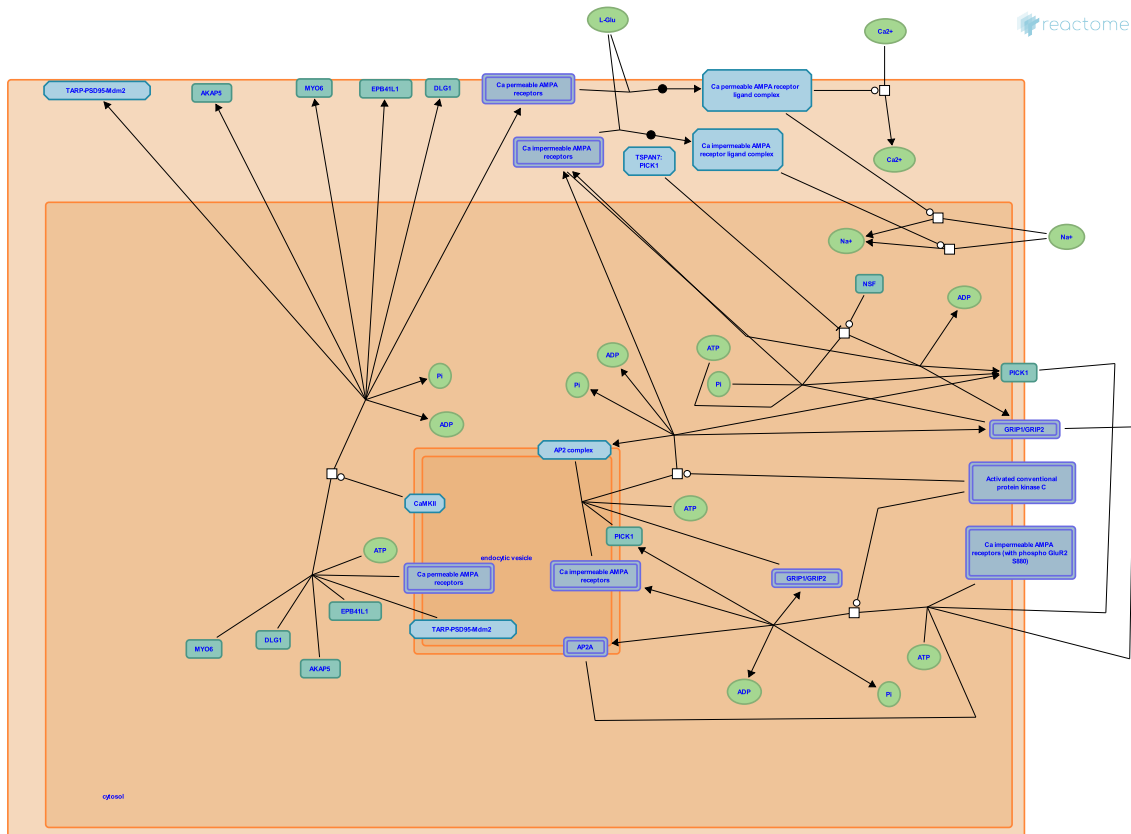


Glutamate binding, activation of AMPA receptors and synaptic plasticity



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook).

