Hippocampal metabotropic glutamate receptor long-term depression in health and disease: focus on mitogen-activated protein kinase pathways

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Abstract

Group I metabotropic glutamate receptor (mGluR) dependent long-term depression (LTD) is a major form of synaptic plasticity underlying learning and memory. The molecular mechanisms involved in mGluR-LTD have been investigated intensively for the last two decades. In this 60th anniversary special issue article, we review the recent advances in determining the mechanisms that regulate the induction, transduction and expression of mGluR-LTD in the hippocampus, with a focus on the mitogen-activated protein kinase (MAPK) pathways. In particular we discuss the requirement of p38 MAPK and extracellular signal-regulated kinase 1/2 activation. The recent advances in understanding the signaling cascades regulating mGluR-LTD are then related to the cognitive impairments observed in neurological disorders, such as fragile X syndrome and Alzheimer's disease.

Keywords: Alzheimer's disease, AMPAR trafficking, ERK1/2, Fragile X syndrome, mGluR-LTD, p38 mitogen-activated protein kinase.

The hippocampus is an area of the brain that is required for the formation and retrieval of various types of memory, including spatial memories in rodents (Neves *et al.* 2008). The loss of hippocampal function causes memory impairment and reduced cognitive ability (Scoville and Milner 1957; Moser *et al.* 1993; Broadbent *et al.* 2004). The fundamental role the hippocampus plays in memory formation has led to extensive investigation of the mechanisms by which the synapses of the hippocampus change, to under- stand the neurophysiology that underpins its function. These processes are forms of synaptic plasticity and include long-term increases in synaptic strength, termed long-term potentiation (LTP), and long-term decreases in synaptic strength, named long-term depression (LTD). These processes, can be induced in many areas of the brain, but are extensively studied in the CA1 region of the hippocampus where they are thought to underlie spatial learning and memory (Neves *et al.* 2008). In the hippocampus, LTD can be triggered by the activation of *N*-methyl-D-aspartate receptors (NMDAR) (Collingridge *et al.* 1983; Fujii *et al.* 1991; Dudek and Bear 1992) or group I metabotropic glutamate receptors (mGluRs) (Palmer *et al.* 1997; Fitzjohn *et al.* 1999). These two forms of LTD differ in many respects (Collingridge *et al.* 2010) and in this review we will focus on mGluR-LTD.

The role of mGluR-LTD in memory processes is beginning to emerge. mGluR5 knockout (KO) animals have impaired mGluR-LTD and show deficits in both acquisition and reversal learning (Lu *et al.* 1997; Xu *et al.* 2009). However, as mGluR5 inhibition also results in deficits in LTP (Lu *et al.* 1997; Manahan-Vaughan and Braunewell 2005) and can dramatically disrupt metaplastic modulation of LTP (Bortolotto *et al.* 2005), dissecting the specific roles that mGluR-LTD play in memory has been challenging. More specific manipulations that are expected to predominantly affect mGluR-LTD have strengthened the case for a role of mGluR-LTD in spatial reversal learning (Eales *et al.* 2014). Novel object recognition has been reported to facilitate hippocampal LTD recorded *in vivo* (Manahan-Vaughan and Braunewell 1999; Kemp and Manahan-Vaughan 2004) and because this facilitation requires mGluR5 as well as NMDARs (Goh and Manahan-Vaughan 2013) it is plausible that mGluR-LTD may play a role in this form of learning. This observation is strengthened as novel object recognition is impaired in mice where signaling pathways involved in mGluR-LTD are disrupted (Di Prisco *et al.* 2014).

The precise mechanisms underlying mGluR-LTD are still under debate, and it is not clear the extent to which the depression in synaptic transmission is caused by a decrease in glutamate release from the pre-synaptic terminal or to changes in the number or properties of the post-synaptic receptors that respond to a fixed amount of glutamate release (Watabe *et al.* 2002; Zakharenko *et al.* 2002; Gladding *et al.* 2009b;

Collingridge *et al.* 2010). In this review, we will discuss the post-synaptic mechanisms underlying the expression of mGluR-LTD with a focus on mitogen-activated protein kinase (MAPK) signaling. We then discuss how mGluR-LTD may be involved in neurological disorders, such as fragile X syndrome and Alzheimer's disease.

Molecular mechanisms involved in the induction of mGluR-LTD

mGluR-LTD is most widely studied in the CA1 area of the hippocampus and can be induced by either application of a group I mGluR agonist, typically (RS)- or (S)-3,5-dihydroxyphenylglycine (DHPG) (Palmer *et al.* 1997; Fitzjohn *et al.* 1999), or by physiological activation of synapses (Bashir *et al.* 1993), typically by using paired-pulse low frequency stimulation (Kemp and Bashir 1997; Huber *et al.* 2000). The expression of mGluR-LTD is mediated, in part, by a reduction in the number of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) on the plasma membrane (Carroll *et al.* 2001; Snyder *et al.* 2001; Xiao *et al.* 2001; Huang *et al.* 2004; Moult *et al.* 2006; Gladding *et al.* 2009a,b; Sanderson *et al.* 2011; Eales *et al.* 2014).

