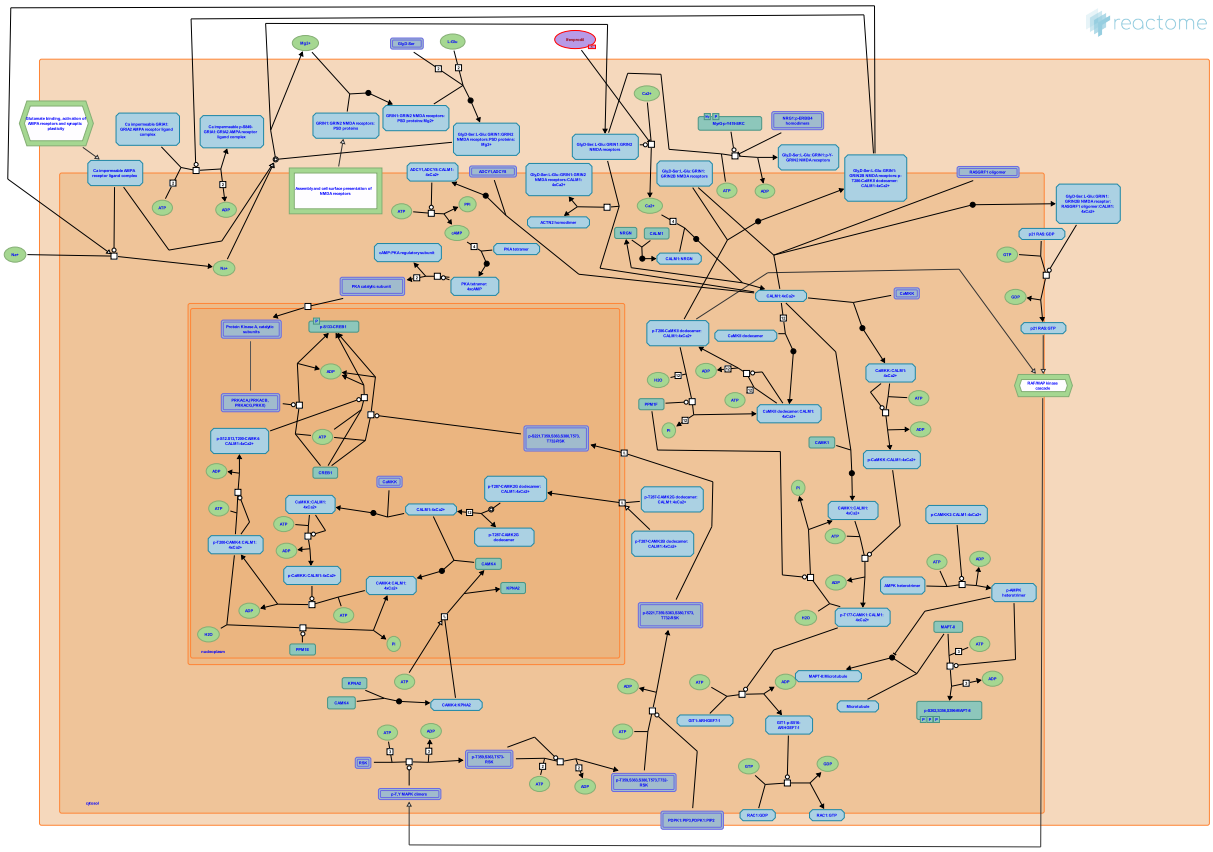
Activation of NMDA receptors and post-synaptic events



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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.

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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. ↗