01/04/2024

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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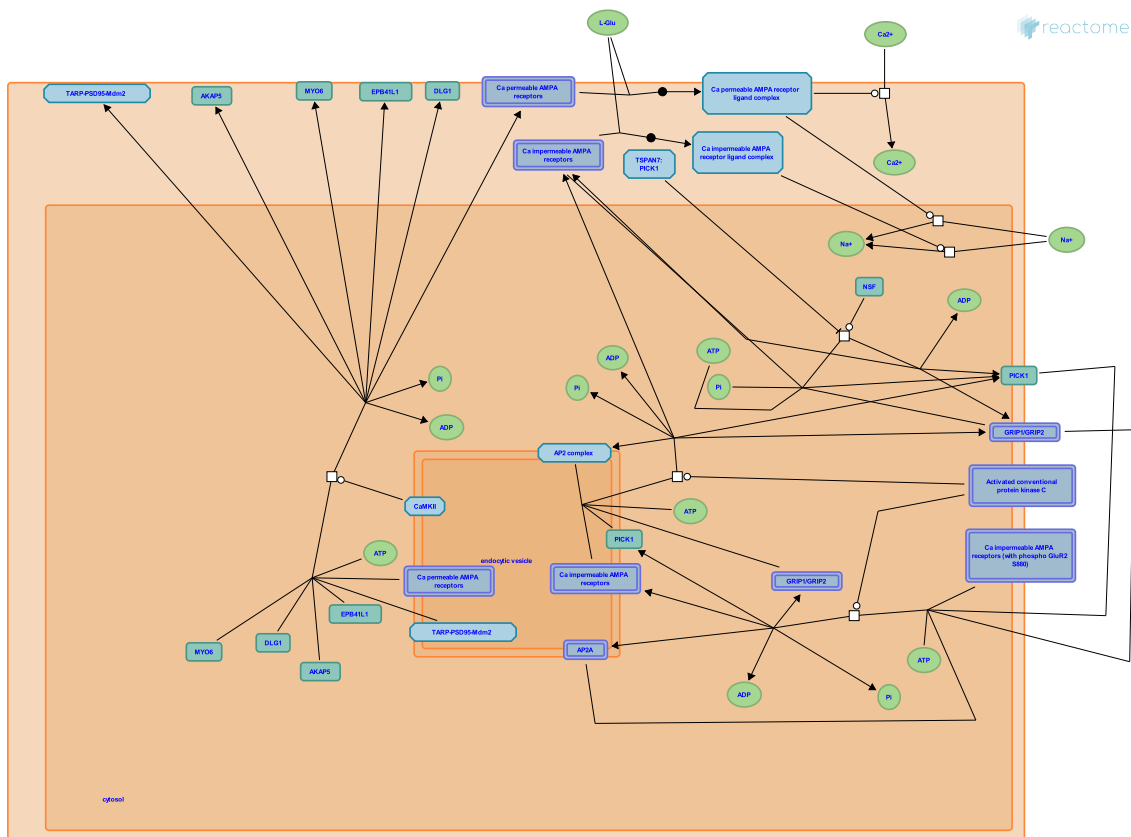
Reactome database release: 88

This document contains 3 pathways ([see Table of Contents](#))

Glutamate binding, activation of AMPA receptors and synaptic plasticity ↗

Stable identifier: R-HSA-399721

Compartments: extracellular region, plasma membrane



Excitatory synaptic transmission in the brain is carried out by glutamate receptors through the activation of both ionotropic and metabotropic receptors. Ionotropic glutamate receptors are of three subtypes based on distinct physiologic properties and their differential binding of exogenous ligands namely NMDA (N-methyl D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and Kainate . The ionotropic receptors are glutamate gated ion channels that initiate signaling by influx of ions, and are comprised of subunits with distinct structures and distinguished based on their agonist binding. Even though all three types of receptors are found at the glutamatergic synapses yet they exhibit great diversity in the synaptic distribution. The metabotropic glutamate receptors are a family of G-protein coupled receptors that are slow acting. Fast excitatory synaptic transmission is carried out through AMPA receptors. Post-synaptic transmission involves binding of the ligand such as glutamate/AMPA to the AMPA receptor resulting in the Na influx which causes depolarization of the membrane. NMDA receptors are blocked by Mg at resting membrane potential. NMDA receptors are activated upon coincident depolarization and glutamate binding are activated following AMPA receptor activation. NMDA receptors are blocked by Mg at resting

membrane potential. NMDA receptors are Ca permeable and their activity leads to increase in Ca which, leads to upregulation of AMPA receptors at the synapse which causes the long lasting excitatory post-synaptic potential (EPSP) which forms the basis of long term potentiation (LTP). LTP is one form of synaptic plasticity wherein the strength of the synapses is enhanced by either change in the number, increase in the efficacy by phosphorylation or change in the type of receptors. Phosphorylation of AMPA receptors changes the localization of the receptors, increases the single channel conductance, and increases the probability of open channel. GluR1 has four phosphorylation sites; serine 818 (S818) is phosphorylated by PKC and is necessary for LTP, serine 831 (S831) is phosphorylated by CaMKII that increases the delivery of receptors to the synapse and also increased their single channel conductance, threonine (T840) is implicated in LTP. Serine 845 (S845) is phosphorylated by PKA which regulates open channel probability. Long term depression is another form of plasticity wherein the number of AMPA receptors is diminished by either phosphorylation of GluR2 at Ser880 or dephosphorylation of GluR1 by protein phosphatase1, protein phosphatase 2A and protein phosphatase 2B (calcineurin).