Group I-mGluRs are composed of mGluR1 and mGluR5, which are both expressed in area CA1 of the hippocampus (Shigemoto *et al.* 1992, 1997; Conquet *et al.* 1994; Lujan *et al.* 1996; Berthele *et al.*1998; Ferraguti *et al.*1998). Both mGluR1 and mGluR5 receptors have been shown to induce mGluR-LTD either singly or in combination (Palmer *et al.* 1997; Fitzjohn *et al.* 1999; Hou and Klann 2004; Volk *et al.* 2006; Moult *et al.* 2008; Neyman and Manahan-Vaughan 2008; Nadif Kasri *et al.* 2011). The variable involvement of the two subtypes may reflect factors such as differences in the induction protocols, the expression mechanism under investigation and the developmental stage of the synapses.

One of the most remarkable discoveries regarding the molecular mechanism regulating mGluR-LTD is the observation that the induction of mGluR-LTD requires rapid mRNA translation (Huber *et al.* 2000). However, it is important to note that mGluR-LTD is not invariably dependent on protein translation. Inhibition of protein translation did not affect the induction of mGluR-LTD in neonatal animals (Nosyreva and Huber 2005) and in hippocampal slices obtained from 10 to 15 week animals mGluR-LTD occurred independently of protein translation, using either synaptic induction protocols (Moult *et al.* 2008) or DHPG (Moult, Fitzjohn, and Collingridge, unpublished observations). The extent to which mGluR-LTD is dependent on *de novo* protein synthesis remains to be established.

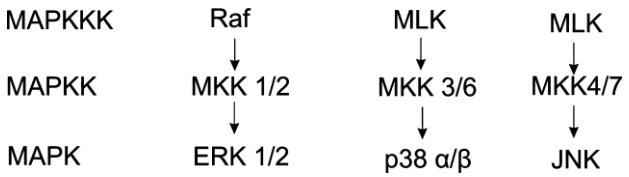

Fig. 1 Steps showing the upstream activation of p38, extracellular signal-regulated kinase 1/2 (ERK1/2), and Jun N-terminal kinases (JNK) in neurons.

Table 1 Summary of the requirement of p38 and extracellular signal-regulated kinase 1/2 (ERK1/2) during mGluR-LTD in the CA1 area of the hippocampus

Induction	Species	Age	p38 Phosphorylation	p38 inhibition effect on mGluR-LTD	ERK 1/2 Phosphorylation	ERK 1/2 inhibition effect on mGluR-LTD	Reference
Schaffer collateral LFS (5 Hz stimulation for 3 min)	Sprague–Dawley rats	P4-11	Increased	Blocked LTD 20 lM SB203580	No effect	Not determined	Bolshakov *et al*., 2000
Schaffer collateral PP-LFS (900 paired-pulses at 1 Hz, 50 ms apart)	Wistar rats	10–15 weeks	Increased	Blocked LTD 5 lM SB203580	Not determined	No effect on LTD 20 lM U0126	Moult *et al*., 2008
DHPG 50 lM 5 min	Sprague–Dawley rats	P21-30	Increased	Blocked LTD 1 lM SB203580	Not determined	No effect on LTD 50 lM PD98059	Huang *et al*., 2004
DHPG 100 lM 10 min	C57/BL6 mice	P0 cultures	Increased	Blocked LTD 5 lM SB203580	Not determined	Not determined	Eales *et al*., 2014
DHPG 100 lM 5 min DHPG 100 lM 5 min	Long-Evans rats C57/BL6 mice	P21-30 P25-30	Not determined Not determined	No effect on LTD 5 lM SB203580 or 1 lM SB202190 Not determined	Increased Increased	Blocked LTD 20 lM U0126 or 50 lM PD98059 Not determined	Gallagher *et al*., Osterweil *et al*., 2010
DHPG 50 lM 5 min	C57/BL6 mice	4 weeks	No effect	Not determined	Increased	Blocked LTD 20 lM U0126	Banko *et al*., 2006

A variety of signaling pathways have been found to be involved in mGluR-LTD. These include tyrosine dephosphorylation (Moult *et al.* 2002, 2006, 2008) involving striatal-enriched protein phosphatase (STEP) (Zhang *et al.* 2008), and the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin (PI3K-Akt-mTOR) signaling cascade (Hou and Klann 2004). The most extensively studied pathways have involved the MAPKs. These are a specific class of serine/threonine kinases that respond to extracellular signals such as growth factors, mitogens, and cellular stress (Fig. 1) and are involved in a diverse array of functions, including proliferation, differentiation, and cell survival. Jun N-terminal kinases (JNK), p38 MAPK (p38), and extracel- lular signal-regulated kinase 1/2 (ERK1/2) are the three best characterized subfamilies of MAPK (Tibbles and Woodgett 1999; Roux and Blenis 2004) and there is evidence to suggest that all of these may be involved in mGluR-LTD in the present article, we have therefore focused on the hippocampus (Bolshakov *et al.* 2000; Rush *et al.* 2002; Curran *et al.* 2003; Gallagher *et al.* 2004; Hou and Klann 2004; Huang *et al.* 2004; Thomas and Huganir 2004; Banko *et al.* 2006; Li *et al.* 2007; Bellone *et al.* 2008; Moult *et al.*2008; Gladding *et al.* 2009b; Osterweil *et al.* 2010; Corrêa and Eales 2012; Seo *et al.* 2012; Hogg *et al.* in press).

