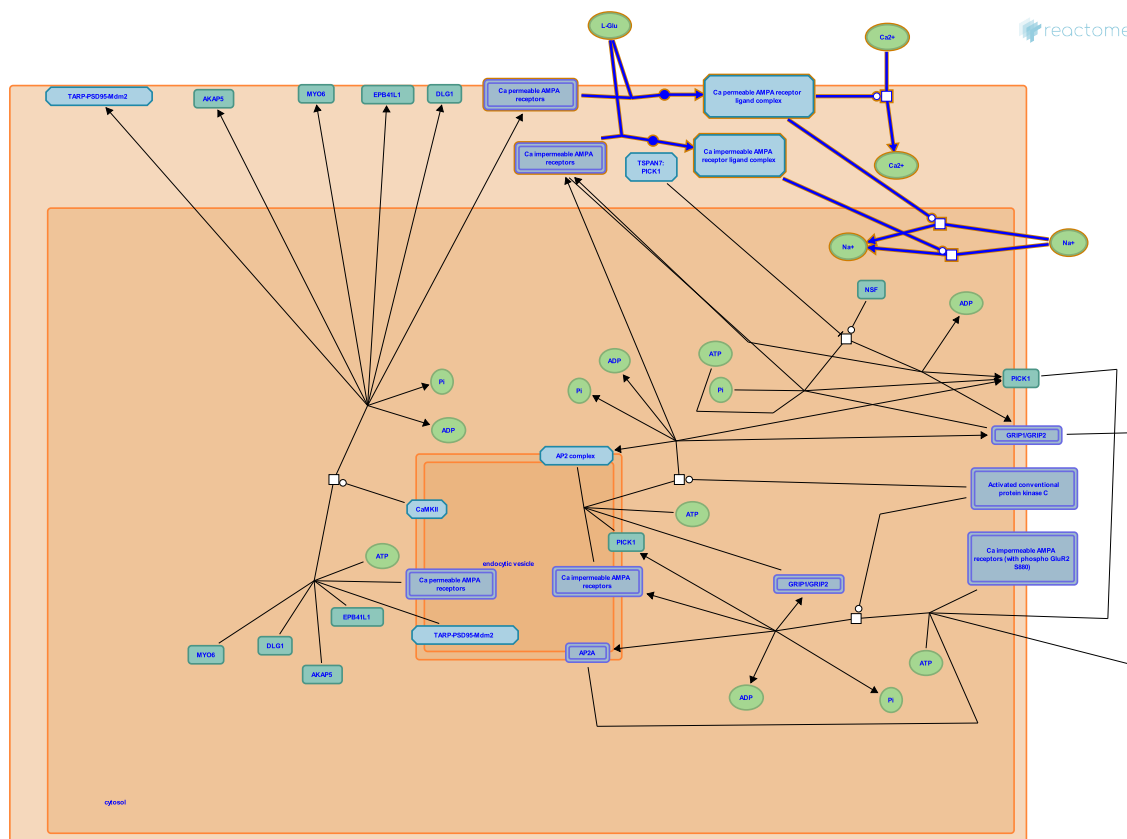


Activation of AMPA receptors



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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).

19/05/2024

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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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. [↗](#)