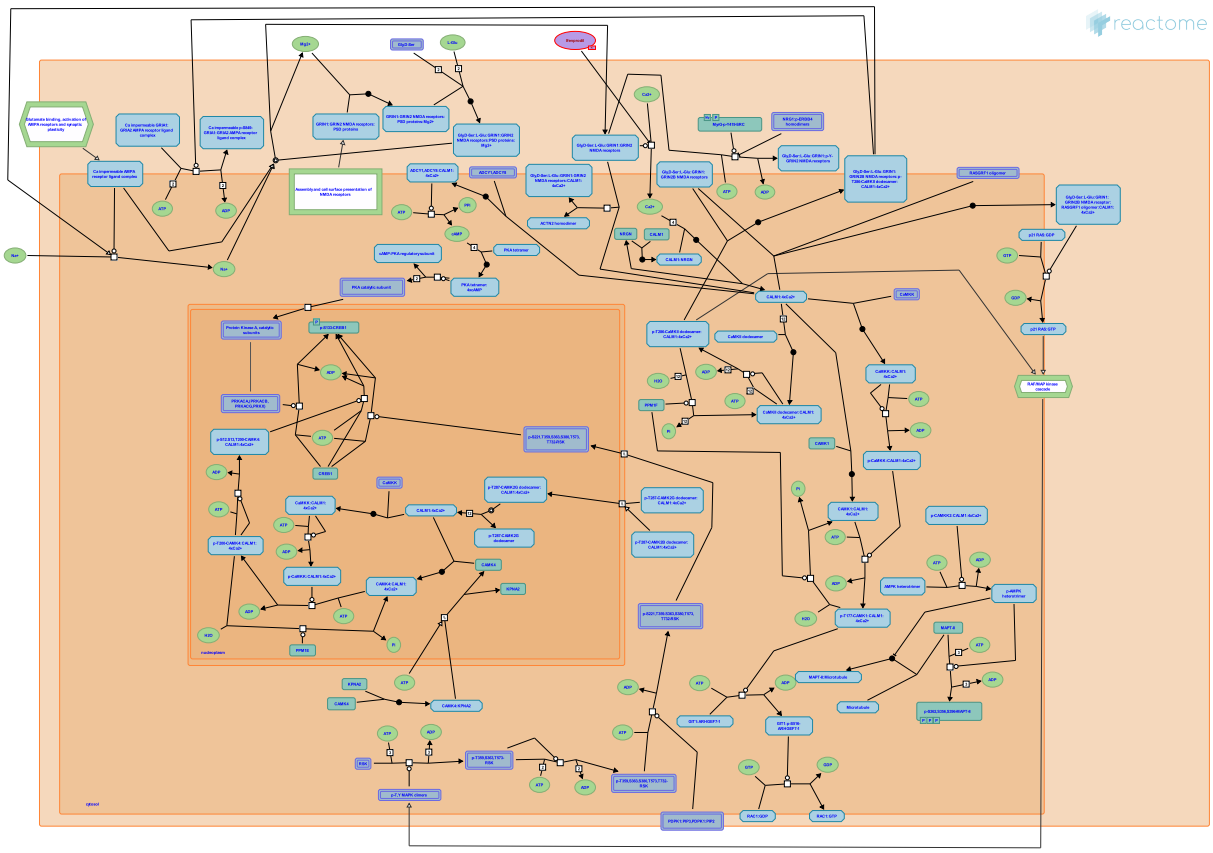
Reactome database release: 88

This document contains 5 pathways (see Table of Contents)

Activation of NMDA receptors and postsynaptic events ↗

Stable identifier: R-HSA-442755

Compartments: extracellular region, plasma membrane, cytosol, nucleoplasm



NMDA receptors are a subtype of ionotropic glutamate receptors that are specifically activated by a glutamate agonist N-methyl-D-aspartate (NMDA). Activation of NMDA receptors involves opening of the ion channel that allows the influx of Ca2+. NMDA receptors are central to activity dependent changes in synaptic strength and are predominantly involved in the synaptic plasticity that pertains to learning and memory. A unique feature of NMDA receptors, unlike other glutamate receptors, is the requirement for dual activation, both voltage-dependent and ligand-dependent activation. The ligand-dependent activation of NMDA receptors requires co-activation by two ligands, glutamate and glycine. However, at resting membrane potential, the pore of ligand-bound NMDA receptors is blocked by Mg2+. The voltage dependent Mg2+ block is relieved upon depolarization of the post-synaptic membrane. NMDA receptors are coincidence detectors, and are activated only if there is a simultaneous activation of both pre- and post-synaptic cell. Upon activation, NMDA receptors allow the influx of Ca2+ that initiates various molecular signaling cascades involved in the processes of learning and memory. For review, please refer to Cohen and Greenberg 2008, Hardingham and Bading 2010, Traynelis et al. 2010, and Paoletti et al. 2013.