The role of JNK1 in mGluR-LTD is not clear as although JNK1 knockout mice were found to have impaired mGluR-LTD in area CA1 (Li *et al.* 2007) and pharmacological inhibition of JNK1 prevented mGluR-LTD in the dentate gyrus (Curran *et al.* 2003), there is also contradictory evidence. The pre-incubation of hippocampal slices with JNK1 inhibitors did not block synaptically induced mGluR-LTD in either the CA1 region (Moult *et al.* 2008) or in the dentate gyrus (Wang *et al.* 2007). Also mGluR-LTD can still be induced in hippocampal slices obtained from transgenic mice displaying alterations in the C-terminus of JNK1 to prevent its phosphorylation (Seo *et al.* 2012). Further experiments are needed to clarify the role of JNK1 in mGluR-LTD and therefore in the present review we focus on the roles of p38 and ERK1/2 (Table 1).

Since the discovery of mGluR-LTD in the hippocampus, similar forms of synaptic plasticity have been identified in several other brain regions (Anwyl 2006) and have been implicated in a diverse range of physiological and patholog ical functions (Table 2; Luscher and Huber 2010). There is currently little evidence for the involvement of MAPKs in mGluR-LTD outside of the hippocampus, apart from the role of ERK1/2 in mGluR-LTD in the cerebellum (Ahn *et al.* 1999; Kawasaki *et al.* 1999). Further work is therefore necessary to explore the possible roles for MAPKs in mGluR-LTD in other brain regions. In the present article, we have focused on the hippocampus, since this is where most mechanistic studies have been performed.

The p38 and ERK1/2 cascades regulating mGluR-LTD

p38 MAPK signaling

Group I mGluRs are G-protein-coupled receptors that couple to the $G\alpha_q$-containing heterotrimeric G protein (Fig. 2a). Consistent with this DHPG or synaptically induced mGluR- LTD cannot be induced if $G\alpha_q$ is knocked out (Kleppisch *et al.* 2001). The mechanism by which mGluRs activate p38 is via the release of the Gbc subunit (Huang *et al.* 2004), which triggers a signaling cascade via Rap1 and MKK3/6 to activate p38 (Fig. 2a; Huang *et al.* 2004). The requirement for p38 activation during mGluR-LTD is well-established (Bolshakov *et al.* 2000; Rush *et al.* 2002; Huang *et al.* 2004; Moult *et al.* 2008), however, until recently few p38 substrates had been identified in mGluR-LTD.

Table 2
Summary of metabotropic glutamate receptor (mGluR)-LTD induction and expression in different areas of the brain and their implications in diseases

Brain region	mGluR dependence	Disease mechanism	References
Amygdala	LTD blocked by group I/II mGluR antagonist		Rammes *et al.*, 2001
Anterior cingulate cortex	LTD blocked by mGluR1 antagonist		Kang *et al.*, 2012
Auditory cortex	LTD blocked by group I mGluR anatgonist		Kudoh *et al.*, 2002
Cerebellum	LTD cannot be induced in mGluR1 knockout mice	Increased mGluR-LTD in fragile X syndrome Blocked mGluR-LTD in Huntingtons disease	Alba *et al.*, 1994; Koekkoek *et al.*, 2005; Coesmans *et al.*, 2003
Perirhinal cortex	LTD blocked by group I mGluR antagonist		Cho *et al.*, 2000
Striatum	LTD blocked by group I mGluR antagonist	Loss of mGluR-LTD in Parkinson's disease	Sung *et al.*, 2001; Kreitzer and Malenka 2007
Ventral tegmental area	LTD blocked by mGluR 1 antagonist	Induction of mGluR-LTD reverses cocaine induced strengthening of excitatory inputs onto dopamine neurons	Mameli *et al.*, 2007

