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Joël Bockaert, Julie Perroy, Fabrice Ango. The Complex Formed by Group I Metabotropic Glutamate Receptor (mGluR) and Homer1a Plays a Central Role in Metaplasticity and Homeostatic Synaptic Scaling. *Journal of Neuroscience*, 2021, 41 (26), pp.5567-5578. 10.1523/JNEUROSCI.0026-21.2021 . hal-03282419

HAL Id: hal-03282419

<https://hal.science/hal-03282419>

Submitted on 8 Oct 2021

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The Journal of Neuroscience

<https://jneurosci.msubmit.net>

JN-VP-0026-21R2

The complex formed by Group I metabotropic glutamate receptor (mGluR) and Homer1a plays a central role in metaplasticity and homeostatic synaptic scaling.

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Commercial Interest:

The complex formed by Group I metabotropic glutamate receptor (mGluR) and Homer1a plays a central role in metaplasticity and homeostatic synaptic scaling.

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Abbreviated title: Non Hebbian neuronal plasticity and mGluR-Homer1a complex

Number of pages: 18

Number of Figures: 5

Number of words:

Total: 5677

-Abstract: 173

-Introduction: 754

-Main text: 3956

-Discussion: 615

Conflict of interest statement: Authors declare no conflicts of interest

Acknowledgments: The authors acknowledge the support provided by The Centre National de la Recherche Scientifique (CNRS) , l'Institut National de la Santé et de la Recherche Médicale (INSERM) and Université de Montpellier. The author would like to thank Patrick Carroll for constructive criticism of the manuscript

Abstract:

G-Protein-coupled receptors can be constitutively activated following physical interaction with intracellular proteins. The first example described was the constitutive activation of Group I metabotropic glutamate receptors (Group I mGluR: mGluR1,5) following their interaction with Homer1a, an activity-inducible early-termination variant of the scaffolding protein Homer that lacks dimerization capacity (Ango et al., 2001). Homer1a disrupts the links, maintained by the long form of Homer (cross-linking Homers), between mGluR1,5 and the Shank-GKAP-PSD-95-ionicotropic glutamate-receptor network. Two characteristics of the constitutive activation of the Group I mGluR-Homer1a complex are particularly interesting. First, it affects a large number of synapses in which Homer1a is up-regulated following enhanced, long-lasting neuronal activity, and second, it mainly depends on Homer1a protein turn-over. The constitutively active Group I mGluR-Homer1a complex is involved in the two main forms of non-Hebbian neuronal plasticity: “metaplasticity” and “homeostatic synaptic scaling” which are implicated in a large series of physiological and pathological processes. Those include non-Hebbian plasticity observed in visual system, synapses modulated by addictive drugs (rewarded synapses), chronically overactivated synaptic networks, normal sleep and sleep deprivation.

Introduction:

G protein-coupled receptors (GPCRs) spontaneously adopt many different active and inactive conformations (Chan et al., 2019; Du et al., 2019; Nygaard et al., 2013). Different agonists can stabilize different active states of a single GPCR, activating distinct signaling pathways. This pharmacological property is called biased agonism or ligand-dependent selectivity (Christopoulos and Kenakin, 2002; Luttrell et al., 2015). For many years, it has been thought that GPCRs could only be activated by extracellular ligands. We know now that GPCRs can also be activated by membrane depolarization (Bezanilla, 2008; Perroy et al., 2002; Vickery et al., 2016), structural modifications caused by mutations (Lefkowitz et al., 1993; Scheer et al., 1996; Vassart and Costagliola, 2011), phosphorylation (Delcourt et al., 2007; Duhr et al., 2014; Karaki et al., 2014; Liggett, 2011; Miller et al., 2003; Murat et al., 2019; Nobles et al., 2011), interactions with small pharmacological ligands (Liu et al., 2017; Liu et al., 2019; Oswald et al., 2016; Zheng et al., 2016), or soluble intracellular GPCR interacting proteins (GIPs) (Ango et al., 2001; Bockaert et al., 2010; Deraredj Nadim et al., 2016; Fagni et al., 2004; Pujol et al., 2020). Twenty years ago, we published the first example of an agonist independent (constitutive) activation of mGluR1a and mGluR5 by an intracellular GIP: Homer1a (Ango et al., 2001).

The C-terminal tail of Group I mGluR contains a binding site (TPPSPF) able to interact with the N-terminal enabled/VASP homology (EVH)-like domain (EVH1) of Homer proteins (Brakeman et al., 1997; Fagni et al., 2002; Kato et al., 1998; Tu et al., 1998; Xiao et al., 1998). There are two classes of Homer proteins (Fagni et al., 2002; Shiraishi-Yamaguchi and Furuichi, 2007). The first one, comprising Homer1b, 1c, 2 and 3, has long C-terminal coiled-coil domains which form a tetrameric Hub structure composed of two antiparallel dimers at the glutamatergic postsynaptic density (Hayashi et al., 2006; Hayashi et al., 2009). A dimer (or tetramer) of long C-terminal forms of Homer crosslinks different proteins, and connects, for example, Group I mGluR with downstream signaling molecules containing a Homer binding site (PPxxFR). These are called “cross-linking Homers”.

The second class of Homer proteins comprises two truncated forms of Homer1, Homer1a and Ania-3 that share similar protein sequences except for few residues at the C-terminal end (Bottai et al., 2002; Brakeman et al., 1997). They are the products of activity-induced immediate early genes (IEGs). Homer1a lacks the C-terminal dimerization domain, but contains, as the other Homers, an EVH1 domain (Shiraishi-Yamaguchi and Furuichi, 2007; Tu et al., 1998; Xiao et al., 1998). It can thus bind to proteins containing a Homer binding site and act as a “dominant negative” interactor that disrupts the complexes formed by cross-linking Homers. In particular, Homer1a releases Group I mGluR from the post-synaptic network maintained by cross-linking Homers (Kammermeier et al., 2000; Xiao et al., 2000) (Figure 1). This results in constitutive activation of the receptors in the absence of glutamate (Ango et al., 2001). The constitutively active Group I mGluR-Homer1a complex has been reported to

be a key actor in Hebbian synaptic plasticity (Clifton et al., 2019) but also in non-Hebbian neuronal plasticity: metaplasticity and homeostatic synaptic scaling. (Chokshi et al., 2019b; Diering et al., 2017; Holz et al., 2019; Hu et al., 2010; Lee and Kirkwood, 2019; Marton et al., 2015).

Homer1a is synthesized via activity-inducible premature termination of transcription of the Homer gene, downstream of exon 5. Homer1a is produced under a great variety of physiological, pathological and pharmacological conditions, generally resulting in neuronal excitation (Bottai et al., 2002). For example, Homer1a is induced by neuronal depolarization (Ango et al., 2000; Ango et al., 2001), brain-derived neurotrophic factor (BDNF) activation (Mahan et al., 2012), epilepsies (Li et al., 2012), traumatic injury (Luo et al., 2014), long-term potentiation (LTP), exposure to psychoactive drugs (Marton et al., 2015; Swanson et al., 2001; Szumlinski et al., 2008; Szumlinski et al., 2006; Zhang et al., 2007), strong AMP production (Marton et al., 2015; Zhang et al., 2007), fear conditioning (Tronson et al., 2010), adenosine A1 receptor activation (Serchov et al., 2015), visual experience following dark rearing (Brakeman et al., 1997; Chokshi et al., 2019b), maintenance of ocular dominance (Chokshi et al., 2019a), neuropathic and inflammatory pain (Miyabe et al., 2006; Tappe et al., 2006), and certain antidepressant treatments (Holz et al., 2019; Serchov et al., 2015).