Literature references

Hardingham, GE., Bading, H. (2010). Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat. Rev. Neurosci., 11*, 682-96. ↗

Cohen, S., Greenberg, ME. (2008). Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. *Annu Rev Cell Dev Biol, 24*, 183-209. ↗

Myers, SJ., Dingledine, R., Ogden, KK., Wollmuth, LP., Menniti, FS., Hansen, KB. et al. (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol. Rev., 62*, 405-96. ↗

Zhou, Q., Paoletti, P., Bellone, C. (2013). NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci., 14*, 383-400. ↗

Editions

2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
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2018-11-02	Reviewed	Hansen, KB., Yi, F.
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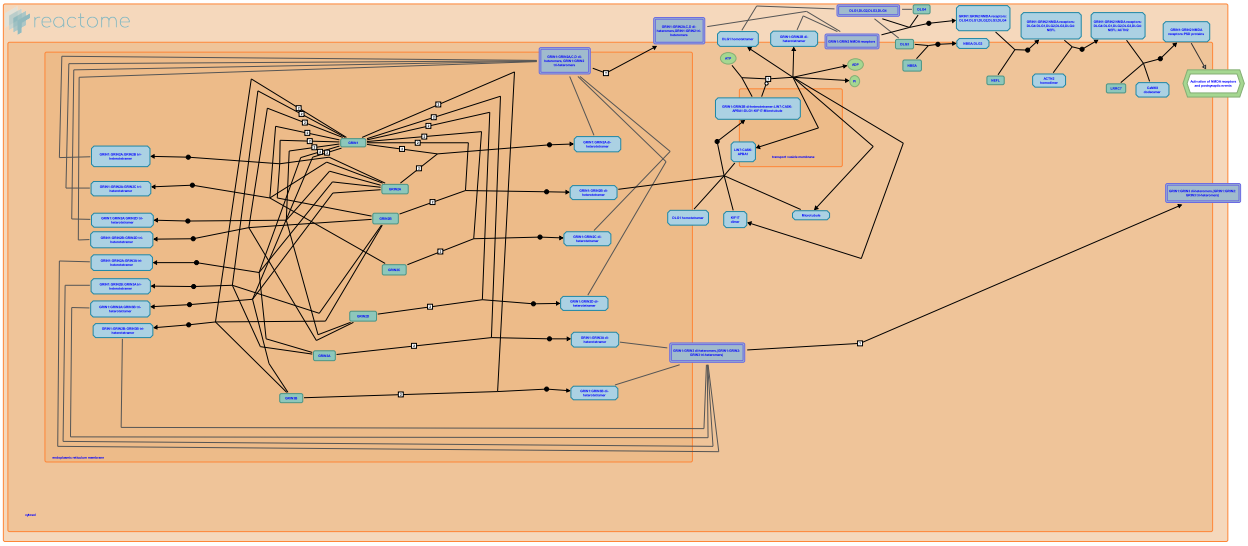
Assembly and cell surface presentation of NMDA receptors ↗

Location: Activation of NMDA receptors and postsynaptic events

Stable identifier: R-HSA-9609736



N-methyl-D-aspartate receptors (NMDARs) are tetramers that consist of two GluN1 (GRIN1) subunits and two subunits that belong to either the GluN2 (GRIN2) subfamily (GluN2A, GluN2B, GluN2C and GluN2D) or the GluN3 (GRIN3) subfamily (GluN3A and GluN3B). The GluN2/GluN3 subunits in the NMDA tetramer can either be identical, constituting an NMDA di-heteromer (di-heterotetramer), which consists of two subunit types, GluN1 and one of GluN2s/GluN3s, or they can be two different GluN2/GluN3 proteins, constituting an NMDA tri-heteromer (tri-heterotetramer), which consists of three subunit types, GluN1 and two of GluN2s/GluN3s (Monyer et al. 1992, Wafford et al. 1993, Sheng et al. 1994, Dunah et al. 1998, Perez-Otano et al. 2001, Chatterton et al. 2002, Matsuda et al. 2002, Yamakura et al. 2005, Nilsson et al. 2007, Hansen et al. 2014, Kaiser et al. 2018, Bhattacharya et al. 2018, Bhattacharya and Traynelis 2018).
NMDA tetramers assemble in the endoplasmic reticulum and traffic to the plasma membrane as part of transport vesicles (McIlhinney et al. 1998, Perez-Otano et al. 2001). NMDA receptor subunits undergo N-glycosylation, which impacts their trafficking from the endoplasmic reticulum to the plasma membrane. Trafficking efficiency may vary among different subunits of NMDARs (Lichnereva et al. 2015). Mechanistic details, such as glycosyl transferases involved and the type of sugar side chains added, are not known.
As there are eight splicing isoforms of GluN1, four different GluN2 and two different GluN3 proteins, many different combinations of NMDAR subunits are possible, but only a handful of distinct NMDAR receptors have been experimentally confirmed and functionally studied. The composition of NMDARs affects trafficking, spatial (including synaptic) localization, ligand preference, channel conductivity and downstream signal transmission. Prevalent NMDARs differ at different stages of neuronal development, in different regions of the central nervous system, and at different levels of neuronal activity. For review, please refer to Lau and Zukin 2007, Traynelis et al. 2010, Paoletti et al. 2013, Pérez-Otaño et al. 2016, Iacobucci and Popescu 2017.

