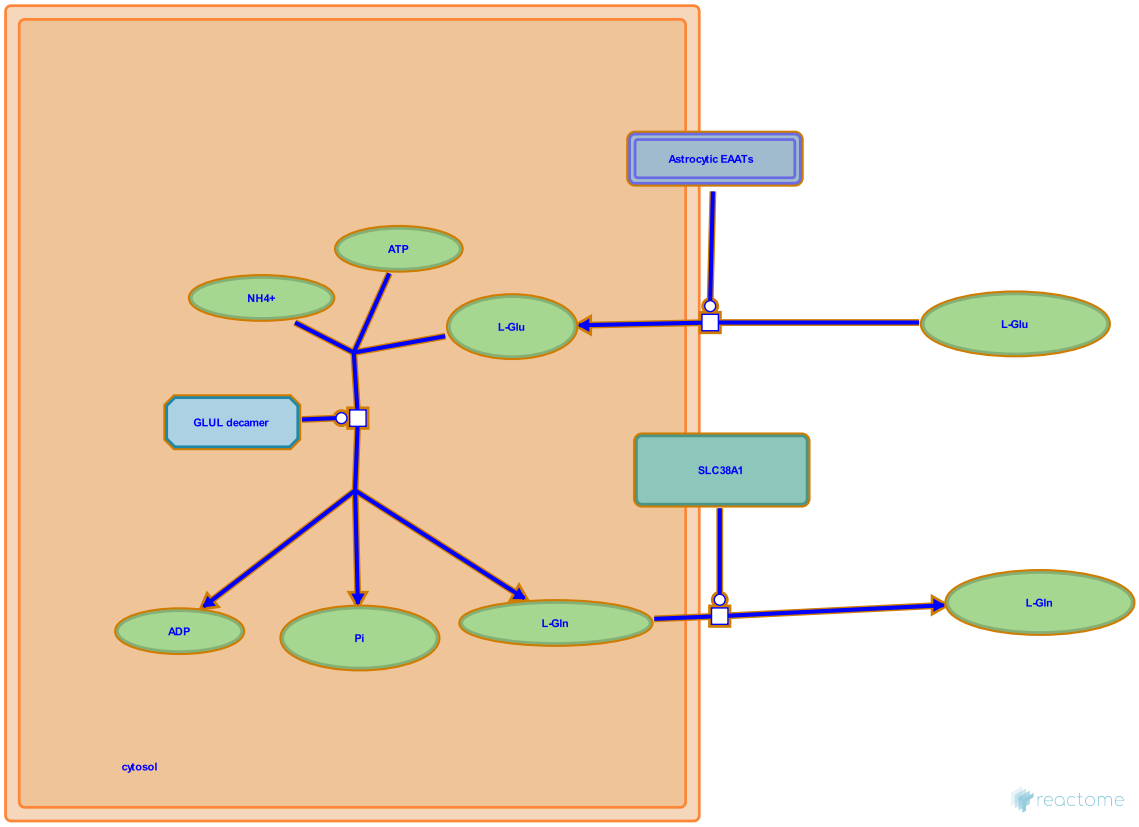
Astrocytic Glutamate-Glutamine Uptake And Metabolism



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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. ↗