Homer1a remodels postsynaptic glutamatergic synapse signaling and structure:

Ionotropic glutamate receptors and channels of spines are inter-connected by cross-linking Homers.

Glutamate receptors are inserted into a dense protein network. NMDA and AMPA (via stargazin) receptors are associated with the scaffolding protein PSD-95 or its homologs, forming a platform (Kim and Sheng, 2004). PSD-95 is also connected, via GKAP, to a second platform constituted by sheets of Shank protein (Kursula, 2019). Shank contains an N-terminal conserved SPN (Shank/ProSAP N-terminal) domain followed by ankyrin repeats, an SH3 domain, a PDZ domain, a “Homer ligand” domain (PPXXF) and a C-terminus containing a SAM domain able to form supramolecular lattices (Kursula, 2019). Like Group I mGluR and Shank, many proteins of the post-synaptic site, and in particular those implicated in Ca²⁺ homeostasis, contain a Homer ligand domain. Those include inositol 1,4,5-triphosphate receptors (IP3-Rs), ryanodine-receptors (RyR), transient receptor potential cation (TRPC) channels, phospholipase (PLC) β , L-type and P/Q-type voltage-dependent calcium channels (VDCC), phosphoinositide 3-kinase (PI3K) enhancer-long (PIKE-L) and dynamin III (Bockaert et al., 2010; Clifton et al., 2019; Fagni et al., 2002; Gray et al., 2003). The EVH1 domain of cross-linking Homers is able to bind the Homer ligand domain of these proteins, and bind them together. For example, cross-linking Homers link Group I mGluR to Shank, IP3-R, Pike and Dynamin III, TRPC channels to IP3-R and L VDCC to RyR (Figure 1) (Bockaert et al., 2010; Clifton et al., 2019; Fagni et al., 2004; Fagni et al., 2002).

Considering this dense cross-linking of receptors and channels by cross-linking Homers, it is not surprising that Homer 1a, acting as a “dominant negative” of these links, remodels spine signaling events.

We have described, twenty years ago, one of the major effect of Homer1a on spine signaling. Using cerebellar granular cells, in which we were studying activation of large-conductance potassium (BigK) channels by endogenously expressed mGluR1a or transfected mGluR5. These cells express only one cross-linking Homer, i.e. Homer3. We studied the effect of its suppression (using an antisense strategy) on the mGluR-induced BigK channel activation. Results were spectacular (Ango et al., 2001). The BigK channel became highly active, much more than when mGluR1a was stimulated by glutamate. Mutation of the Homer ligand domain of mGluR or overexpression of Homer1a, both of which result in a disconnection of Homer3 from mGluR, had similar effects (Figure 2) (Ango et al., 2001). The hypothesis that BigK channels were overactivated, due to constitutive activation of mGluR after its release from the Homer3 network was tested and confirmed. Indeed inverse-agonists of mGluR1a (BAY 36-7620) or mGluR5 (MPEP), but not competitive antagonists, were able to suppress this overactivation of BigK channels (Figure 2) (Ango et al., 2001). We also showed that suppression of the coupling of mGluR to cross-linking Homers results in constitutive activation of inositol phosphate formation, which should result in an increase in intracellular Ca²⁺ release (Ango et al., 2001). The constitutive activity of the Group I mGluR-Homer1a complex has been largely confirmed (Chokshi et al., 2019b; Diering et al., 2017; Holz et al., 2019; Hu et al., 2010).

Similarly, it was shown that disconnection of TRPC from the Homer network by Homer1a results in constitutive activation of TRPC (Yuan et al., 2003) (Figure 1). The constitutive activation of Group I mGluR and TRPC suggests that Homer1a accumulation in the spine tends to increase the level of

Ca²⁺. The disconnection of RyRs (particularly RyR2) from L-type VSCC (Cav1.2) by Homer1a also increases calcium elevation resulting from membrane depolarization, as well as the efficiency of calcium-induced calcium release (Huang et al., 2007; Worley et al., 2007).

These and other results (Clifton et al., 2019; Worley et al., 2007) indicate that cross-linking Homers buffer the intensity of basal Ca²⁺ signals in excitable (but also in non-excitable) cells and that Homer1a reverses this process. Calcium in spines is decisive for spike-timing dependent synaptic plasticity and the direction of changes in synaptic strength (Kampa et al., 2006). Thus, it is not surprising that Homer1a contributes to synaptic plasticity (Luscher and Huber, 2010). Another effect of the constitutively active Group I mGluR-Homer1a complex is activation of the mTOR pathway known to increase protein-synthesis, including synthesis of synaptic proteins such as AMPA receptors (Bouquier et al., 2020; Guo et al., 2016; Holz et al., 2019) (Figures 1,5). In conclusion one is expecting that the profound remodeling of spine signaling, by Homer1a, will have important physiological implications.

The crosstalk between Group I mGluR and NMDA-receptors has been thoroughly investigated. Both positive and negative effects of Group I mGluR on NMDA current were reported depending on the neuronal cells investigated and protocol used (Awad et al., 2000; Fitzjohn et al., 1996; O'Neill et al., 2018; Yu et al., 1997). In the scope of this review, one particularly interesting crosstalk concern the effects of the Group I mGluR-Homer1a complex on NMDA receptor activity. Indeed, we have shown that Group I mGluR-Homer1a strongly inhibited NMDA receptors (Bertaso et al., 2010; Perroy et al., 2008). We have shown, using BRET (Bioluminescence resonance energy transfer) technology, a direct interaction between mGluR and NMDA receptors (Moutin et al., 2012). It is generally accepted that Group I mGluR are localized at the edge of spines whereas NMDA receptors are localized within the synaptic cleft (Nusser et al., 1994; Shigemoto et al., 1993). However, combining single-molecule super-resolution microscopy, electrophysiology, and modeling, it has been shown recently that mGluR5 is homogenously dispersed at the post-synaptic membrane (Goncalves et al., 2020). Ca²⁺ entry through NMDA receptors activates CamKII, which can phosphorylate cross-linking Homers, reducing their interaction with mGlu5 (Guo et al., 2015). In this condition, the expression of Homer1a induced by neuronal activity competes favorably with the cross-linking Homers for binding to the mGlu5 receptor. (Moutin et al., 2012). Released from the Shank-GKAP-PSD-95 complex, the mGlu5-Homer1a complex directly binds to and inhibits NMDA receptors. Similarly, Homer1a has been shown to decrease NMDA and AMPA membrane-associated receptors and currents, PSD-95 clusters, and spine density and size (Sala et al., 2003). The inhibition of NMDA receptors induced by the Group I mGluR-Homer1a complex likely explains the inhibition of LTP following overexpression of Homer1a (Hu et al., 2010; Rozov et al., 2012). Indeed, inhibition of NMDA currents results in an inhibition of AMPA-receptor accumulation within post-synaptic membranes due in part to reduced tyrosine phosphorylation of the GluA1/GluA2 subunit (Diering et al., 2017; Hu et al., 2010). Reciprocally, deleting either the Homer1 gene or the short Homer1 isoform results in an upregulation of postsynaptic AMPA receptors and currents (Hu et al., 2010; Rozov et al., 2012). Those effects of Group I mGluR-Homer1a complex on ionotropic glutamate receptors are further amplified by the increase of Group I mGluR traffic to the plasma membrane. Indeed, a pool of Group I mGluR associated with cross-linking Homers is retained in the endoplasmic reticulum (ER) (Ango et al., 2000; Ango et al., 2002; Brakeman et al., 1997; Okada et al., 2009; Roche et al., 1999). The induction of Homer1a through neuronal excitation interrupts this retention (Ango et al., 2002), permitting mGluR trafficking to the plasma membrane.