Literature references

Bhattacharya, S., DiRaddo, JO., Khatri, A., Hansen, KB., Yi, F., Swanger, SA. et al. (2018). Triheteromeric GluN1/GluN2A/GluN2C NMDARs with Unique Single-Channel Properties Are the Dominant Receptor Population in Cerebellar Granule Cells. *Neuron, 99*, 315-328.e5. ↗

Askalany, AR., Yamakura, T., Baba, H., Sakimura, K., Petrenko, AB., Kohno, T. (2005). The NR3B subunit does not alter the anesthetic sensitivities of recombinant N-methyl-D-aspartate receptors. *Anesth. Analg., 100*, 1687-92. ↗

Larsen, RS., Pérez-Otaño, I., Wesseling, JF. (2016). Emerging roles of GluN3-containing NMDA receptors in the CNS. *Nat. Rev. Neurosci., 17*, 623-35. ↗

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Zhou, Q., Paoletti, P., Bellone, C. (2013). NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci., 14*, 383-400. ↗

Editions

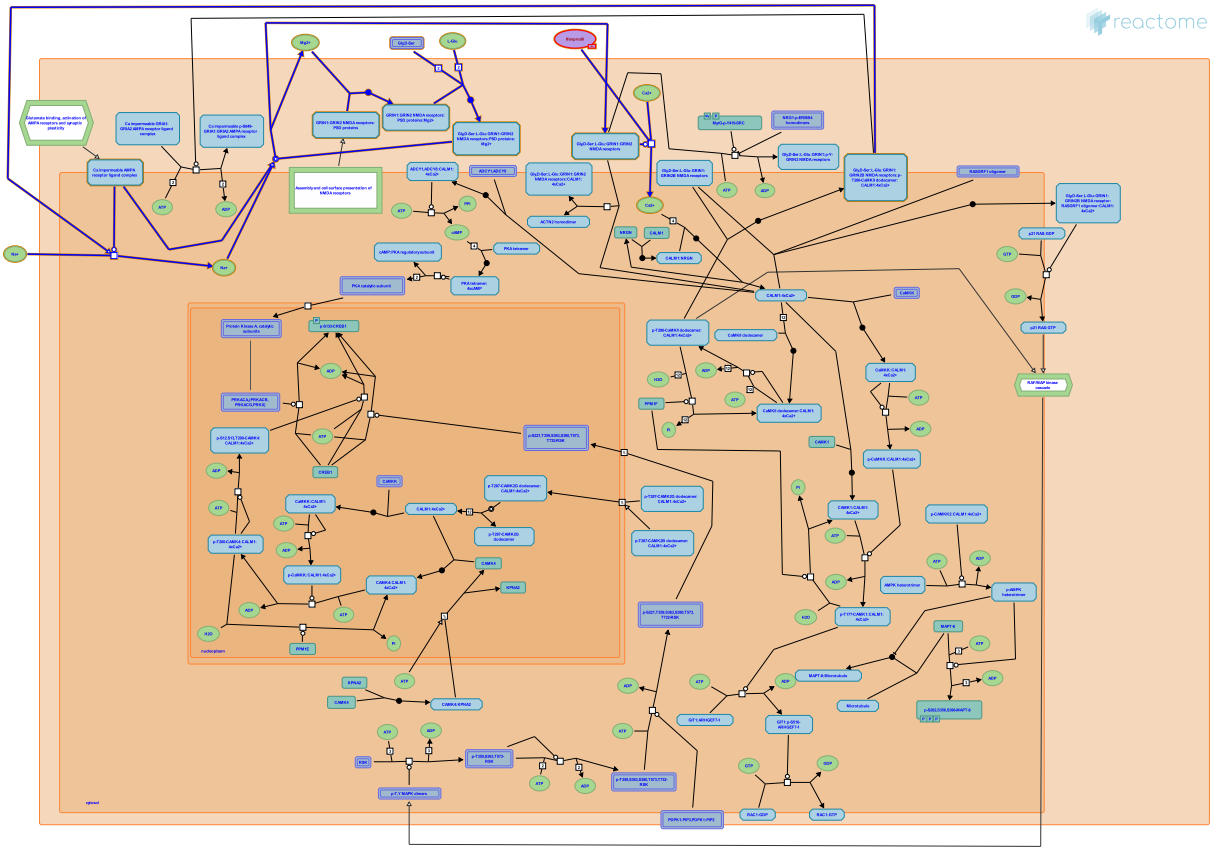
2019-01-05	Authored	Orlic-Milacic, M.
2019-02-11	Reviewed	Traynelis, SF., Bhattacharya, S., Camp, C.
2019-02-19	Edited	Orlic-Milacic, M.

