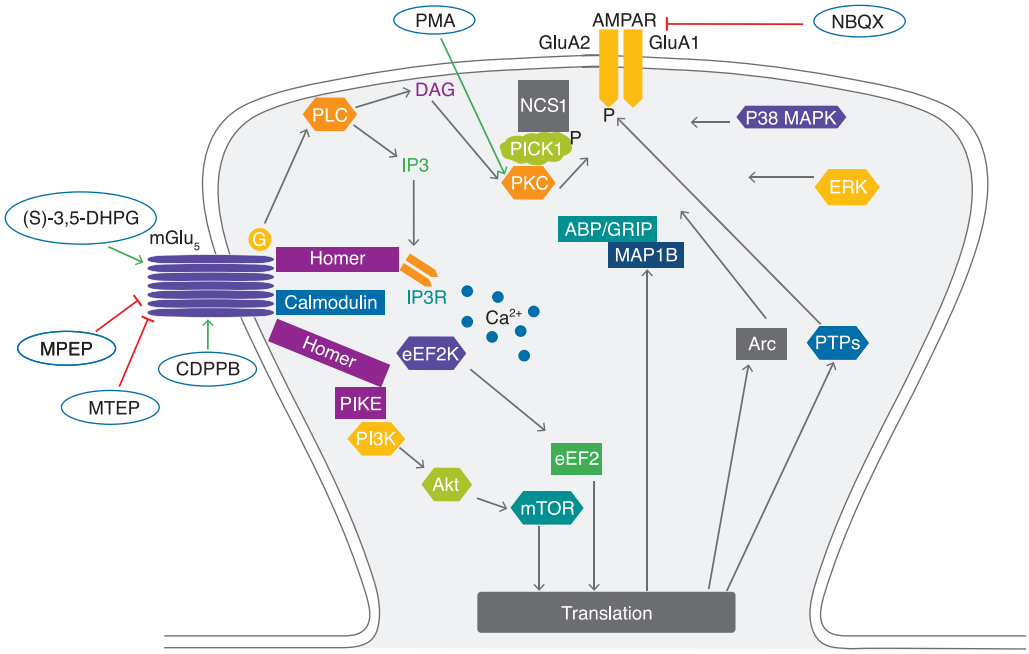
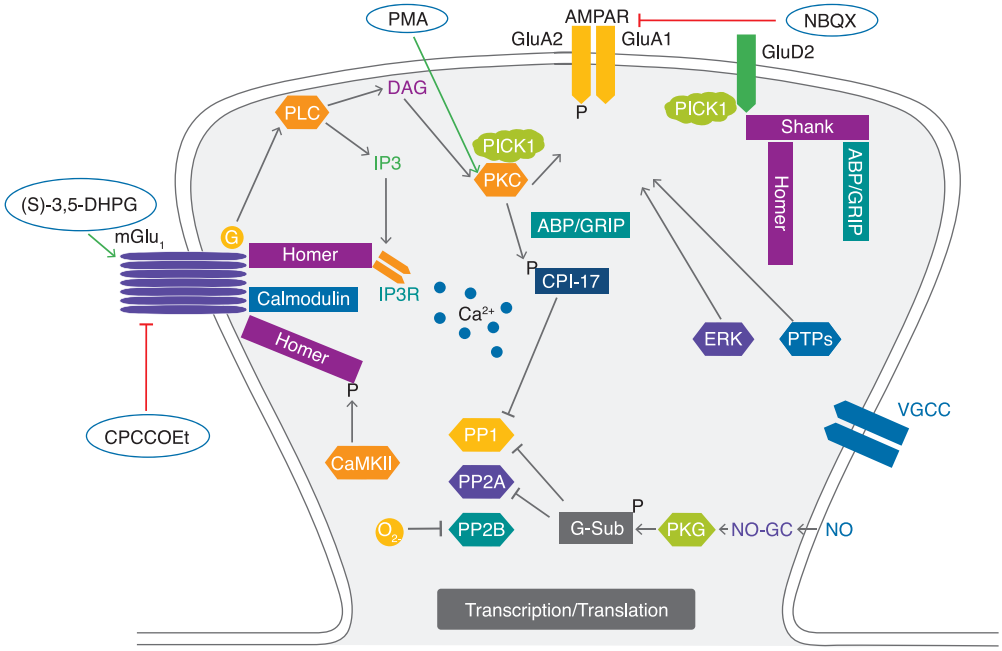
Major signaling mechanisms involved in $mGlu_5$ and $mGlu_1$ LTD

$mGlu_5$ LTD pathway



$mGlu_1$ LTD pathway



key.