There are also conditions in which the constitutive activation of Group I mGluR by Homer1a can lead to an increase in glutamate synaptic transmission. One potential mechanism involved in this increase is a coincident binding of Homer1a to the Homer ligand domain once phosphorylated by kinases that target proline-adjacent serine or threonine (proline-directed kinases; PDK), such as Cdk5 and ERK (Hu et al., 2012; Orlando et al., 2009; Park et al., 2013). The phosphorylation of the Homer ligand by PDK is a complex mechanism. Group I mGluR and PDK are first assembled by an anchoring protein called FRMPD4/Preso1 forming a microdomain. FRMPD4/Preso1 is a multidomain protein containing a FERM domain that binds cytoplasmic tails of Group I mGluR, an Homer binding domain and a C-terminal PDZ-binding-ligand that interacts with PSD-95 (Hu et al., 2012; Lee et al., 2008; Wang et al., 2020). FRMPD4/Preso1 is crucial for the formation of excitatory synapses and dendritic spines and for physiological regulation of synaptic mGluR (Lee et al., 2008). Consistent with this, genetic studies

have identified several mutations of FRMPD4 in patients with X-linked intellectual disability (Hu et al., 2016; Piard et al., 2018; Piton et al., 2013) and FRMPD4 knock-out mice displayed deficits in hippocampal spatial and learning memory (Piard et al., 2018). Once phosphorylated by PDK, mostly on the Serine 1126 (TPPpS1126-PF), the affinity of mGluR-Homer ligand for the Homers EVH1 domain is increased (Park et al., 2013). Note that phosphorylated Homer ligand associated with cross-linking Homers cannot bind another important protein i.e. the prolyl isomerase (PIN1). It is only when Homer1a expression level is sufficiently high to displace cross-linking Homers from the phosphorylated Homer ligand of mGluR that PIN1 can bind and accelerate isomerization of the pS1126-P bond by more than a thousand-fold (Park et al., 2013). This creates a cis conformation of the pS1126-P bond, forming a tight hairpin turn between phenylalanine and the N-terminus of the Homer ligand (Figure 3). Thus, when Group I mGluR are associated with Homer1a, phosphorylated by Cdk5 or ERK (for example after cocaine intake, BDNF stimulation of TrkB or activation of Group I mGluR themselves), a particular structure of their C-terminal is stabilized. There is evidence that this particular mGluR conformation activates NMDA receptors and thus induces membrane accumulation of AMPA receptors (Marton et al., 2015; Park et al., 2013).

In conclusion, following CDK-induced phosphorylation of the Homer ligand of mGluR and its isomerization by PIN, the Group I mGluR-Homer1a complex is no longer inhibiting but rather is activating NMDA receptors (Marton et al., 2015).

Constitutively active Group I mGluR-Homer1a complex is involved in metaplasticity and homeostatic synaptic scaling.

Hebbian LTP and LTD induces rapid changes of the strength of specific synapses. These bidirectional activity-dependent modifications of excitatory synaptic strength are essential for learning and storage of new memories. NMDA receptor activation is required for these forms of plasticity (Huganir and Nicoll, 2013), but Group I mGluR are also implicated, via different molecular mechanisms, in both LTD (Luscher and Huber, 2010) and LTP (Wang et al., 2020).

Changes in synaptic activity also occur over longer timescales and are called “non-Hebbian neuronal plasticity”. The two main forms of non-Hebbian plasticity include “sliding threshold metaplasticity” and “homeostatic synaptic scaling” (Ibata et al., 2008; Lee and Kirkwood, 2019). Sliding threshold metaplasticity” involves a change in the threshold needed for LTP induction which depend on the past neuronal activity. For example, a decrease in overall activity (for example during visual deprivation) decreases the induction threshold for LTP due to an up-regulation of synaptic expression of GluN2B-containing NMDA receptors. In contrast, an increase in activity (for example after rapid exposure to light after visual deprivation) increases the threshold for LTP, favoring LTD. This can be obtained by reducing synaptic expression of GluN2B-containing NMDA receptors (Lee and Kirkwood, 2019). Homeostatic synaptic scaling changes the overall activity level of neuronal network while maintaining the relative strengths of synapses by effectively scaling up or down the strengths of all synapses by the same multiplicative factor. This is generally produced by a change in AMPA receptor activity, without altering NMDA receptor activity (Lee and Kirkwood, 2019). During the last 10 years, it has been shown that the Group I mGluR-Homer1a complex is a central component of both forms of non-Hebbian plasticity.

Sliding threshold metaplasticity plasticity in the visual system.

Experience-dependent metaplasticity mechanisms in vivo have been widely studied in the mouse visual system (Whitt et al., 2014). For example, in juvenile mice, a few days of visual deprivation (dark experience; DE) results in up-regulation of GluN2B-containing NMDA receptors in primary visual cortex which promotes LTP in layer L2/3 pyramidal neuron of V1 (i.e. a sliding threshold metaplasticity). In V1 layer 2/3 (L2/3) pyramidal neurons that receive inputs from lateral intracortical neurons, a sliding threshold favoring LTD is observed when DE is reversed by re-exposure to light (light experience; LE (Bridi et al., 2018; Guo et al., 2012; Petrus et al., 2015; Philpot et al., 2003) (Figure 3). This LE-induced visual metaplasticity involves NMDA and mGluR5 receptors and is associated with rapid induction of Homer1a synthesis (Chokshi et al., 2019b). Genetic KO of Homer1a (H1aKO) suppresses the LE-induced metaplasticity (Chokshi et al., 2019b). The interaction between mGluR5 and Homer1a is necessary for this LE-induced homeostatic plasticity since it is

absent in knock-in mice in which the mGluR5 Homer ligand domain has been mutated (Chokshi et al., 2019b). Furthermore, MPEP, an inverse agonist of mGluR5 (but not an inverse agonist of mGluR1) suppresses LE-induced weakening of IC synapses. Thus, Chokshi et al (Chokshi et al., 2019b) propose that the constitutive activation of mGluR5 following its interaction with Homer1a and the subsequent inhibition of NMDA receptors is involved in LE metaplasticity. In this hypothesis, the previously observed inhibition of NMDA receptor by constitutively active mGluR5-Homer1a complex (Perroy et al., 2008) is the likely molecular mechanism involved (Ango et al., 2001; Bertaso et al., 2010; Moutin et al., 2012).