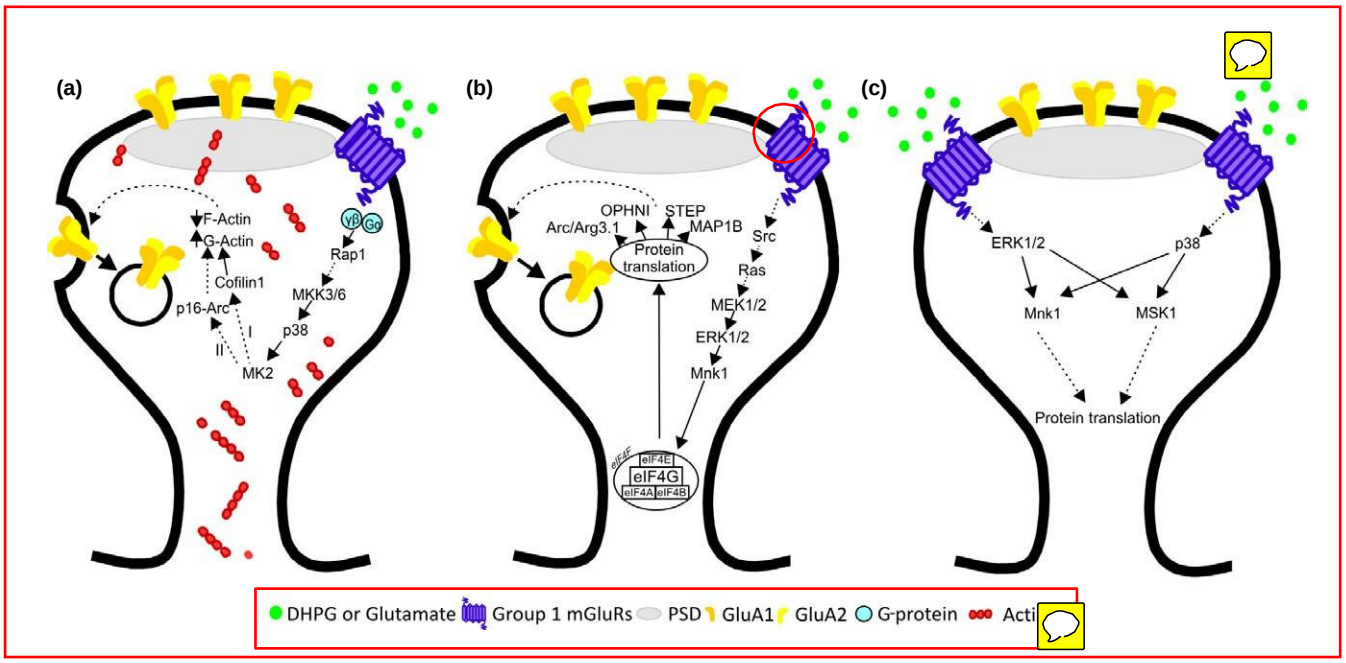

Fig. 2 Putative model illustrating the mechanism by which the p38 and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling cascades regulate mGluR-LTD by either individual (a, b) or comple- mentary pathways (c). (a) Activation of mGluRs by DHPG or glutamate stimulates the release of the bc subunit from the Gaq G protein coupled receptor. This leads to the activation of Rap 1 that activates MKK 3/6 and consequently p38, which binds and phospho- rylates MK2. The activation of MK2 potentially activates two MK2- downstream cascades leading to the actin reorganization and endocytosis of AMPARs. (I) MK2 regulates cofilin1 phosphorylation which results in changes in dendritic spine morphology (Eales *et al.* 2014). The activation of the p38-MK2 cascade leads to dephospho- rylation and activation of cofilin1 which triggers AMPAR internalization and actin reorganization caused by a decrease in the amount of filamentous actin (F-actin) and an increase in globular actin (G actin). (II) MK2 directly phosphorylates p16-Arc one of the subunits of the Arp2/3 complex which regulates actin branching and has been shown to regulate AMPARs internalization (Singh *et al.* 2003; Rocca *et al.* 2008). (b) The steps linking the binding of mGluRs agonist to ERK1/2 activation have not yet been clearly demonstrated. In non-neuronal systems ERK1/2 is activated via Src and Ras (Thandi *et al.* 2002; Wang *et al.* 2007). In neurons mGluR activation results in phospho- rylation of Mnk1 and eukaryotic initiation factors which regulate translation of proteins that are known to regulate internalization of AMPAR including Arc/Arg3.1, MAP1B, OPHN1, and striatal-enriched protein phosphatase (STEP). (c) Pathways showing how p38 and ERK1/2 can both activate MSK1 and Mnk1 (McCoy *et al.* 2005; Chrestensen *et al.* 2007). Downstream these pathways can lead to changes in the levels of protein translation and expression, which results in enhanced AMPAR endocytosis required for mGluR-LTD.

Recently MAP kinase-activated protein kinases 2 and 3 (MK2/3), which are kinases specifically phosphorylated by p38a/b subunits (Clifton *et al.* 1996; Gaestel 2006; White *et al.* 2007; Corrêa and Eales 2012), and not by ERK1/2, have been found to be required for the induction of mGluR-LTD (Corrêa and Eales 2012; Eales *et al.* 2014). Supporting the involvement of a p38-MK2/3 cascade in mGluR-LTD is the observation that expression of activity-regulated cytoskeleton-associated protein (Arc/Arg3.1), a protein required for mGluR-LTD (Waung *et al.* 2008), is significantly reduced in hippocampal tissue from MK2/3 double knockout (DKO) mice at 4 weeks compared to tissue obtained from wild-type littermates. Further supporting these findings is the observation that the impairment of mGluR-LTD is accompanied by deficits in AMPAR trafficking in hippocampal cultures obtained from MK2/3 DKOs (Eales *et al.* 2014). Arc/Arg3.1 has been shown to control synaptic strength by facilitating endocy- tosis of AMPARs (Bramham *et al.* 2008, 2010; Shepherd and Bear 2011) and is thought to play a role in AMPAR trafficking in mGluR-LTD (Park *et al.* 2008; Waung *et al.* 2008).

It is well established that p38 together with its substrate MK2 are important in the expression of serum response element-driven immediate early genes (IEGs) by direct phosphorylation of serum response factor at Ser 103 (Ronkina *et al.* 2011; Corrêa and Eales 2012). The finding that transcriptional activation of the neuronal specific IEG Arc/Arg3.1 is dependent on serum response factor activation in primary cortical neurons may provide a mechanism by which p38 regulates transcription of neuronal proteins to regulate synaptic plasticity (Pintchovski *et al.* 2009; Bramham *et al.* 2010; Ronkina *et al.* 2011). It is important to further investigate whether the p38 cascade has a role in activity-dependent transcription of IEGs in neurons indepen- dently of ERK1/2 activation.

