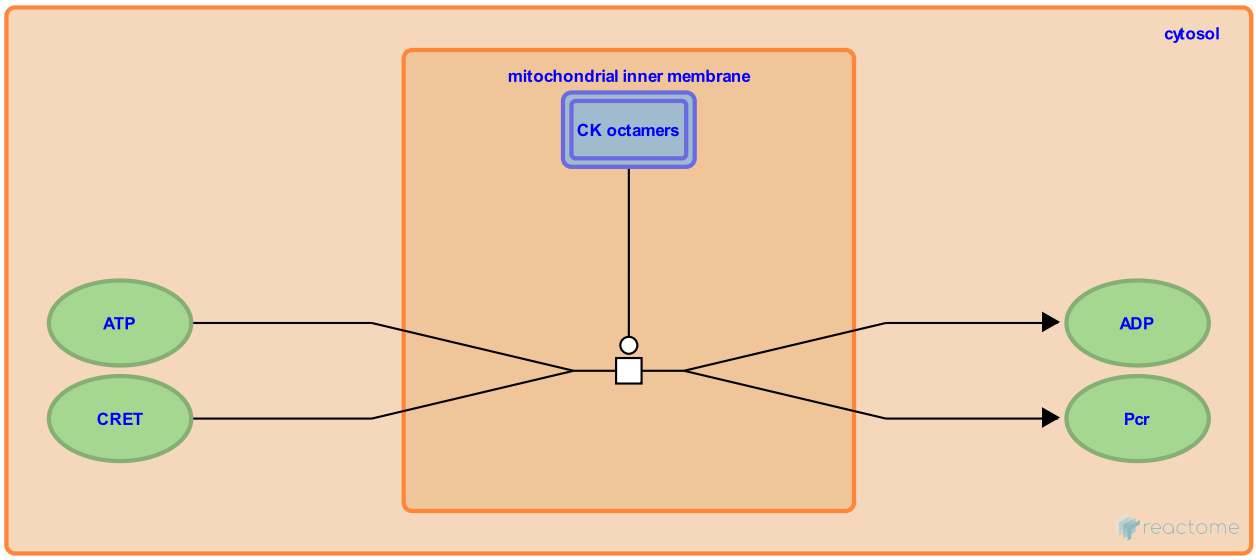
creatine + ATP => phosphocreatine + ADP [CK octamer]

Location: Creatine metabolism

Stable identifier: R-HSA-200326

Type: transition

Compartments: mitochondrial inner membrane, cytosol



Creatine kinase octamers associated with the inner mitochondrial membrane catalyze the reaction of creatine and ATP to form phosphocreatine and ADP. Two mitochondrial creatine kinase proteins have been identified, one encoded by CKMT1A and B that is found in many tissues and one encoded by CKMT2 that is found in sarcomeres (Haas et al. 1988; Haas and Straus 1990). Studies of sarcomeric creatine kinase octamers suggest that their organization and association with phospholipids in the inner mitochondrial membrane may facilitate energy transfer from ATP generated in the mitochondrial matrix to cytosolic phosphocreatine (Khuchua et al. 1998; Schlattner et al. 2004).

Preceded by: Creatine transport across the plasma membrane, guanidinoacetate + S-adenosylmethionine => creatine + S-adenosylhomocysteine

Followed by: phosphocreatine + H2O => creatinine + orthophosphate

Literature references

Haas, RC., Strauss, AW. (1990). Separate nuclear genes encode sarcomere-specific and ubiquitous human mitochondrial creatine kinase isoenzymes. *J Biol Chem, 265*, 6921-7.

Gehring, F., Vial, C., Neumann, D., Vernoux, N., Wallimann, T., Tokarska-Schlattner, M. et al. (2004). C-terminal lysines determine phospholipid interaction of sarcomeric mitochondrial creatine kinase. *J Biol Chem, 279*, 24334-42.

Saks, VA., Cheng, J., Boero, J., Khuchua, ZA., Strauss, AW., Payne, RM. et al. (1998). Octamer formation and coupling of cardiac sarcomeric mitochondrial creatine kinase are mediated by charged N-terminal residues. *J Biol Chem, 273*, 22990-6.

Haas, RC., Korenfeld, C., Roman, D., Perryman, B., Zhang, Z., Strauss, AW. (1989). Isolation and characterization of the gene and cDNA encoding human mitochondrial creatine kinase. *J Biol Chem, 264*, 2890-7.

Editions

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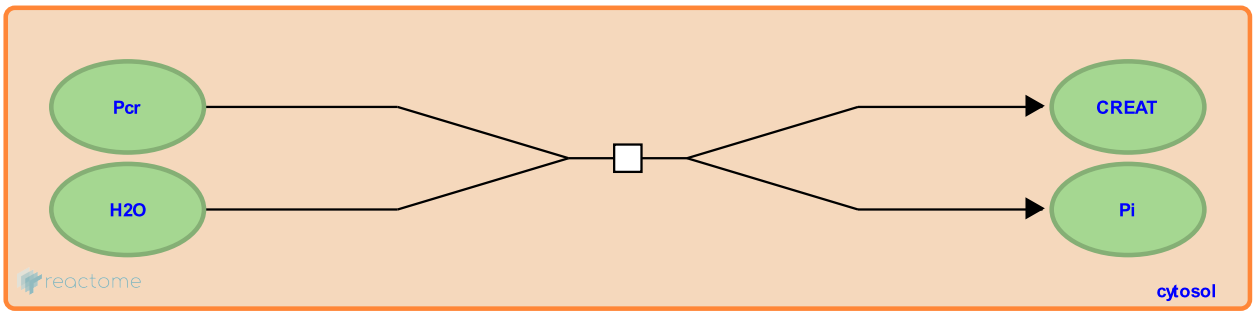
phosphocreatine + H2O => creatinine + orthophosphate ↗