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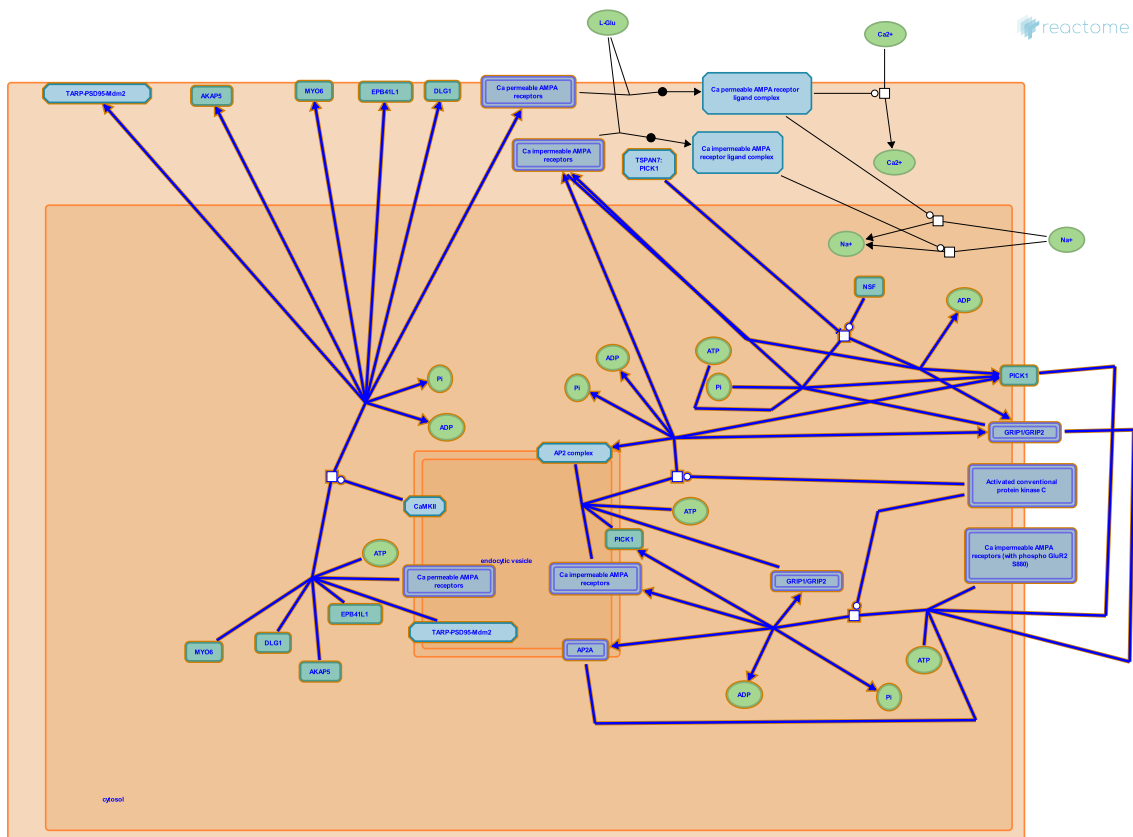
Editions

2008-01-14	Authored, Edited	Mahajan, SS.
2009-05-15	Reviewed	Ziff, EB.

Trafficking of AMPA receptors ↗

Location: Glutamate binding, activation of AMPA receptors and synaptic plasticity

Stable identifier: R-HSA-399719



Repetitive presynaptic activity causes long lasting changes in the postsynaptic transmission by changing the type and the number of AMPA receptors. These changes are brought about by trafficking mechanisms that are mainly controlled by activity dependent phosphorylation/desphosphorylation of the GluR1/GluR2 subunits.