In addition to impaired hippocampal mGluR-LTD, MK2/3 DKO mice display distinctive deficits in hippocampal-dependent reversal of spatial learning when tested on the Barnes Maze task (Eales *et al.* 2014). Previous findings have shown that mGluR5 knockout mice display deficits in reversal learning and mGluR-LTD (Xu *et al.* 2009; Menard and Quirion 2012). The extent to which mGluR-LTD signaling, via the p38 MAPK cascade, is involved in reversal learning warrants further investigation.

ERK1/2 signaling

The signaling cascade by which mGluRs activate ERK1/2 is less understood compared to that of p38. In non-neuronal preparations mGluR signaling can activate ERK1/2 through the $G\alpha_q$ subunit leading to activation of the Src, Ras, and MEK1/2 cascade (Fig. 2b; Thandi *et al.* 2002; Wang *et al.* 2007). Downstream of ERK1/2 the picture is clearer, as signaling proteins that are known to regulate cap-dependent protein translation are activated. These include MAPK-interacting protein kinase 1 (Mnk1) and its phosphorylation target, eukaryotic elongation factor 4E (eIF4E; Banko *et al.* 2006), providing a route which links protein translation and mGluR activation. Cap-dependent protein translation is a highly regulated procedure (see Proud 2007; Joshi and Platanias 2014) and can be divided into three stages: Initiation (which is specifically modulated by ERK1/2- dependent signaling in mGluR-LTD), elongation, and termination. Each of these steps is regulated by translation factors that in eukaryotic cells are known as eukaryotic initiation factors (eIFs), eukaryotic elongation factors (eEFs), and eukaryotic release factors (eRFs). Rapid modulations in mRNA translation can be brought about by changes in the association or activity of these factors. Initiation requires eIFs that form a protein complex known as eIF4F. This is composed of a primary scaffolding component, eIF4G, and three other proteins eIF4A, eIF4B, and eIF4E. Translation is initiated when the last of these, eIF4E, recognizes the 5^0 mRNA cap, and this allows recruitment of the small ribosome subunit (Gingras *et al.* 1999). Phosphorylation of eIF4E by Mnk1 is thought to regulate protein translation, however, the precise mechanism is not clear (Fig. 2b; Proud 2007; Joshi and Platanias 2014). One hypothesis is that phosphorylation of eIF4E may play a role in the recycling of eIF4E from one round of translation initiation to the next, as phosphorylation has been found to reduce the affinity of eIF4E for the 5^0 cap (Scheper and Proud 2002). Phosphorylation of eIF4E has been found to be important for translation only under certain conditions, leading to the additional suggestion that phosphorylation of eIF4E may play a role in ensuring a subset of mRNAs are expressed (Costa-Mattioli *et al.* 2009). This hypothesis has been extended to suggest that increased translation of a subset of proteins involved in mGluR-LTD, via this mechanism, may play a role in regulating the magnitude of mGluR-LTD (Bhakar *et al.*2012).

Possible points of convergence between p38 ERK1/2 MAPK signaling

Phosphorylation of Mnk1 at two residues, by either p38 MAPK or ERK1/2, is required for its activation (Fig. 2c; Chrestensen *et al.* 2007). In rats these residues are Thr209/ Thr214 and in mice these residues are Thr197/Thr202 (Shveygert *et al.* 2010). As mentioned above, the DHPG- induced activation of Mnk1 is ERK1/2 but not p38 MAPK dependent, however, p38 MAPK is involved in maintaining the basal phosphorylation state of Mnk1 in these conditions (Banko *et al.* 2006). Therefore, both p38 and ERK1/2 may regulate Mnk1 activity, possibly in some experimental conditions ERK1/2 plays a more significant role and in others p38 MAPK. In certain physiological responses p38 MAPK is known to induce Mnk1 activation (Fukunaga and Hunter 1997; Waskiewicz *et al.* 1997; Wu *et al.* 2013) therefore it is plausible that in preparations in which p38 MAPK is involved in mGluR-LTD it may act in part via Mnk1.

Mitogen- and stress-activated protein kinase 1 (MSK1) is also a point of convergence for p38 and ERK1/2 signaling as they can both phosphorylate Thr 581 and Ser 360 on the c- terminal docking region to activate MSK1 (Fig. 2c; McCoy *et al.* 2005; Corrêa *et al.* 2012; Frenguelli and Corrêa 2012). The activation of MSK1 could be instrumental in mGluR-LTD through its downstream cascade leading to activity- dependent transcription of Arc/Arg 3.1 (Corrêa *et al.* 2012) which facilitates the endocytosis of AMPARs. However, the role of MSK1 in mGluR-LTD has not been fully investigated and further studies are required to establish whether MSK1 is involved in mGluR-LTD.