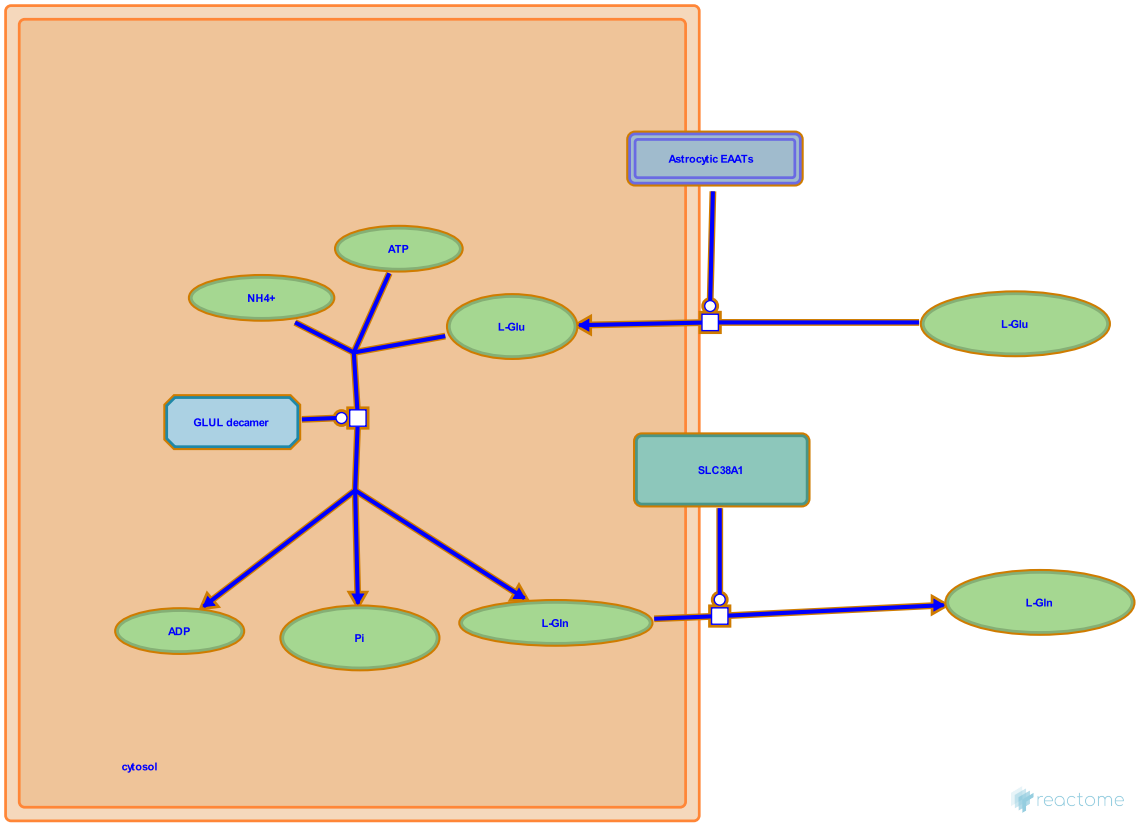
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Astrocytic Glutamate-Glutamine Uptake And Metabolism ↗

Stable identifier: R-HSA-210455

Compartments: cytosol



In astrocytic glutamate-glutamine cycle, the excess glutamate released by the pre-synaptic neuron in the synaptic cleft is transported into the astrocyte by a family glutamate transporters called the excitatory amino acid transporters 1 and 2, EAAT1 and EAAT2. Astrocytes carrying these transporters exist in close apposition to the synapse to clear excess glutamate to prevent excessive activation of neurons and hence neuronal death. Glutamate in astrocytes is converted to glutamine by glutamine synthetase. Glutamine is then transported into the extracellular space by system N transporters. The glutamate in the extracellular space is available for neuronal uptake.