- VGCC — Voltage-gated Ca^{2+} channels
- NO — Nitric Oxide
- NCS1 — Neuronal calcium sensor
- PICK1 — Protein interacting with C-kinase 1
- PP2A — Protein phosphatase 2A
- PP1 — Protein phosphatase 1
- IP3R — IP3 receptor
- ABP/GRIP — AMPAR-binding + glutamate receptor-interacting protein
- PTPs — Protein tyrosine phosphatases
- eEF2 — Eukaryotic elongation factor 2
- PIKE — PI3-K enhancer
- MPEP — Potent $mGlu_5$ antagonist
- CDPPB — $mGlu_5$ PAM
- PMA — PKC activator
- NO-GC — Nitric oxide - guanylyl cyclase
- DAG — Diacylglycerol
- G-Sub — G substrate
- CPI-17 — C-kinase potentiated Protein phosphatase-1 Inhibitor
- PP2B — Protein phosphatase 2B
- PLC — Phospholipase C
- IP3 — Inositol trisphosphate
- MAP1B — Microtubule associated protein 1B
- eEF2K — Eukaryotic elongation factor-2 kinase
- Arc — Activity-regulated cytoskeleton-associated protein
- (S)-3,5-DHPG — Group I agonist
- MTEP — Potent $mGlu_5$ antagonist
- NBQX — AMPAR antagonist
- CPCCOEt — Selective $mGlu_1$ antagonist

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Major signaling mechanisms involved in $mGlu_5$ and $mGlu_1$ LTD

mGluR-long term depression (LTD) is thought to be involved in many processes such as goal-directed learning and in pathological conditions such as Alzheimer's disease, Parkinson's disease and drug addiction. Many signaling mechanisms are involved in this process.

$mGlu_5$ LTD

Stimulation of group I mGlu receptors ($mGlu_1$ and $mGlu_5$), leads to the activation of the PLC pathway which releases Ca^{2+} from intracellular stores and activates PKC. LTD in the hippocampus is induced primarily through $mGlu_5$ activation and AMPAR mediation.

PICK1 forms a complex with NCS-1 which is thought to act as a Ca^{2+} sensor for LTD. PICK1 may also bind PKC-α to phosphorylate the GluA2 subunit of the AMPAR and dissociate ABP-GRIP. This may lead to removal of AMPARs from synapses.

Many other enzymes, pathways and proteins such as MAP1B, PTPs, ARC, ERK and P38 MAPK are also required or involved in $mGlu_5$ LTD although not all downstream effectors are yet fully understood.

The PI3K/AKT/mTOR pathway is thought to be involved in the control of translation and eEF2K/eEF2 may act as a regulator of translation.

$mGlu_1$ LTD

$mGlu_1$ is expressed primarily in the cerebellum and $mGlu_1$ activation at synapses between cerebellar parallel fiber and Purkinje cells induces LTD. This occurs when both climbing and parallel fibers are activated.

Many similar proteins and cascades are involved in both $mGlu_1$ and $mGlu_5$ LTD, such as activation of the PLC pathway leading to subsequent PKC activation and Ca^{2+} release.

$mGlu_1$ LTD is dependent on intracellular Ca^{2+} increase and in a secondary pathway initiated by climbing fiber activation, Ca^{2+} enters the synapse through VGCCs to increase intracellular Ca^{2+}.

Many other proteins and pathways are also involved in $mGlu_1$ LTD such as the δ2 glutamate receptor (GluD2) which plays an important role supporting LTD induction.

The NO-cGMP cascade is also involved and $mGlu_1$ LTD is thought to be NO dependent in which NO acts as a crucial mediator.

Other enzymes such as serine/threonine phosphatases e.g. PP1, PP2A and PP2B are involved in LTD.

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