AMPAR trafficking underlying mGluR-LTD via MAPK signaling

It is well established that the endocytosis of AMPARs plays an important role in mGluR-LTD (Carroll *et al.* 2001; Snyder *et al.* 2001; Xiao *et al.* 2001; Huang *et al.* 2004; Moult *et al.* 2006; Gladding *et al.* 2009a; Sanderson *et al.*

2011; Eales *et al.* 2014). Immunofluorescence imaging studies have shown that DHPG exposure results in the loss of AMPARs from the surface of cultured hippocampal neurons and the use of an acid stripping protocol reveals a corresponding increase in internalized AMPARs (Snyder *et al.* 2001; Moult *et al.* 2006). Another study found that a minority of puncta disappeared rapidly during perfusion of DHPG, an effect that lasted for at least 30 min and was accompanied by an increase in fluorescence intensity in the cell body (Xiao *et al.* 2001). This study confirms that at least part of the effect of DHPG is to promote AMPAR internalization at the post-synaptic membrane. Surface biotinylation experiments using acute hippocampal slices have confirmed that AMPARs are internalized following DHPG application (Huang *et al.* 2004; Moult *et al.* 2006; Gladding *et al.* 2009a).

The fact that AMPAR trafficking may not be uniform at all synapses is suggested by live cell imaging of GluA2 tagged with the pH-sensitive variant of green fluorescent protein, known as super ecliptic pHluorin (SEP-GluA2). The pH sensitivity of SEP results in quenching of its fluorescence when SEP-GluA2 is internalized, as endocytic vesicles are acidic. Surprisingly, in primary hippocampal neuronal cultures, DHPG application did not result in an average decrease in SEP-GluA2 fluorescence, rather it caused an increase in the variability between puncta (Sanderson *et al.* 2011). Thus, the factors that determine the extent to which DHPG induces AMPAR trafficking at individual synapses requires further investigation.

MAPK signaling has been found to be directly involved in DHPG-induced internalization of AMPARs as inhibition of the p38 cascade prevents AMPAR endocytosis because of its regulation of clathrin-coated vesicle formation (Huang *et al.* 2004; Eales *et al.* 2014). p38 activation increases the formation of a complex that promotes the recycling of the small GTPase Rab5, a molecule that is essential for clathrin- coated vesicle formation (Huang *et al.* 2004).

The emerging role for the p38 substrates MK2 and 3 in mGluR-LTD and AMPAR trafficking, is surprising as MK2/3 are classically thought of as being involved in the production and release of inflammatory cytokines in mammalian cells (Ronkina *et al.* 2007; Ghasemlou *et al.* 2010). The deletion of MK2 in mammalian cells reduces the production of proinflammatory factors, in particular tumor necrosis factor alpha (TNFa) (Kotlyarov *et al.* 1999). Based on this finding, it has been hypothesized that reduced expression of TNFa may play a role in the block of mGluR- LTD that is observed in the MK2/3 DKO mice (Hogg *et al.* in press). A potential explanation for this is that TNFa is necessary for basal synaptic transmission and synaptic scaling (Beattie *et al.* 2002; Stellwagen and Malenka 2006) and has a role in enhancing the exocytosis of AMPARs (Stellwagen *et al.* 2005). Thus, in MK2/3 DKO mice the reduction in mGluR-LTD magnitude may be because of a reduced amount of TNFa at the synapse that is below the level required to maintain basal surface AMPAR levels. As the presence of GluA2-containing AMPARs has been shown to be necessary for mGluR-LTD (Zhou *et al.* 2011), this may imply that mGluR-LTD is disrupted in MK2/3 DKO mice because the number or assortment of AMPARs necessary to trigger mGluR-LTD at synapses is not correct. This hypothesis is supported by the observation that the amplitude of AMPAR-mediated miniature excita- tory post-synaptic currents (mEPSCs) is reduced in MK2/3 DKO hippocampal neurons (Eales *et al.* 2014). Further investigation is required to determine whether there is a significant reduction in the production of TNFa in the hippocampus of MK2/3 DKO mice and its potential effect on mGluR-LTD.

The loss of surface AMPARs is blocked by the translation inhibitor cyclohexamide, indicating that this process lies downstream of the enhanced protein translation suggested to be involved in mGluR-LTD (Snyder *et al.* 2001). Indeed, many of the proteins that are up-regulated by DHPG exposure play a role in AMPAR endocytosis. These include Arc/Arg3.1, the depletion of which causes increased synaptic transmission because of reduced AMPAR internalization (Chowdhury *et al.* 2006; Shepherd *et al.* 2006) and reduced DHPG-induced internalization of AMPARs (Park *et al.* 2008; Waung *et al.* 2008). Accordingly, Arc/Arg3.1 has been shown to control the trafficking of AMPARs through its interaction with clathrin-adaptor protein 2, dynamin, and endophilin (Chowdhury *et al.* 2006; Waung *et al.* 2008; Peebles *et al.* 2010; Corrêa *et al.* 2014; Mabb *et al.* 2014).

Corroborating these findings is the observation that depletion of Triad3A, which is a protein required for targeting Arc/ Arg3.1 protein for degradation, results in enhanced mGluR- dependent synaptic depression whereas over-expression of this protein promotes the opposite effect (Mabb *et al.* 2014). Other proteins up-regulated in mGluR-LTD that play a role in AMPAR internalization include oligophrenin-1 (OPHN1), microtubule-associated protein 1B (MAP1B), and STEP (Davidkova and Carroll 2007; Zhang *et al.* 2008; Nadif Kasri *et al.* 2011). Since ERK1/2 is involved in the regulation of translation, it is possible that it regulates the translation of proteins involved in AMPAR internalization.

