**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**


Reactome database release: 79

This document contains 1 pathway and 8 reactions (see Table of Contents)
Communication at the synapse involves the release of glutamate from the presynaptic neuron and its binding to glutamate receptors on the postsynaptic cell to generate a series of events that lead to propagation of the synaptic transmission. This process begins with the formation of synaptic vesicles in the presynaptic neuron, proceeds to the loading of glutamate into the vesicles, and concludes with the release of glutamate into the synaptic cleft.

The glutamate life cycle in the neuron begins with the loading of the nascent synaptic vesicles with cytosolic glutamate with the help the transporter protein, VGLUT1, located in the synaptic vesicular membrane. Glutamate loaded vesicles are formed in the cytoplasm and then transported to a site close to the plasma membrane where the vesicle is docked with the help of several proteins. One of the key players in the docking process is Munc 18, which interacts with syntaxin (in the plasma membrane), MINT (Munc18 interacting molecule), and DOC2. These interactions along with the secondary interactions are needed for docking the synaptic vesicle to the plasma membrane.

The docked synaptic vesicle is not ready for release until it undergoes molecular changes to prime it for fusion with the plasma membrane. Munc13 is one of the main players in the priming process. Munc 13 interacts with RIM (Rab3A interacting molecule) located in the synaptic vesicle. Munc 13 also interacts with DOC2. The precise molecular mechanisms of the interactions that result in docking versus priming are not clear and the docking and priming process have been combined in this annotation of this pathway. Once primed the synaptic vesicle is ready for release.

Synaptic transmission involves an action potential that is generated in the presynaptic cell which induces the opening of voltage gated Ca2+ channels (VGCC) located in the plasma membrane of the presynaptic neuron. Typically N, P/Q and R type of VGCCs are involved in the neurotransmitter release. Ca2+ influx through these channels results in the rise of intracellular Ca2+ concentration. In the microdomain of...
glutamatergic synapses, the Ca$^2+$ concentration could rise between 10-25 micro molar. Synaptotagmin, a Ca$^2+$-binding protein located in the synaptic vesicular membrane, responds to the rise in the Ca$^2+$ levels in the microdomain and induces a synaptic vesicle membrane curvature that favors vesicle fusion. Fusion of the synaptic vesicle with the plasma membrane is characterized by the formation of a trimeric trans-SNARE complex that involves VAMP2 from the synaptic vesicle membrane, and syntaxin and SNAP-25 from plasma membrane. Vesicle fusion incorporates the synaptic vesicle membrane into the plasma membrane, releasing the vesicle contents (glutamate) into the synaptic cleft. Postfusion the synaptic vesicle membrane proteins (VAMP2, Rab3A, VGLUT1, and synaptotagmin) are also found in the plasma membrane.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008-01-14</td>
<td>Authored, Edited</td>
<td>Mahajan, SS.</td>
</tr>
<tr>
<td>2008-04-24</td>
<td>Reviewed</td>
<td>Kavalali, E.</td>
</tr>
</tbody>
</table>
L-Glutamine transport into neurons

**Location:** Glutamate Neurotransmitter Release Cycle

**Stable identifier:** R-HSA-212642