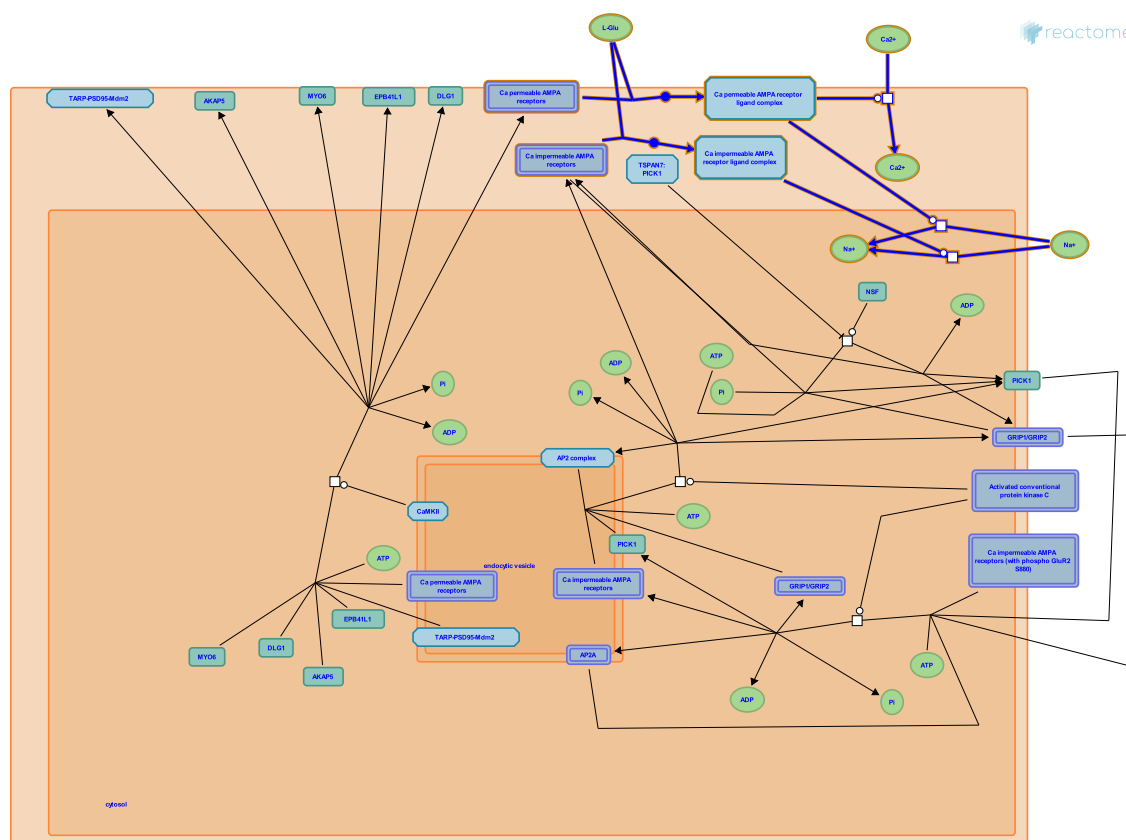
Reactome database release: 88

This document contains 1 pathway and 5 reactions ([see Table of Contents](#))

Activation of AMPA receptors ↗

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.

Literature references

- Niu, L., Huang, Z., Pei, W. (2007). GluR3 flip and flop: differences in channel opening kinetics. *Biochemistry*, 46, 2027-36. ↗
- Burnashev, N., Schoepfer, R., Mosbacher, J., Ruppersberg, JP., Seeburg, PH., Monyer, H. (1994). A molecular determinant for submillisecond desensitization in glutamate receptors. *Science*, 266, 1059-62. ↗
- Schuman, EM., Seeburg, PH. (2006). Signalling mechanisms. *Curr Opin Neurobiol*, 16, 247-50. ↗

Editions

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

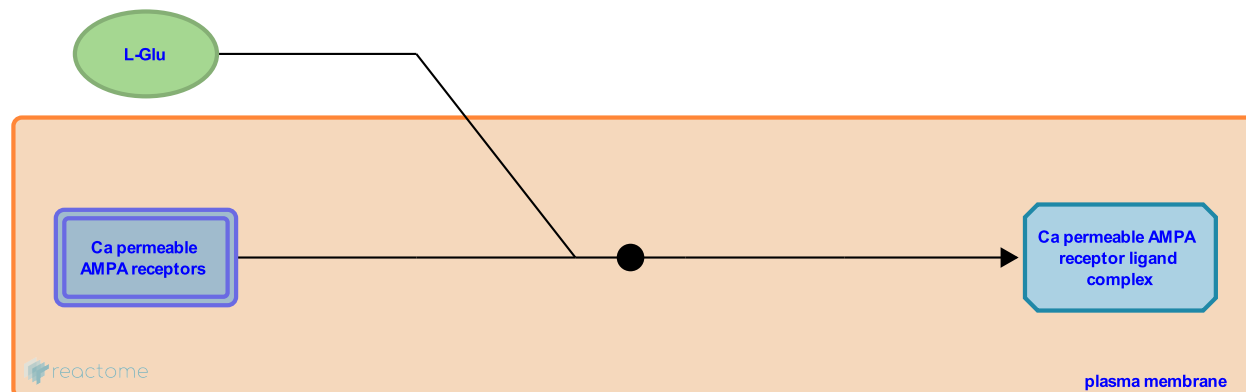
Ca permeable AMPA receptor ligand binding ↗

Location: [Activation of AMPA receptors](#)

Stable identifier: R-HSA-420977

Type: binding

Compartments: plasma membrane, extracellular region



AMPA receptors bind glutamate, released in the synaptic cleft by the presynaptic cell, in the ligand binding region in the N terminal domain.