Editions

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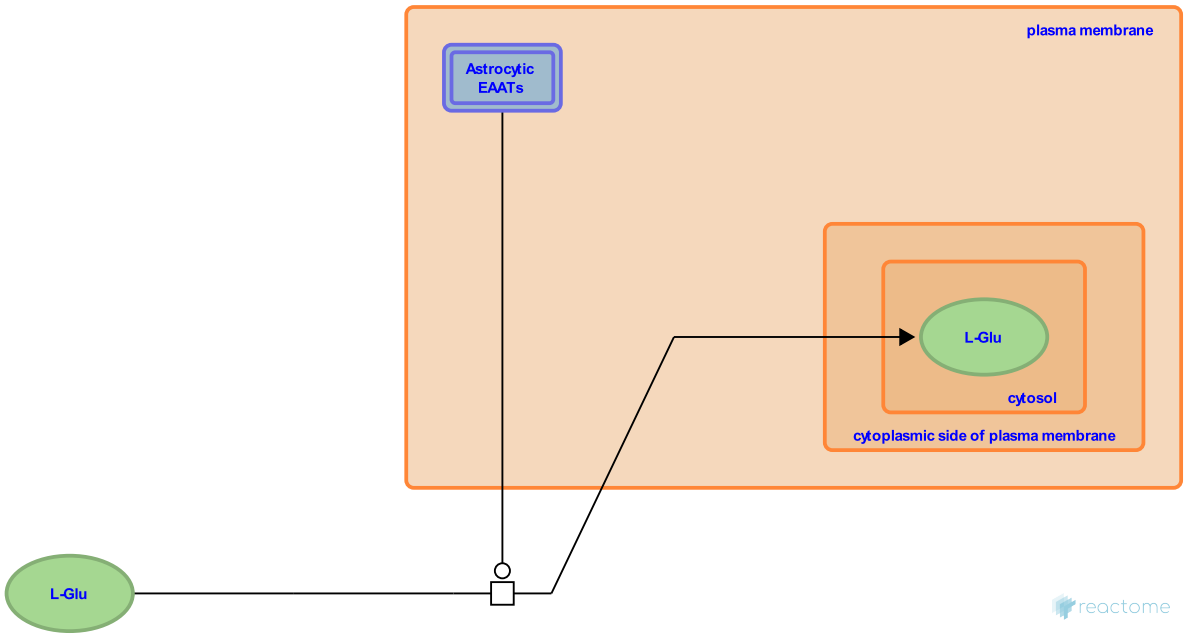
glutamate uptake by astrocytes ↗

Location: Astrocytic Glutamate-Glutamine Uptake And Metabolism

Stable identifier: R-HSA-210439

Type: transition

Compartments: extracellular region, cytosol



There are two classes of glutamate transporters; the excitatory amino acid transporters (EAATs) which depend on an electrochemical gradient of Na+ ions and vesicular glutamate transporters (VGLUTs) which don't. Together, these transporters uptake and release glutamate to mediate this neurotransmitter's excitatory signal and are part of the glutamate-gluatamine cycle. The SLC1 gene family includes five high-affinity glutamate transporters encoded by SLC1, 2, 3, 6 and 7. These transporters can mediate transport of L-Glutamate (L-Glu), L-Aspartate and D-Aspartate with cotransport of 3 Na+ ions and H+ and antiport of a K+ ion. This mechanism allows glutamate into cells against a concentration gradient thus excess L-Glu released by the pre-synaptic neuron in the synaptic cleft is cleared. This is a crucial factor in the protection of neurons against glutamate excitotoxicity in the CNS. SLC1A2 and 3 are mainly expressed by astrocytes whereas SLC1A1 and 6 are predominantly neuronal.
SLC1A1 is expressed throughout the CNS however SLC1A6 is predominantly localized to purkinje cells. SLC1A7 is highly expressed in rod photoreceptor and bipolar cells of the retina. Astrocytic SLC1As are expressed in astrocytes in close apposition to the synapses and neuronal SLC1As are expressed in the extra-synaptic or peri-synaptic locations on the neurons. Astrocytic SLC1As are responsible for majority of the glutamate uptake, neuronal transporters are responsible for glutamate clearance in specialized synapses in cerebellum where the spatial relationship between the glutamate receptors and SLC1As is altered and glutamate receptors are expressed in the peri-synaptic region (Zhou & Danbolt 2014).
Defects in the SLC1A1 gene may be a cause of dicarboxylicamino aciduria (glutamate-aspartate transport defect in the kidney and intestine) (Jen et al. 2005).
PRA1 family protein 3 (ARL6IP5 aka ADP-ribosylation factor-like protein 6-interacting protein 5) is a microtuble-associated protein that is able to regulate intracellular concentrations of glutamate as well as tuarine. It negatively regulates SLC1A1 by decreasing its affinity for glutamate (L-Glu). The activity of human SLC1A1 is based on similarity to rat Eaac1 (aka GTRAP3-18) (Lin et al. 2001).