Most neurons in V1 respond to inputs from both eyes, but show varying degrees of preference toward one or the other eye. This is termed ocular dominance (OD). In rodents, V1 neurons exhibit a strong bias toward the contralateral eye. OD development depends largely on spontaneous activity (Espinosa and Stryker, 2012; Rakic, 1976). Notably, alterations in visual experience during early postnatal life (3–5 weeks postnatally) can shift OD patterns. During this critical period, monocular deprivation (MD) induces a shift in OD toward the open eye. Two periods are observed following MD. In the first period, a depression of the deprived eye response (2–3 d MD) through homosynaptic LTD mechanisms is observed (Dudek and Bear, 1992). In the second period (5–6 d MD), a homeostatic mechanism leads to the strengthening of open-eye responses. Using optical imaging of intrinsic signals in V1 neurons, H1aKO mice, and a mouse model that has reduced Homer1 binding to mGluR5, Chokshi et al. (Chokshi et al., 2019a) demonstrated that the mGluR5-Homer1a complex is required for establishing the normal postnatal development of contralateral bias in V1 neurons and for the homeostatic plasticity allowing maintenance of OD during the longer period (5–6 d) of MD. In contrast, in H1aKO mice, the OD shift observed in short-term MD (2–3d) was unchanged, suggesting that the initial phase of MD is not dependent on Homer1a expression (Chokshi et al., 2019a).

Sliding threshold metaplasticity in reward-related excitatory synapses.

Drug addiction is now believed to be a form of learning that occurs at synapses that are reinforced by reward. The important role of mGluR5 in behavioral responses to cocaine was first demonstrated in mGluR5 KO mice (Chiamulera et al., 2001). Cocaine-induced locomotion, cocaine motor sensitization, and cocaine self-administration are all reduced in these KO mice (Bird and Lawrence, 2009). After cocaine exposure, motor sensitization results from enhancement of cortical input to the striatum (Pascoli et al., 2011). This enhancement involves stimulation of both mGluR5 and dopamine D1 receptors (Marton et al., 2015).

D1 receptors enhance synaptic strength by reducing LTD of cortico-striatal synapses, thus favoring LTP (Centonze et al., 2006). Using a large series of transgenic mice, it has been shown that D1 receptors induce threshold metaplasticity depend on Homer1a induction, mGluR5 phosphorylation, and PIN1-induced isomerization of phosphorylated mGluR5 (Marton et al., 2015; Park et al., 2013). Marton et al. (Marton et al., 2015) propose that the molecular mechanisms involved could be as follows (see Figure 3). During high activity of some corticostriatal neurons, Homer 1a expression is induced in striatal neurons. It will take tens of minutes to synthesize enough Homer1a to dissociate mGluR5 from cross-linking Homers (Marton et al., 2015). In synapses that do not receive dopamine (non-rewarded synapses), the constitutively active mGluR5 will inhibit NMDA receptors and induce an increase of the threshold for LTP, favoring LTD, upon further synaptic activation (Figure 3). In contrast, in rewarded synapses, D1 receptors activate ERK via the cAMP pathway, leading to phosphorylation of mGluR5. Activation of mTORC1 by the mGluR5-Homer1a complex further activates ERK via phosphorylation of DARPP-32 (Lin et al., 2020). This may create a positive feedback loop for the phosphorylation of mGluR5 by ERK. As we discussed earlier in this review, phosphorylated mGluR5 displaced from cross-linking Homers by Homer1a, binds PIN1 and isomerizes. Isomerized mGluR5 activates (instead of inhibiting, as when non-phosphorylated) NMDA receptors (Marton et al., 2015; Park et al., 2013). This will reduce the threshold for homeostatic plasticity, blocking depotentiation upon further synaptic activation (Marton et al., 2015). Thus, in corticostriatal synapses that have been active enough to accumulate Homer1a, a cocaine-induced increase in D1 receptor stimulation introduces a bias toward potentiation (rewarded synapses) compared to synapses not exposed to cocaine (Figure 3). This may occlude further plasticity of rewarded synapses. It has been recently reported that in D1-receptor-containing synapses, persistent activation of mTORC1 occludes further dynamic D1 signaling and D1-receptor-mediated responses

such as dynamic gene expression, cortico-striatal plasticity synapses and some behavioral responses such as sociability (Lin et al., 2020).

Homeostatic synaptic scaling in synaptic networks:

The first demonstration of an involvement of the Group I mGluR-Homer1a complex in homeostatic synaptic scaling was reported by Hu et al. (Hu et al., 2010). Studying the scaling down of synaptic networks in DIV 14 cortical neurons in culture chronically overactivated by a bicuculline treatment, Hu et al. (Hu et al., 2010) observed that this treatment reduced the membrane level of AMPA receptors (GluA1 and GluA2/3). The unexpected finding was that the co-presence of mGluR1 and mGluR5 inverse agonists (Bay 36-7620 and MPEP respectively) but not the co-presence of neutral antagonists of mGluR5 and mGluR1 (CPCCOEt plus (S)-MCPG respectively) were able to inhibit this homeostatic down-scaling of the network. One caveat is that inverse agonists have much higher affinity than neutral antagonists, and accordingly, the authors were using much higher concentrations (20-100 times higher) of neutral antagonists than of inverse agonists.

In addition, Hu et al. (Hu et al., 2010) showed that the hydrolysis of glutamate in the culture with glutamate pyruvate transaminase and sodium pyruvate did not modify the homeostatic down-scaling after bicuculline treatment, excluding a role of endogenous glutamate in the activation of mGluR5 in the process. This strongly establishes that the down-regulation of AMPA receptors requires a constitutively active form, and not a glutamate-activated form of mGluR1 and mGluR5. Furthermore, Homer1a induction with Sindbis virus was sufficient to produce down-scaling of the network independently of stimulation of Group I mGluR by glutamate, but blocked by mGluR inverse agonists (Hu et al., 2010). It was further established that the Homer1a-constitutively active Group I mGluR complex reduces tyrosine phosphorylation of GluA2 receptors, which is implicated in their trafficking to synaptic membranes. This effect of Homer1a on the phosphorylation of GluA2 was confirmed *in vivo* by showing GluA2 phosphorylation is enhanced in Homer1a KO mice (Hu et al., 2010). In conclusion these results support a model in which constitutive activation of Group I mGluR due to their association with Homer1a results in reduced GluA2 tyrosine phosphorylation, leading to less GluA2 membrane insertion and consequently weakening of synaptic strength.

Homeostatic synaptic scaling of excitatory synapses during sleep.