Dendritic spine morphology in mGluR-LTD

In recent years several reports have suggested a direct link between dendritic spine shrinkage, endocytosis of AMPARs and decreases in AMPAR-mediated synaptic transmission in mGluR-LTD. Interestingly, application of agents that prevent

both polymerization and depolymerization of actin have been shown to block mGluR-LTD, but not NMDAR-dependent LTD (Xiao *et al.* 2001; Morishita *et al.* 2005; Moult *et al.* 2006). Furthermore, there is a correlation between actin reorganization and AMPAR endocytosis after the induction of mGluR-LTD (Vanderklish and Edelman 2002; Zhou *et al.* 2011; Eales *et al.* 2014). At dendritic spines, actin is found in either monomeric globular (G)-actin or filamentous (F)-actin forms, and the shift between these two arrangements promotes actin remodeling and subsequent changes in spine morphology (Cingolani *et al.* 2008). However, the mecha- nism by which activation of group I-mGluRs results in dendritic spine morphological changes and reductions in synaptic transmission promoted by AMPAR internalization are only recently beginning to emerge.

A key component of the regulation of the actin cytoskeleton during mGluR-LTD is cofilin1. The requirement of cofilin1 activity in actin remodeling in multiple forms of synaptic plasticity is well-documented (Hotulainen and Hoogenraad 2010; Mizuno 2013). Significantly, it has been shown that preventing the activation of cofilin1 blocks the induction of mGluR-LTD (Zhou *et al.* 2011; Asrar and Jia 2013). Several elements of the upstream regulators of cofilin1 during mGluR-LTD have been identified and these include Ras-related C3 botulinum toxin substrate 1 (Rac), p- 21-activated kinase, and LIM kinase (Chevy *et al.* 2015). Recent findings demonstrated that the p38-MK2 cascade is required to regulate cofilin1 activity in hippocampal neurons, as inhibition of p38 blocked the DHPG-induced activation of cofilin1 (Eales *et al.* 2014). Furthermore, dendritic spines of hippocampal neurons obtained from MK2/3 DKO mice displayed deficits in spine morphology and impaired DHPG- LTD, a phenotype that was rescued by re-introducing MK2, but not MK3, wild-type proteins into hippocampal neurons obtained from MK2/3 DKO mice (Eales *et al.* 2014). These findings corroborate the suggested mechanism that mGluR- LTD is associated with cytoskeleton reorganization resulting in spine morphological changes.

The activation of the mGluR-p38-MK2 pathway could potentially regulate actin remodeling via the activity of the actin-related protein 2 and 3 (Arp2/3) proteins complex. The MK2 protein has been shown to interact and phosphorylate the p16-Arc subunit of the Arp2/3 complex (Fig. 2a (II); Singh *et al.* 2003). The mechanism by which the Arp2/3 complex mediates actin nucleation, spine morphology, and trafficking of AMPARs in NMDAR-dependent LTD has been well-characterized (Rocca *et al.* 2008, 2013; Henley *et al.* 2011). However, initial experiments have not found a role for Arp2/3 in mGluR-LTD (Rocca *et al.* 2013).

The interaction between AMPAR subunit GluA2 and the cell adhesion molecule N-cadherin has been found to be essential for mGluR-LTD (Zhou *et al.* 2011). These proteins are both required to induce the cofilin1-dependent actin reorganization that is necessary for mGluR-LTD. The trafficking of AMPARs is not only required for the expression of mGluR-LTD, but AMPARs play a role in the activation of signaling cascades that coordinate the processes leading to structural changes. The activation of the ERK1/2 pathway could also orchestrate changes in actin reorganization via the STEP-bcatenin-Rac-p-21-activated kinase pathway to regulate cofilin1 activity (Asrar and Jia 2013).

The role of MAPK signaling in neurological diseases

Fragile X syndrome and tuberous sclerosis

Fragile X syndrome is the leading cause of inherited mental retardation after Downs syndrome and is associated with a fragile site on the X chromosome (at site Xq27.3). The clinical symptoms (reviewed in Gallagher and Hallahan 2012) include severe intellectual disability, reduced executive function, deficits in short-term memory, and deficits in attention. As well as these cognitive deficits, patients often suffer from epilepsy, facial dysmorphism, and macro-orchidism. This condition is caused by a mutation in the fragile X mental retardation 1 (*FMR1)* gene which results in a CGG triplet repeat being expanded, resulting in silencing of the gene (Verkerk *et al.* 1991). A detailed description of the function of the product of FMR1, FMR protein (FMRP), is beyond the scope of this article (reviewed in Darnell and Klann 2013). In summary, FMRP acts as a translational repressor (Laggerbauer *et al.* 2001; Li *et al.* 2001; Zhang *et al.* 2001; Aschrafi *et al.* 2005; Qin *et al.* 2005; Bolduc *et al.* 2008), targeting a specific set of mRNAs that include 30% of the post- synaptic density proteome (Darnell *et al.* 2011). Therefore, fragile X syndrome may be the result of de-regulated translation of the mRNAs targeted by FMRP and may involve diverse synaptic phenotypes.

mGluR-LTD is of potential relevance to fragile X syndrome, since in *FMR1* KO animals the magnitude of mGluR-LTD is enhanced (Huber *et al.* 2002; Till *et al*. 2015) and it is insensitive to mRNA translation inhibitors (Nosyreva and Huber 2006; Till *et al*. 2015), leading to the theory that fragile X syndrome is related to enhanced mGluR-LTD (Bear *et al.* 2004). This enhanced mGluR-LTD may be because of the elevated expression of proteins (Qin *et al.* 2005), including Arc/Arg3.1 and MAP1B (Zalfa *et al.* 2003; Darnell *et al.* 2011), as a result of the absence of regulation by FMRP.