Followed by: glutamate + NH4+ + ATP => glutamine + ADP + orthophosphate [GLUL]

Literature references

Wong, V., Rothstein, JD., Maragakis, NJ., Rao, MS., Xue, H., Mayer-Proschel, M. et al. (2004). Glutamate transporter expression and function in human glial progenitors. *Glia, 45*, 133-43. ↗

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2009-11-19	Edited	Gillespie, ME.

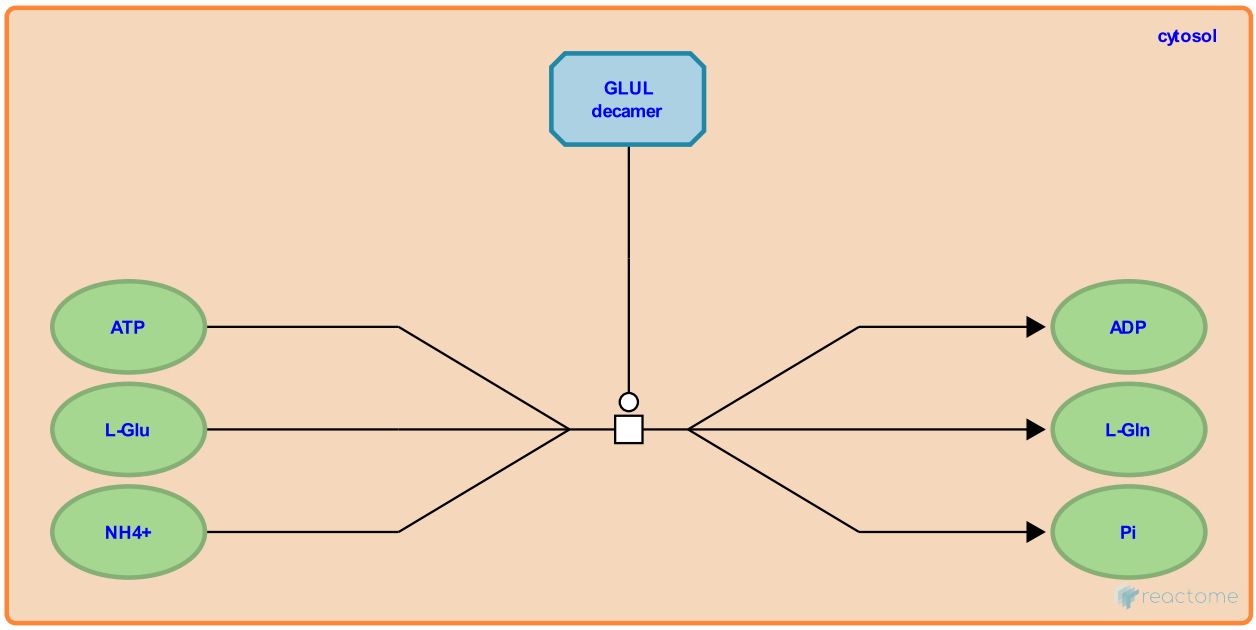
glutamate + NH4+ + ATP => glutamine + ADP + orthophosphate [GLUL] ↗

Location: Astrocytic Glutamate-Glutamine Uptake And Metabolism

Stable identifier: R-HSA-70606

Type: transition

Compartments: cytosol



Cytosolic glutamine synthetase (glutamate-ammonia ligase - GLUL) catalyzes the reaction of glutamate, ammonia, and ATP to form glutamine, ADP, and orthophosphate. The enzyme is a decamer (Krajewski et al. 2008). Mutations in the gene encoding GLUL cause glutamine deficiency in vivo (Haberle et al. 2005).