Synapses undergo homeostatic down-scaling during sleep (Diering et al., 2017). This may be important to increase the signal/noise ratio of synapses that underwent LTP during waking life and facilitate memory consolidation (Tononi and Cirelli, 2014). Adenosine is one of the neuromodulators which accumulates during waking and influences sleep induction (Wigren et al., 2007)). During waking life, Homer 1a is synthesized, but its accumulation within the PSD is blocked by activation of α and β adrenergic receptors (Figure 4) (Diering et al., 2017). In contrast, during sleep, Homer1a accumulates within the PSD, a process facilitated by adenosine acting on adenosine A1 receptors (Diering et al., 2017) (Figure 4). The analysis of protein content of PSDs and two-photon imaging of wake/sleep synapses indicate that synapses contain less GluA1 and GluA2 AMPA receptor subunits during sleep. In addition, these synapses show decreased phosphorylation of GluA1 at S845 and S831, decreased levels of the PKA catalytic unit and AKAP 50, and decreased levels of mGluR5, PKC and IP3-Rs (Diering et al., 2017). All these modifications are absent in Homer1a KO mice. Blocking mGluR5 with the inverse agonist, MPEP during sleep induces a low but significant increase in GluA1 expression. Thus, Diering et al. (Diering et al., 2017) propose that during waking life and learning, Homer1a is synthesized but excluded from spines by adrenergic receptor activation. During sleep induction, characterized by a decrease in noradrenaline and an increase in adenosine, Homer1a is targeted to the synapses, and interacts with mGluR5. Constitutive activation of mGluR5 remodels the signaling pathways, induces a scaling down of synapses by decreasing AMPA receptor phosphorylation, and therefore decreasing AMPA receptor membrane insertion (Figure 4). Whether the constitutive activation of mGluR5 also inhibits NMDA receptor activity during sleep, as expected, has not been studied. The roles of Homer1a and mGluR in sleep properties in different species have been reported. Genetic deletion of the unique orthologue of Homer in *Drosophila* results in fragmented sleep and an incapacity to undergo long bouts of sleep even under sleep deprivation (Naidoo et al., 2012). In addition, genetic disruption of the putative binding site for Homer on DmGluRA, the unique mGluR in *Drosophila* (Parmentier et al., 1996) reduces sleep (Ly et al., 2020).

In mice, a polymorphism of the Homer1a gene is associated with sleep drive (Mackiewicz et al., 2008). H1aKO mice show reduced wakefulness with an inability to sustain long bouts of wakefulness active periods (dark periods) and display a modest change in circadian period (Naidoo et al., 2012). A study in the Brazilian population suggests that the rs3822568 polymorphism in the Homer gene might have an impact on sleep quality and sleep structure. People carrying this mutation showed higher sleep latency, lower sleep efficiency, reduced number of arousals per hour, lower apnea-hypopnea index and lower theta spectral power than GG genotyped individuals (Pedrazzoli et al., 2020). In the latter two studies, the involvement of Group I mGluR was not established.

Homeostatic synaptic scaling of excitatory synapses during sleep deprivation and other antidepressant treatments.

It has been shown that the antidepressant effects of sleep deprivation (SD), imipramine, ketamine, electroconvulsive treatment (ECT), repetitive transcranial magnetic stimulation (rTMS) and photic stimulation involved Homer1a (Holz et al., 2019; Sakagami et al., 2005; Serchov et al., 2015; Sun et al., 2015; van Calker et al., 2018; Yamamoto et al., 2011). Knock-in mice with an mGluR Homer ligand mutation that abrogates binding to cross-linking Homers have an antidepressant phenotype (Guo et al., 2016). Silencing the Homer1a gene with small interfering RNA (siRNA) increases depressive-like behavior and blunts the antidepressant action of SD, imipramine or ketamine (Serchov et al., 2015). In addition to Homer1a transcription, most of these antidepressant therapies including SD (Schmitt et al., 2016) involve transcriptional regulation of BDNF and TrkB, and thus Trk B stimulation (van Calker et al., 2018). An up-regulation of AMPA receptor density and activity is also associated with antidepressant effect of BDNF (Fortin et al., 2012; van Calker et al., 2018). Since AMPA receptor activation increases BDNF a virtuous circle may be on board.

It is thus possible that long-lasting up-regulation of AMPA receptors at glutamatergic synapses, within mPFC is a common component of all antidepressant treatments (Duman et al., 2016). Note that this is the definition of homeostatic up-scaling of excitatory synapses. In other term, antidepressants, by up-regulating AMPA receptor expression of the mPFC glutamatergic synapses should increase the overall neuronal network activity while maintaining the relative strengths of synapses. The mechanisms by which all those treatments converge to homeostatic up-scaling is not clear but Homer1a may be central since almost all antidepressant treatments up-regulate Homer1a (van Calker et al., 2018).

Recently, it has been shown that TAT-Homer1a, a membrane permeable derivative of Homer1a, has antidepressant action (Holz et al., 2019). Not surprising for us, TAT-Homer1a, like SD, constitutively activates mGluR5, specifically in excitatory CaMK2a neurons, increases mTOR pathway activity and finally the translation and synaptic expression of GluA1 (Holz et al., 2019) (Figure 5). These effects are blocked by MPEP, an mGluR5 inverse agonist (Holz et al., 2019). Trk-B receptors may also act, in synergy with mGluR5-Homer1a, to over-activate mTOR (Duman et al., 2012).

Note that the mGluR5-Homer1a complex induces homeostatic up-scaling of excitatory synapses following SD whereas it has an opposite effect during normal sleep (Diering et al., 2017).

However, during normal sleep, Homer1a is not synthesized but it is only its traffic within spines which is increased (Diering et al., 2017). It is possible that during SD the activation of mTOR and ERK and thus AMPA receptor synthesis is so high that the dephosphorylation and endocytosis of AMPA receptors induced by the mGluR5-Homer1a complex, as seen during normal sleep (Diering et al., 2017), became negligible.

Conclusion:

The possibility of activating GPCRs by intracellular proteins in addition to their classical stimulation by extracellular ligands has only recently been recognized (Ango et al., 2002; Bockaert et al., 2010; Chaumont-Dubel et al., 2020; Duhr et al., 2014; Pujol et al., 2020). A major difference between GPCR activation by extracellular ligands or by intracellular proteins is the timing. The action of extracellular ligands is fast (100 msec to min.) and rapidly reversible. Activating GPCRs by intracellular proteins is a slow process depending on protein turn-over. Some are only synthesized following particular events. This is the case for products of immediate early genes such as Homer1a. The activation of Group I mGluR by Homer1a occurs after neural excitation of diverse sources which take tens of minutes and last until Homer1a is degraded (hours). Therefore, it is not surprising that constitutive activation of