Literature references

Kessels, HW., Malinow, R. (2009). Synaptic AMPA receptor plasticity and behavior. *Neuron*, 61, 340-50. ↗

Editions

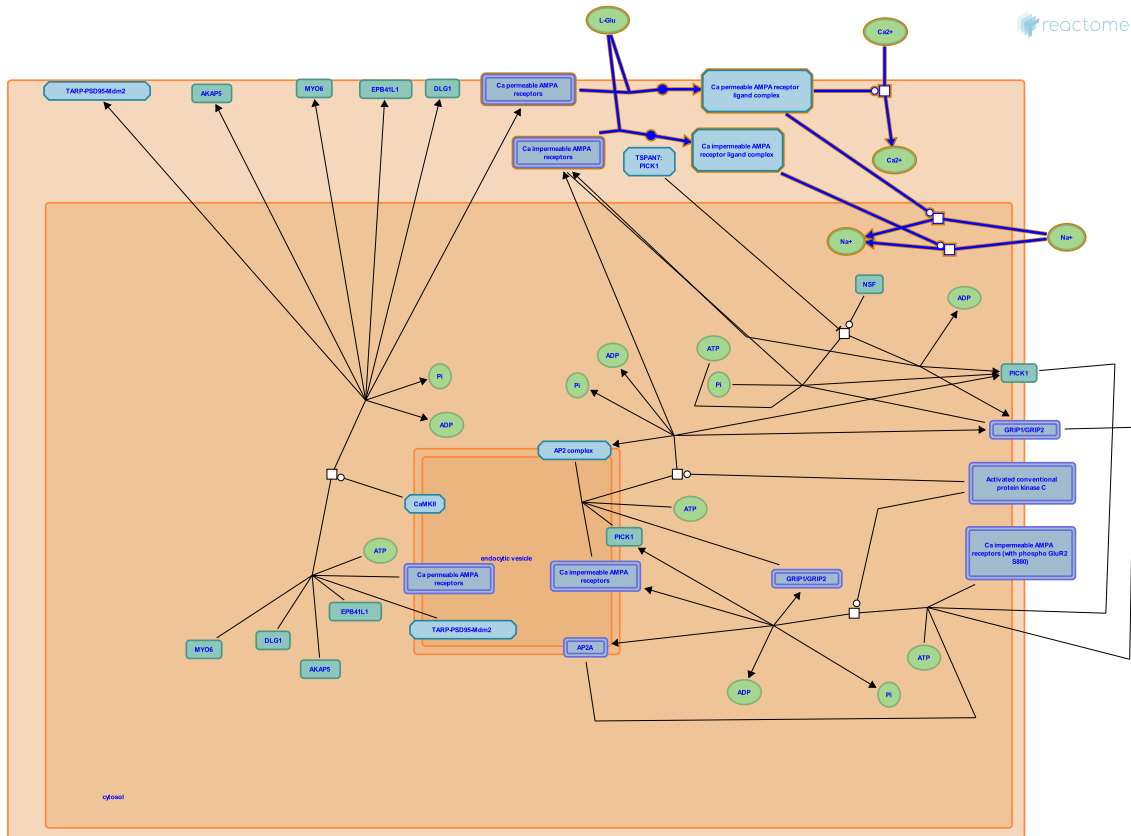
2008-01-14	Authored, Edited	Mahajan, SS.
2009-05-15	Reviewed	Ziff, EB.

Activation of AMPA receptors ↗

Location: Glutamate binding, activation of AMPA receptors and synaptic plasticity

Stable identifier: R-HSA-399710

Compartments: plasma membrane, extracellular region



AMPA receptors are functionally either Ca permeable or Ca impermeable based on the subunit composition. Ca permeability is determined by GluR2 subunit which undergoes post-transcriptional RNA editing that changes glutamine (Q) at the pore to arginine (R). Incorporation of even a single subunit in the AMPA receptor confers Ca-limiting properties. Ca permeable AMPA receptors permit Ca and Na whereas Ca impermeable AMPA receptors permit only Na. In general, glutamatergic neurons contain Ca impermeable AMPA receptors and GABAergic interneurons contain Ca permeable AMPA receptors. However, some synapses do contain a mixture of Ca permeable and Ca impermeable AMPA receptors. GluR1-4 are encoded by four genes however, alternative splicing generates several functional subunits namely long and short forms of GluR1 and GluR2. GluR4 has long tail only and GluR3 has short tail only. Besides the differences in the tail length, flip/flop isoforms are generated by an interchangeable exon that codes the fourth membranous domain towards the C terminus. The flip/flop isoforms determine rate of desensitization/resensitization and the rate of channel closing. Receptors homomers or heteromers assembled from the combination of GluR1-4 subunits that vary in C tail length and flip/flop versions generates a whole battery of functionally distinct AMPA receptors.

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Editions

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