Preceded by: glutamate uptake by astrocytes

Followed by: Glutamine transport from astrocytes

Literature references

Holmberg-Schiavone, L., Jones, TA., Mowbray, SL., Collins, R., Krajewski, WW., Karlberg, T. (2008). Crystal structures of mammalian glutamine synthetases illustrate substrate-induced conformational changes and provide opportunities for drug and herbicide design. *J Mol Biol, 375*, 217-28. ↗

Gelot, A., Häussinger, D., Toutain, A., Häberle, J., Suc, AL., Hohne, W. et al. (2005). Congenital glutamine deficiency with glutamine synthetase mutations. *N Engl J Med, 353*, 1926-33. ↗

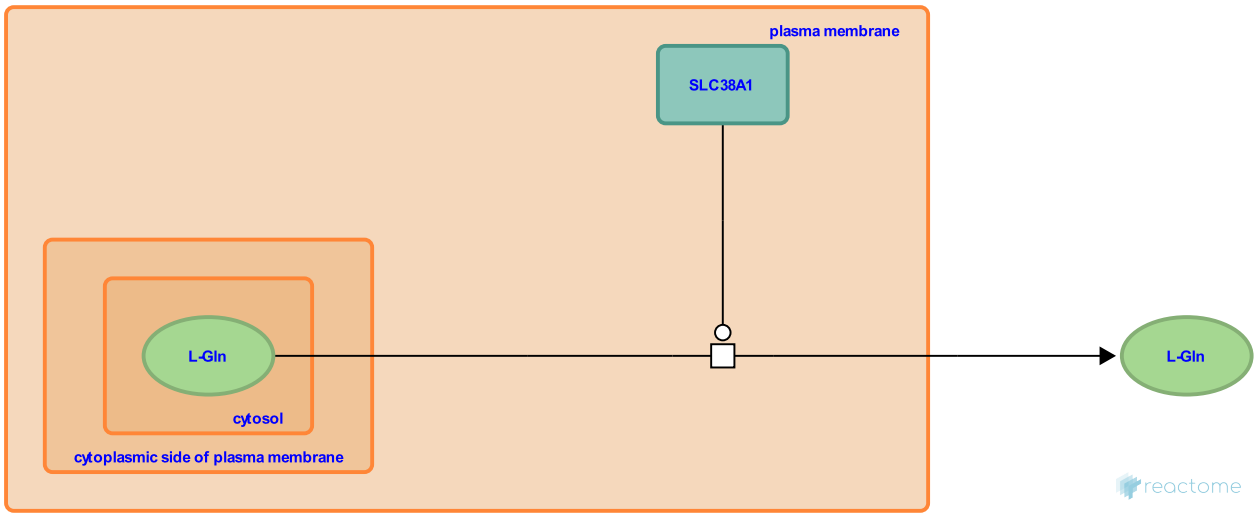
Glutamine transport from astrocytes ↗

Location: Astrocytic Glutamate-Glutamine Uptake And Metabolism

Stable identifier: R-HSA-212614

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Glutamine from the astrocytes is exported to the extracellular compartment via the system N amino acid transporter. The system N transporter is Na+ dependant transporter that has substrate specificity to aspargine, glutamine and histidine.

Preceded by: glutamate + NH4+ + ATP => glutamine + ADP + orthophosphate [GLUL]

Literature references

Pirozhkova, I., Gegelashvili, M., Gegelashvili, G., Zhang, J., Rodriguez-Kern, A., Sung, L. (2006). High-affinity glutamate transporter GLAST/EAAT1 regulates cell surface expression of glutamine/neutral amino acid transporter ASCT2 in human fetal astrocytes. *Neurochem Int, 48*, 611-5. ↗

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Table of Contents