Group I mGluR by Homer1a has been selected as a key mechanism for inducing long-lasting non-Hebbian synaptic plasticity “Sliding threshold metaplasticity” and “Homeostatic synaptic scaling” The Group I mGluR-Homer1a complex increases the threshold for LTP induction in some synapses by the molecular mechanism that we described twenty years ago. Homer1a induces disconnection of Group I mGluR from cross-linking Homers, which leads to allosteric constitutive activation of mGluR1 or 5, which in turn inhibit NMDA receptors and therefore increase the threshold for LTP induction (Ango et al., 2001; Perroy et al., 2008). This metaplasticity has been described in V1 layer 2/3 (L2/3) pyramidal neuron synapses receiving inputs from lateral intracortical neurons when a dark experience (DE) is reversed by re-exposure to light (LE) (Chokshi et al., 2019b). It is also present in corticostriatal synapses that do not receive a coincident dopaminergic input (non-rewarded synapses) (Marton et al., 2015). However, in corticostriatal synapses receiving D1-input (following cocaine intake) in advance (rewarded synapses), a decrease in threshold for LTP induction is observed. Here, the “past” of synaptic state include a modulation of NMDA receptor activity by D1 receptors. The mGluR5-Homer1a complex is again involved. However, there is a coincident phosphorylation of the mGluR5 receptors by the D1/cAMP/ERK pathway followed by their isomerization by the prolyl isomerase PIN1. The result is an activation of NMDA receptors by the phosphorylated mGluR5 receptors (via an unknown mechanism) and a bias toward potentiation of those synapses (Marton et al., 2015; Park et al., 2013).

Another type of non-Hebbian plasticity in which the Group I mGluR-Homer1a complex is involved is homeostatic synaptic scaling. During synaptic network overstimulation (Hu et al., 2010) and during sleep (Diering et al., 2017) the constitutive activation of mGluR1 or 5 by Homer1a results in a scaling down of synapses via a decrease in AMPA receptor phosphorylation, and thus a decrease in synaptic AMPA receptor concentration.

It is intriguing that scaling up homeostatic synaptic plasticity observed during SD, known to induce antidepressant effects, also involves the mGluR5-Homer1a complex. Here, high activation of the mTOR pathway by the mGluR5-Homer1a complex, followed by translational synthesis of new AMPA receptors is involved (Holz et al., 2019). BDNF activation of the mTOR pathway during SD may also contribute to this enhancement of AMPA (Schmitt et al., 2016).

It is highly probable that there exist other physiological and pathological situations in which the constitutively active Group I-mGluR-homer1a complex is implicated. This includes neuroprotection against traumatic brain injury, enhancement of contextual fear (Tronson et al., 2010), obsessive-compulsive disorder-like behavior in mice in which GKAP (Sapap3) has been knocked out (Ade et al., 2016) and finally some forms of autism spectrum disorders (ASD) such as fragile X syndrome (Guo et al., 2015; Guo et al., 2016).

Legends of Figures:

Figure 1: Spine signaling under basal conditions and after activation-induced Homer1a accumulation.

A- Under basal conditions, glutamate receptors, channels, intracellular platform proteins are cross-linked by cross-linking Homers.

B: After neuronal activity-induced Homer1a accumulation spine signaling is remodeled.

B1-The constitutively active mGluR1,5-Homer1a complex triggers dephosphorylation and internalization of AMPA receptors (AMPA receptors, left), physically interacts and inhibits NMDA receptors (NMDA receptor, center), and allows the constitutive activation of PI3-kinase and mTOR (right).

B2- Homer1a also frees cross-linked Ca²⁺ channels, increasing their activity (TRPC and L-VDCC, left) while the constitutively active mGluR1,5-Homer1a complex increases PLC activation, leading to increased activity of IP₃ receptors and thus Ca²⁺ release from the ER (mGluR1/5-agonist independent increased in IP₃R Ca²⁺-release, right)

(*) on mGluR1,5 receptors or TRPC channel indicates that they are constitutively activated.

Figure 2: The constitutively active mGluR1,5-Homer1a complex strongly activates BigK channels in cerebellar granule cells.

Left: Under basal conditions, mGluR1 and Shank are cross-linked by Homer 3. Transient activation of mGluR1 by an mGluR1,5 agonist (DHPG) activates, in a reversible manner, BigK channels recorded in cell-attached patches (physiological recordings shown underneath).

Right, Homer3 antisense or activity-induced Homer1a induction release mGluR1 from cross-linking and they become constitutively active. This leads to constitutive activation of BigK channels recorded in cell-attached patches (physiological recordings shown underneath). The BigK channels are recorded in cell-attached patches. Application of DHPG does not further activate these channels whereas application of an mGluR1 inverse agonist (Bay 36-7620) but not a neutral antagonist (not shown) inhibits the constitutive activation of BigK channels. The asterisk (*) on mGluR1,5 receptors indicates that they are constitutively activated.

Figure 3: Sliding threshold metaplasticity in the visual system and in cortico-striatal excitatory rewarded and unrewarded synapses.

A: Synapses between lateral intracortical neurons (IC) and V1 layer 2/3 (L2/3) pyramidal neurons. When a dark experience (DE) is reversed by a light experience (LE), sliding homeostatic plasticity occurs. Newly synthesized Homer1a constitutively activates mGluR5, which inhibits NMDA receptors through a direct interaction (Chokshi et al., 2019b). This leads to an increase in the threshold required for LTP induction.

B: Cortico-striatal synapses. Two types of sliding homeostatic plasticity occur. In the absence of D1 dopamine receptor stimulation, activation these synapses (unrewarded synapses) triggers, in downstream striatal neurons, similar signaling events as we have seen above in the visual system after LE. A decrease in LTP/LTD ratio is observed. In contrast, when D1 receptors are activated before activation of the cortico-striatal synapses (rewarded synapses), Homer1a is synthesized, constitutively and activates mGluR5. In addition, the D1-receptor-cAMP-ERK activated pathway allows the phosphorylation and isomerization (by PIN) of mGluR5. The phosphorylated and isomerized mGluR activate (instead of inhibiting) NMDA receptors by an unknown mechanism, leading to an increase in the LTP/LTD ratio (Marton et al., 2015).

The asterisk (*) on mGluR1,5 receptors indicates that they are constitutively activated.

Figure 4: Homeostatic glutamatergic synaptic down-scaling during sleep periods.

During wake periods, cross-linking Homers are fully operational. Neuronal activity-induced Homer1a accumulates outside the dendritic spine because spine entry is blocked by α and β -activated adrenergic receptors via an unknown mechanism.

During a sleep period, Homer1a entry into spine is facilitated by the activation of adenosine A1 receptors via an unknown mechanism. The constitutively active mGluR1,5-Homer1a complex increases the dephosphorylation of AMPA receptors. This induces homeostatic down-scaling glutamatergic synapses. The asterisk (*) on mGluR1,5 receptors indicates that they are constitutively activated.

Figure 5: Homeostatic mPFC glutamatergic synaptic up-scaling during sleep deprivation: an antidepressant treatment.

The molecular mechanisms by which SD modifies mPFC excitatory synapses have been recently deciphered, at least in part (Holz et al., 2019). A Tat-Homer1a cell-permeable peptide, disconnecting mGluR5 from cross-linking Homer mimics the signaling pathways and antidepressant effect of SD. This peptide and SD activate mTOR signaling and AMPA receptor translation, a key step in antidepressant therapeutic effect. These signaling events are triggered by the constitutive mGluR5-Homer1a complex because they are blocked by MPEP, an inverse agonist of mGluR5. mTOR is also activated by TrkB. The asterisk (*) on mGluR1,5 receptors indicates that they are constitutively activated.