Followed by: [Activation of Ca permeable AMPA receptors](#)

Literature references

Keinänen, K., Joupila, A., Koskelainen, S., Coleman, SK., Rivera, C., Korpi, ER. et al. (2009). Agonist occupancy is essential for forward trafficking of AMPA receptors. *J Neurosci*, 29, 303-12. ↗

Niu, L., Li, G., Pei, W. (2003). Channel-opening kinetics of GluR2Q(flip) AMPA receptor: a laser-pulse photolysis study. *Biochemistry*, 42, 12358-66. ↗

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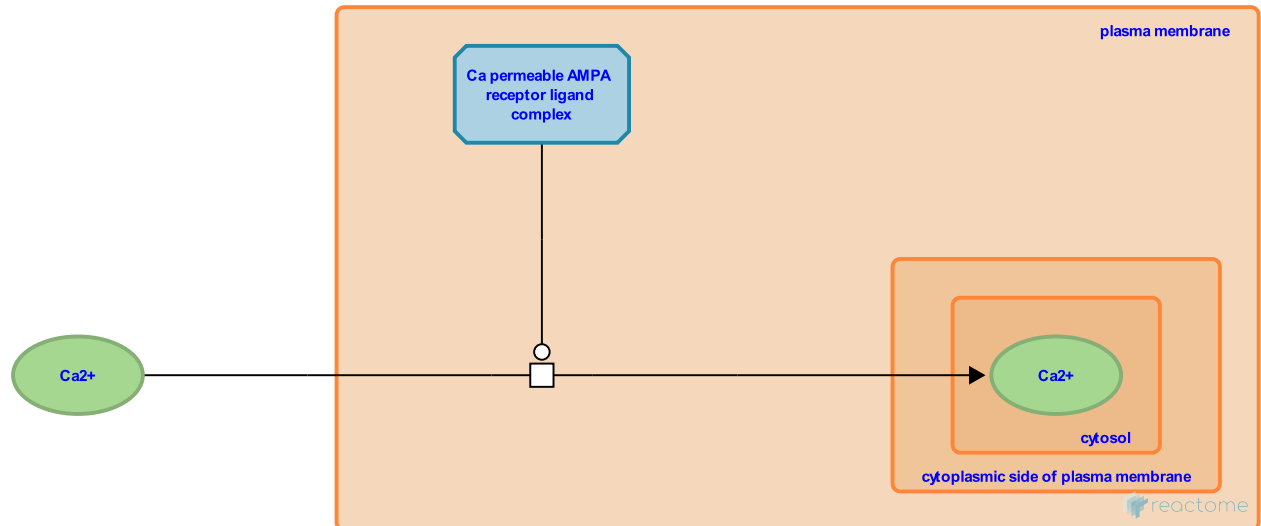
Activation of Ca permeable AMPA receptors ↗

Location: [Activation of AMPA receptors](#)

Stable identifier: R-HSA-399712

Type: transition

Compartments: plasma membrane



Each AMPA receptor subunit binds one glutamate molecule in the ligand binding site in the N terminus. Each receptor is capable of binding four glutamate molecule, however, channel opens when two sites are occupied by the ligand and the current increases with increased ligand binding. Ca permeable AMPA receptors containing homomers of GluR1 or heteromers containing GluR1, GluR3 and GluR4 conduct Ca upon glutamate or agonist namely AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) binding. Calcium permeable AMPA receptors conduct Ca and other cations such as Na. The ionic flux leads to Ca or Na currents that leads to either increase in the intracellular Ca concentration leading to further Ca-dependent signaling or increase in depolarization that opens voltage gated channels such as NMDA receptors that require both membrane depolarization and glutamate binding for activation.