Location: Creatine metabolism

Stable identifier: R-HSA-71287

Type: transition

Compartments: cytosol



Cytosolic phosphocreatine spontaneously hydrolyzes to yield creatinine and orthophosphate (Borsook and Dubnoff 1947). Creatinine cannot be metabolized further and is excreted from the body in the urine. Creatinine formation proceeds at a nearly constant rate and the amount produced by an individual is a function of muscle mass, so urinary creatinine output is clinically useful as a normalization factor in assays of urinary output of other molecules. Iyengar et al. (1985) have suggested that an alternative reaction sequence, proceeding via phosphocreatinine but also spontaneous, may contribute to creatinine formation.

Preceded by: creatine + ATP => phosphocreatine + ADP [CKB,CKM], creatine + ATP => phosphocreatine + ADP [CK octamer]

Literature references

Dubnoff, JW., Borsook, H. (1947). The hydrolysis of phosphocreatine and the origin of urinary creatinine. *J Biol Chem , 168*, 493-510. ↗

Iyengar, MR., Butler, TM., Coleman, DW. (1985). Phosphocreatinine, a high-energy phosphate in muscle, spontaneously forms phosphocreatine and creatinine under physiological conditions. *J Biol Chem, 260*, 7562-7. ↗

Editions

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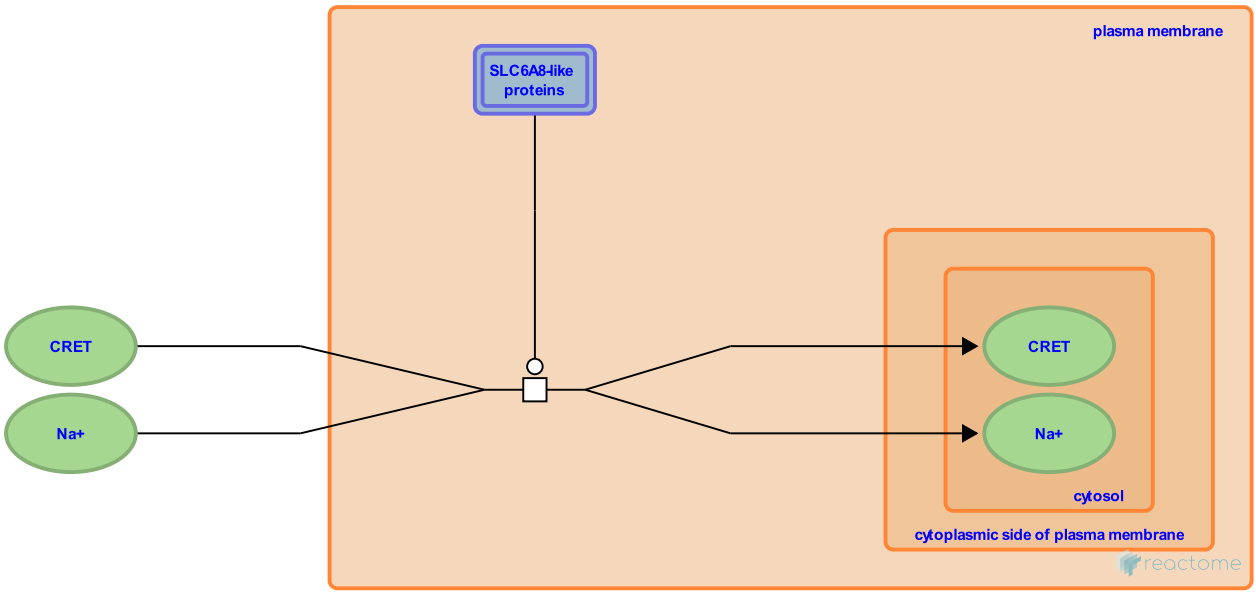
Creatine transport across the plasma membrane ↗

Location: Creatine metabolism

Stable identifier: R-HSA-200396

Type: transition

Compartments: plasma membrane



The SLC6A8 transport protein associated with the plasma membrane mediates the uptake of extracellular creatine and a sodium ion (Sora et al. 1994). Molecular and biochemical studies of patients deficient in SLC6A8 protein confirm this function in vivo (e.g., Salomons et al. 2003).

Followed by: creatine + ATP => phosphocreatine + ADP [CKB,CKM], creatine + ATP => phosphocreatine + ADP [CK octamer]

Literature references

van Dooren, SJ., Verhoeven, NM., Schwartz, C., DeGrauw, TJ., Marsden, D., Salomons, GS. et al. (2003). X-linked creatine transporter defect: an overview. *J Inherit Metab Dis, 26*, 309-18. ↗

Santoro, G., Roeske, WR., Horvath, R., Yamamura, HI., Sora, I., Richman, J. et al. (1994). The cloning and expression of a human creatine transporter. *Biochem Biophys Res Commun, 204*, 419-27. ↗

Editions

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