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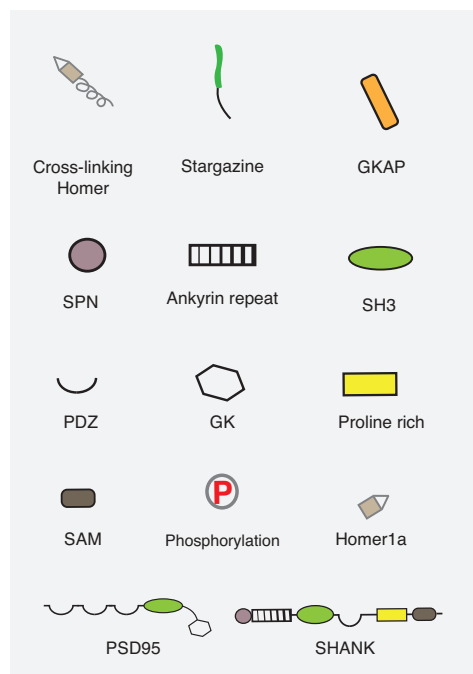
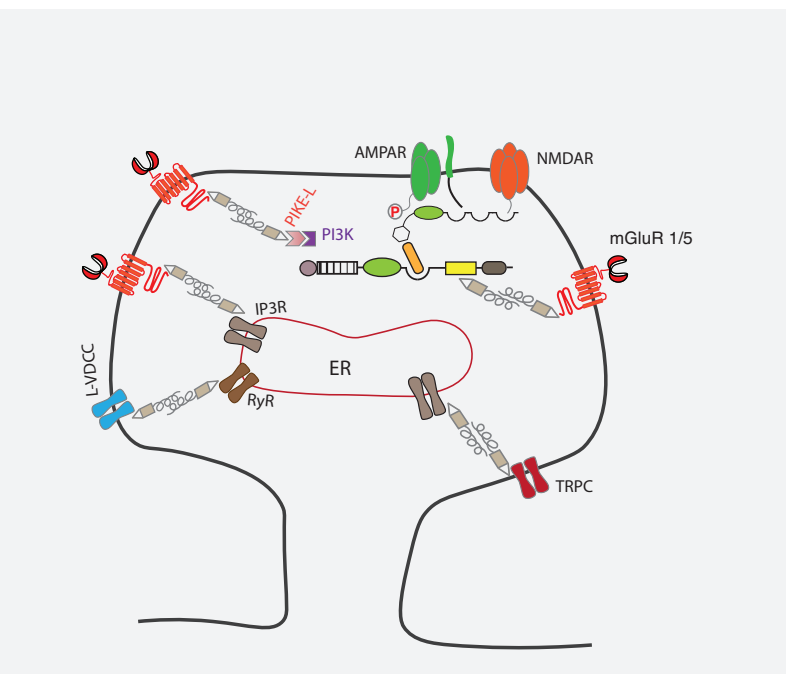
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A

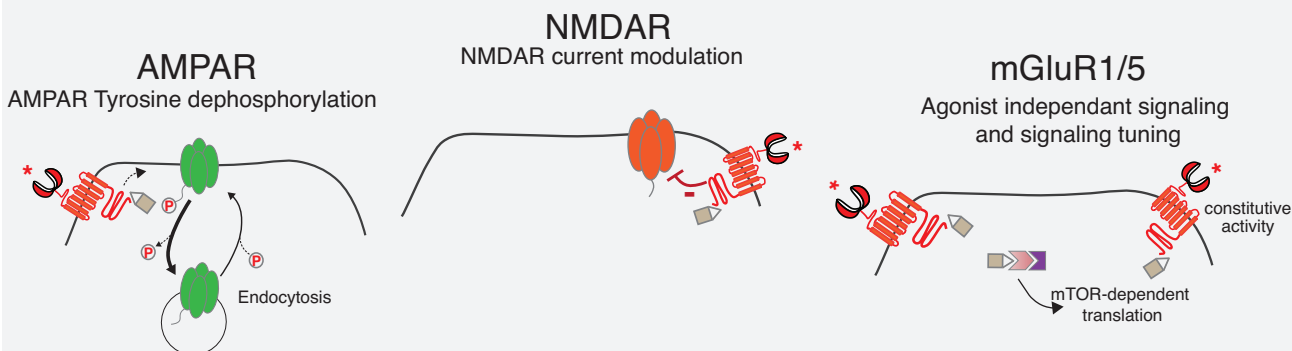
Glutamatergic spine under basal conditions



B

Spine signaling after activity-induced upregulation of Homer1A

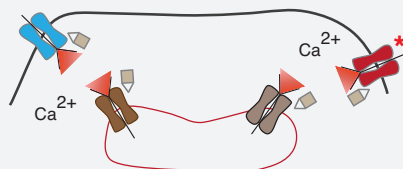
B1



B2

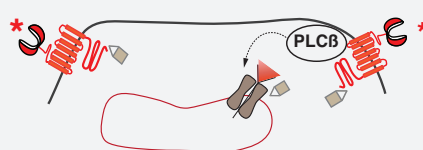
TRPC and L-VDCC

Increased Calcium signaling

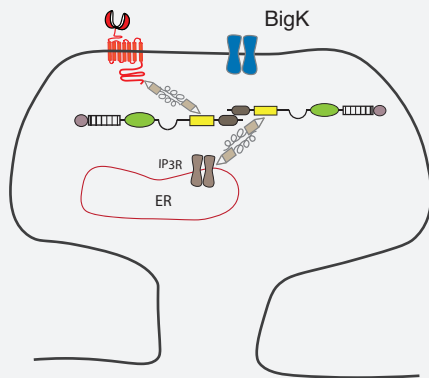


mGluR1/5

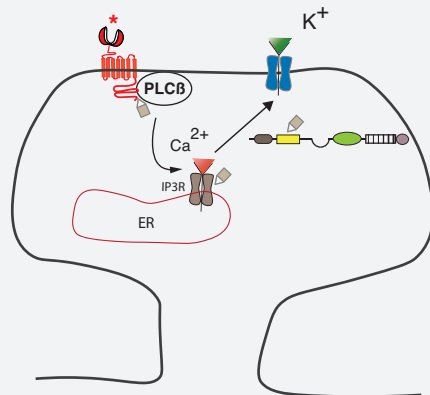
Agonist independent increased in IP3R Ca^{2+} released



Under basal condition



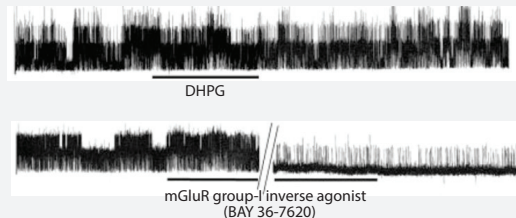
Activity induced upregulation of Homer1a or Homer3 antisense