Preceded by: [Ca permeable AMPA receptor ligand binding](#)

Literature references

Kurihara, H., Tamura, M., Sasaki, T., Nakazato, Y., Yamada, N., Miwa, A. et al. (2002). Blockage of Ca(2+)-permeable AMPA receptors suppresses migration and induces apoptosis in human glioblastoma cells. *Nat Med*, 8, 971-8. ↗

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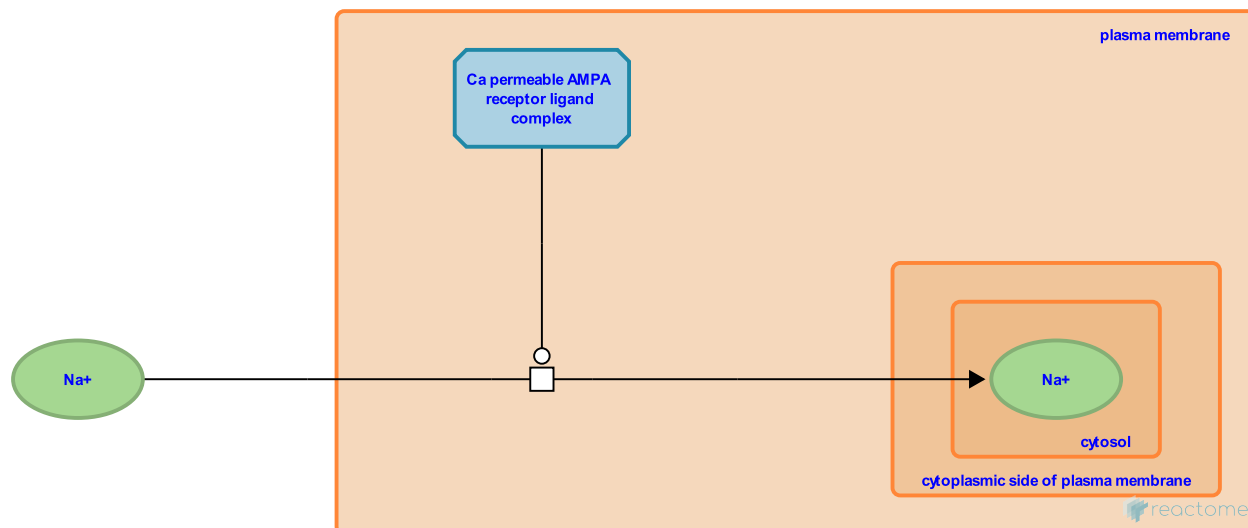
Activation of Ca permeable AMPA receptors ↗

Location: [Activation of AMPA receptors](#)

Stable identifier: R-HSA-420980

Type: transition

Compartments: plasma membrane



Each AMPA receptor subunit binds one glutamate molecule in the ligand binding site in the N terminus. Each receptor is capable of binding four glutamate molecule, however, channel opens when two sites are occupied by the ligand and the current increases with increased ligand binding. Ca permeable AMPA receptors containing homomers of GluR1 or heteromers containing GluR1, GluR3 and GluR4 conduct Ca upon glutamate or agonist namely AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) binding. Calcium permeable AMPA receptors conduct Ca and other cations such as Na. The ionic flux leads to Ca or Na currents that leads to either increase in the intracellular Ca concentration leading to further Ca-dependent signaling or increase in depolarization that opens voltage gated channels such as NMDA receptors that require both membrane depolarization and glutamate binding for activation.

Literature references

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

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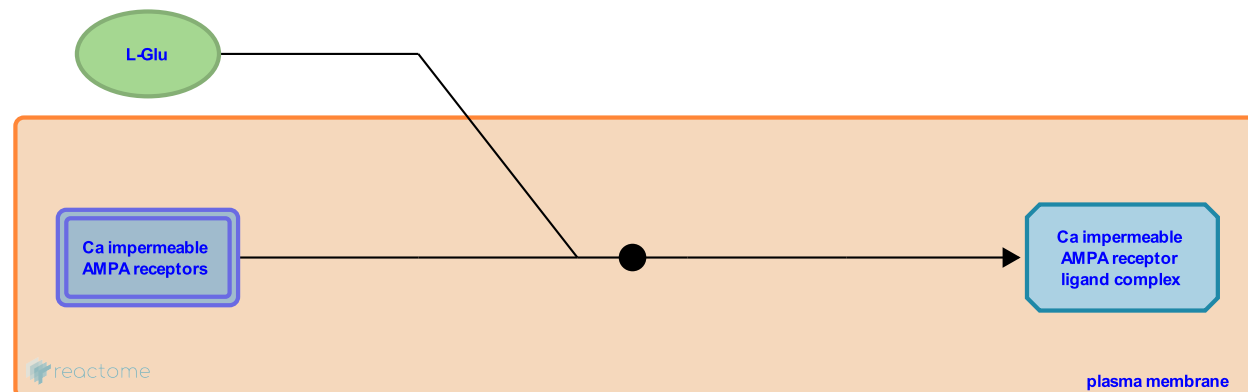
Ca impermeable AMPA receptor ligand binding ↗

Location: [Activation of AMPA receptors](#)

Stable identifier: R-HSA-420975

Type: binding

Compartments: plasma membrane, extracellular region



AMPA receptors bind glutamate, released in the synaptic cleft by the presynaptic cell, in the ligand binding region in the N terminal domain.