Unblocking of NMDA receptors, glutamate binding and activation ↗

Location: Activation of NMDA receptors and postsynaptic events

Stable identifier: R-HSA-438066

Compartments: plasma membrane



At resting membrane potential, the NMDA receptor ion channel is blocked by extracellular Mg2+ ions and is unable to mediate ion permeation upon binding of ligands (glutamate, glycine, D-serine, NMDA). The voltage block is removed upon depolarization of the post-synaptic cell membrane and Mg2+ is expelled from the NMDA receptor pore (channel), resulting in activated ligand-bound NMDA receptors. The depolarization of the membrane may happen in response to activation of Ca2+ impermeable AMPA receptors, which facilitates Na+ influx, contributing to the unblocking of NMDA receptors. For review, please refer to Traynelis et al. 2010, Paoletti et al. 2013, and Iacobucci and Popescu 2017.

Literature references

Popescu, GK., Iacobucci, GJ. (2017). NMDA receptors: linking physiological output to biophysical operation. *Nat. Rev. Neurosci., 18*, 236-249. ↗

Myers, SJ., Dingledine, R., Ogden, KK., Wollmuth, LP., Menniti, FS., Hansen, KB. et al. (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol. Rev., 62*, 405-96. ↗

Zhou, Q., Paoletti, P., Bellone, C. (2013). NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci., 14*, 383-400. ↗