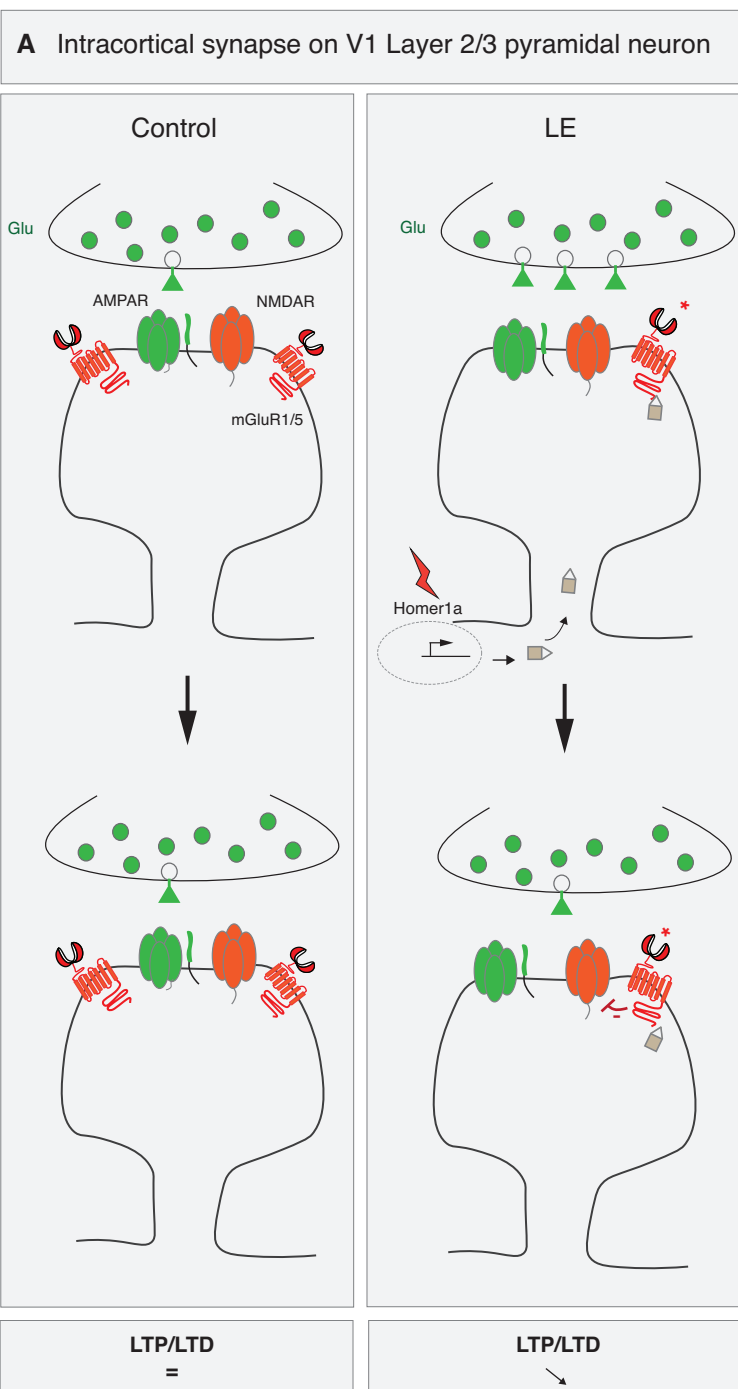


BigK channel activity



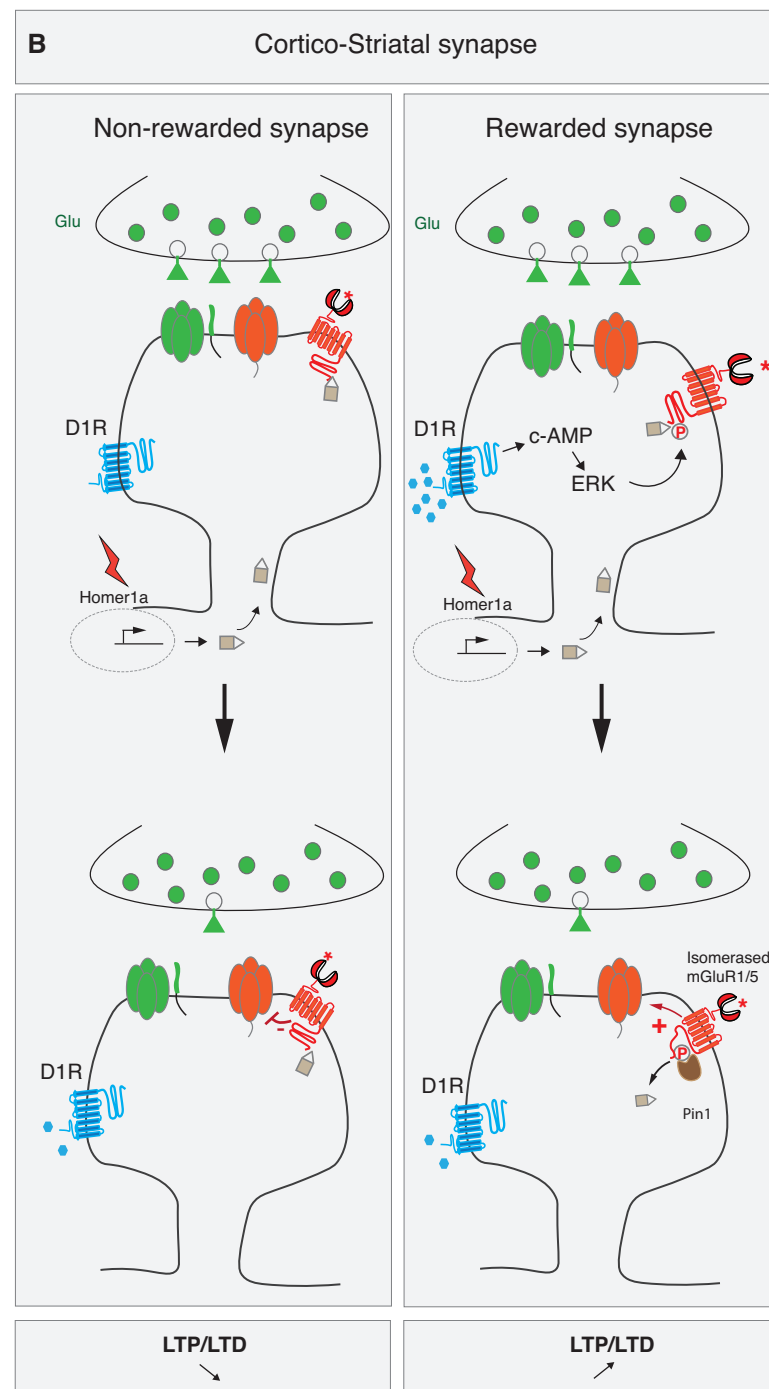
BigK channel activity





Normal condition

Sliding threshold metaplasticity in LE



Sliding threshold metaplasticity in non-rewarded synapse

Sliding threshold metaplasticity in rewarded synapse