Followed by: [Activation of Ca impermeable AMPA receptors](#)

Literature references

Keinänen, K., Joupila, A., Koskelainen, S., Coleman, SK., Rivera, C., Korpi, ER. et al. (2009). Agonist occupancy is essential for forward trafficking of AMPA receptors. *J Neurosci*, 29, 303-12. ↗

Niu, L., Li, G., Pei, W. (2003). Channel-opening kinetics of GluR2Q(flip) AMPA receptor: a laser-pulse photolysis study. *Biochemistry*, 42, 12358-66. ↗

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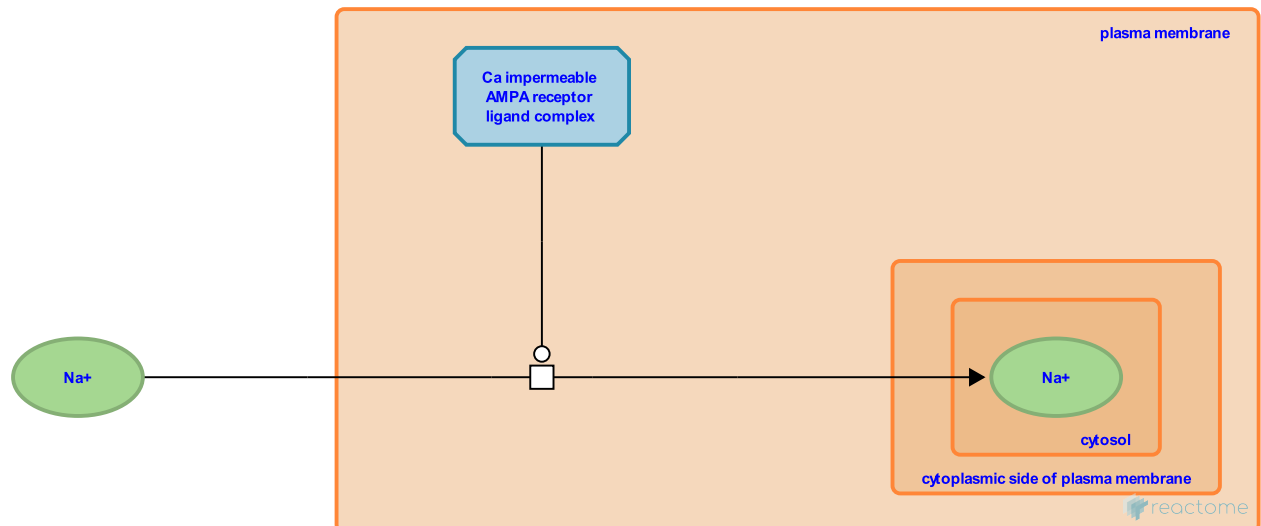
Activation of Ca impermeable AMPA receptors ↗

Location: [Activation of AMPA receptors](#)

Stable identifier: R-HSA-399711

Type: transition

Compartments: plasma membrane



Each AMPA receptor subunit binds one glutamate molecule in the ligand binding site in the N terminus. Each receptor is capable of binding four glutamate molecules however, channel opens when two sites are occupied by the ligand and the current increases with increased ligand binding. Ca impermeable AMPA receptors containing GluR2 subunit conduct Na currents upon activation by either glutamate binding or agonist, AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) binding. The Na currents mainly lead to depolarization of the membrane leading to activation of voltage gated channels such as NMDA receptors that require both agonist binding and depolarization for their activation.

Preceded by: [Ca impermeable AMPA receptor ligand binding](#)

Literature references

Hollmann, M., Körber, C., Werner, M., Kott, S. (2007). Electrophysiological properties of AMPA receptors are differentially modulated depending on the associated member of the TARP family. *J Neurosci*, 27, 3780-9. ↗

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