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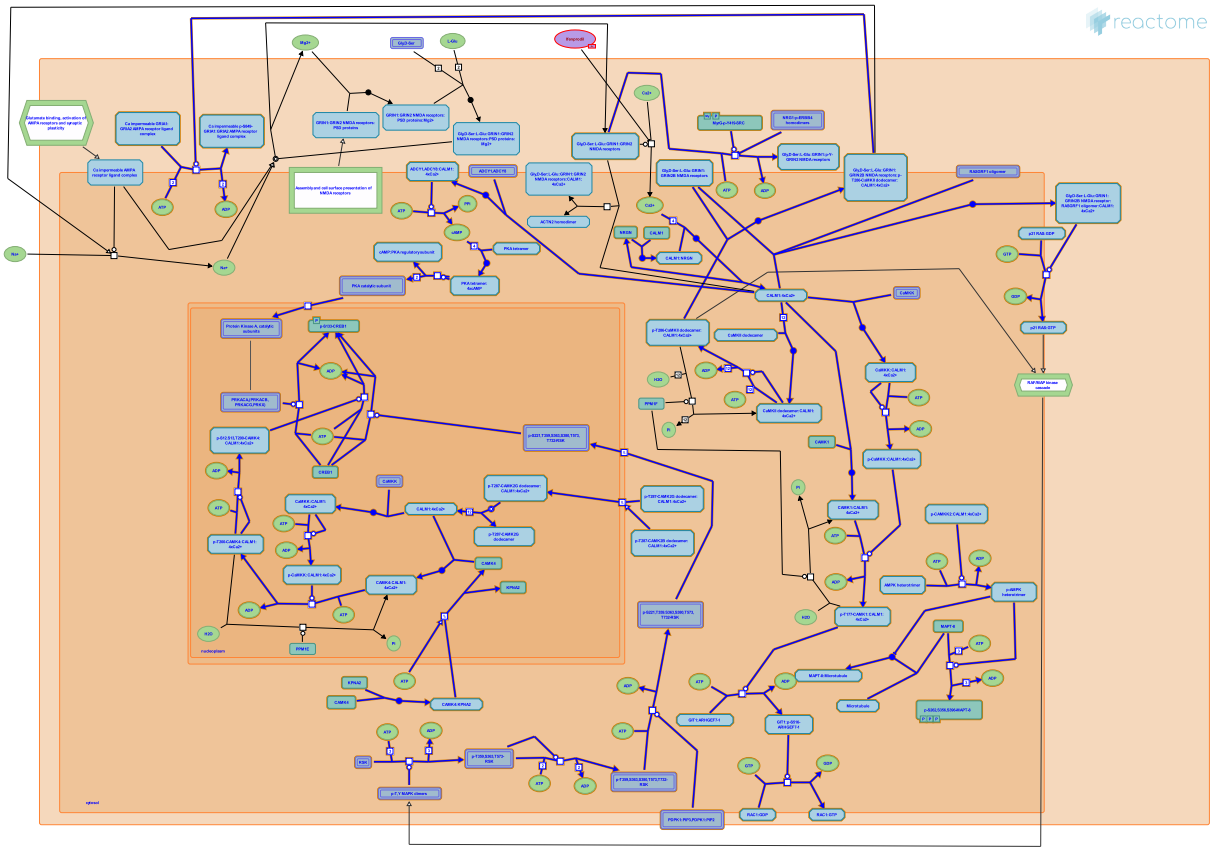
Post NMDA receptor activation events ↗

Location: Activation of NMDA receptors and postsynaptic events

Stable identifier: R-HSA-438064

Compartments: nucleoplasm, plasma membrane, cytosol



Ca2+ influx through the NMDA receptor initiates subsequent molecular pathways that have a defined role in establishing long-lasting synaptic changes. The molecular signaling initiated by a rise in Ca2+ within the spine leads to phosphorylation of Cyclic AMP Response Element binding protein (CREB1) at serine S133, leading to transcription of genes involved in long lasting changes at the synapse. The phosphorylation of CREB1 triggered by increased Ca2+ can be brought about by distinct molecular pathways that may involve MAP kinase, activation of adenylate cyclase and activation of CaMKIV (reviewed by Cohen and Greenberg 2008 and Hunt and Castillo 2012).

Literature references

Castillo, PE., Hunt, DL. (2012). Synaptic plasticity of NMDA receptors: mechanisms and functional implications. *Curr. Opin. Neurobiol., 22*, 496-508. ↗

Cohen, S., Greenberg, ME. (2008). Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. *Annu Rev Cell Dev Biol, 24*, 183-209. ↗

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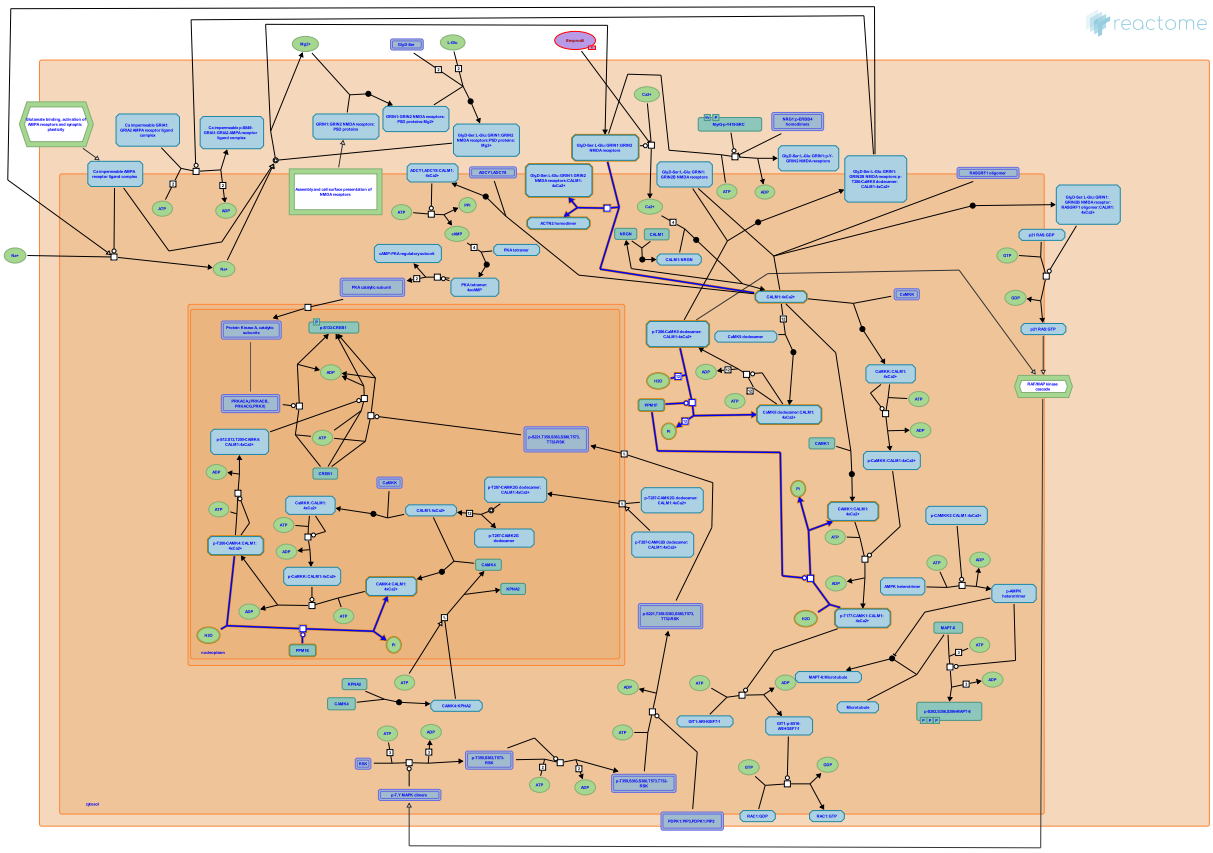
Negative regulation of NMDA receptor-mediated neuronal transmission

Location: Activation of NMDA receptors and postsynaptic events

Stable identifier: R-HSA-9617324



The duration of NMDA receptor-mediated neuronal transmission can be limited by binding of the activated calmodulin to the activated NMDA receptor. In addition to shortening the NMDA channel pore open state, calmodulin interferes with ACTN2-mediated anchoring of NMDA receptors to the postsynaptic density (Ehlers et al. 1996, Wyszynski et al. 1997). Protein phosphatases PPM1E and PPM1F dephosphorylate activated calcium/calmodulin-dependent kinases (CaMKs), thus halting CaMK-mediated signaling (Ishida, Okuno et al. 1998, Ishida et al. 1998, Kitani et al. 2003).

Literature references

Ishida, A., Fujisawa, H., Kameshita, I. (1998). A novel protein phosphatase that dephosphorylates and regulates Ca2+/calmodulin-dependent protein kinase II. *J. Biol. Chem., 273*, 1904-10.

Beggs, AH., Wyszynski, M., Lin, J., Craig, AM., Sheng, M., Nigh, E. et al. (1997). Competitive binding of alpha-actinin and calmodulin to the NMDA receptor. *Nature, 385*, 439-42.

Bernhadt, JP., Zhang, S., Huganir, RL., Ehlers, MD. (1996). Inactivation of NMDA receptors by direct interaction of calmodulin with the NR1 subunit. *Cell, 84*, 745-55.

Ishida, A., Fujisawa, H., Kitani, T., Kameshita, I., Okuno, S. (1998). Regulation of multifunctional Ca2+/calmodulin-dependent protein kinases by Ca2+/calmodulin-dependent protein kinase phosphatase. *Biochem. Biophys. Res. Commun., 253*, 159-63.

Fujisawa, H., Okuno, S., Kitani, T., Takeuchi, M. (2003). Subcellular distributions of rat CaM kinase phosphatase N and other members of the CaM kinase regulatory system. *J. Neurochem., 86*, 77-85.

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2018-10-10	Authored	Orlic-Milacic, M.
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