ERK1/2 signaling may play a crucial role in the patho- physiology of this disease since the elevated protein expression in FMR1 KO mice is normalized to wild-type levels by ERK1/2 inhibition (Osterweil *et al.* 2010). The basal

phosphorylation state of ERK1/2 was found to be unaltered, leading the authors to suggest that the elevated protein expression levels may be because of greater sensitivity of the translation machinery to ERK1/2 signaling (Osterweil *et al.* 2010). ERK1/2 is also a target of FMRP (Darnell *et al.* 2011), therefore it may be that the protein synthesis machinery is responding to elevated levels of ERK1/2, which may result from the loss of translational repression by FMRP. p38 MAPK phosphorylation was found to be decreased in FMR1 KO mice (Osterweil *et al.* 2010) and it was suggested that this may be a compensatory down- regulation in response to elevated protein synthesis. This may represent another area of cross talk between p38 MAPK and ERK1/2 signaling.

Regulating mGluR5 function has been explored as a potential strategy to treat fragile X syndrome (D6len *et al.* 2010). However, clinical trials to investigate drugs acting at mGluR5 have not been successful to date. A drug currently approved to treat hypercholesterolemia, Lovestatin, is suggested to be able to correct enhanced mGluR-LTD as well as epileptiform activity in FMR1 KO mice via inhibition of the Ras-ERK1/2 pathway (Osterweil *et al.* 2013). Therefore, currently available drugs may potentially be utilized to treat this condition via this mechanism. It is worth noting that elevated protein translation observed in FMRP KO mice can be rescued to basal levels by inhibiting the mTOR cascade (Sharma *et al.* 2010). Thus, a variety of different potential therapeutic targets downstream of mGluRs can be considered for the treatment of fragile X syndrome.

There are also links between fragile X syndrome and other conditions; in particular autism spectrum disorders (ASD) are over represented in fragile X syndrome patients (Gallagher and Hallahan 2012). It is therefore of interest that animal models of another genetic condition that is linked with ASD, tuberous sclerosis (Bolton *et al.* 2002) also exhibit altered mGluR-LTD. However, in the two tuberous sclerosis animal models studied to date, the magnitude of mGluR-LTD is reduced rather than increased in the hippocampus (Auerbach *et al.* 2011; Chevere-Torres *et al.* 2012). This disease is also the result of deregulation of protein translation, and is because of the loss of either hamartin (TSC1) or tuberin (TSC2). The disease was modeled in these studies using either heterozygous TSC2 knockouts (Auerbach *et al.* 2011) or by introducing a loss of function mutation into TSC2 (Chevere-Torres *et al.* 2012). Enhanced ERK1/2 activation was detected in the second of these models, and the deficit in mGluR-LTD was prevented by ERK1/2 inhibition, suggesting that enhanced ERK1/2 signaling may play a role in the pathophysiology of this disease (Chevere-Torres *et al.* 2012). In the first model (TSC2 knockouts) the decreased mGluR- LTD was prevented by rapamycin, an mTOR inhibitor (Auerbach *et al.* 2011), again pointing to a balance in MAPK and mTOR signaling which may be driven in different directions depending on the experimental conditions.

In summary, in ASD-related models of disease ERK1/2 inhibition can reduce aberrantly enhanced mGluR-LTD (Osterweil *et al.* 2010, 2013) and can increase pathologically reduced mGluR-LTD (Chevere-Torres *et al.* 2012). These results may indicate that an optimal level of ERK1/2 activation is necessary for the correct expression of mGluR-LTD and associated cognitive function.

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes cognitive impairments. Atrophy of the hippocampus is seen at an early stage of the disease (Sabuncu *et al.* 2012) and hippocampal volume continues to decrease as the disease progresses (Simic *et al.* 1997; Sabuncu *et al.* 2012). The neuropathology of AD is characterized by the presence of extracellular senile plaques composed of amyloid beta (Ab) and intracellular neurofibrillary tangles formed from hyperphosphorylated tau (Spire- Jones and Hyman 2014). The investigation of hippocampal mGluR-LTD in Alzheimer's disease is limited compared to other forms of synaptic plasticity, such as LTP (Klyubin *et al.* 2012). However, it is vital to further examine mGluR- LTD in this disease as the signaling pathways associated with mGluR-LTD have been implicated in the generation of Ab, hyperphosphorylation of tau and loss of synapses, which are all involved in the pathology of AD. The potential importance of mGluR-LTD in Alzheimer's is supported by the observation that deletion or inhibition of mGluR5 rescued spatial learning and reduced Ab plaque load in an AD mouse model (Um *et al.* 2013; Hamilton *et al.* 2014).

Exogenous application of soluble Ab to hippocampal slices enhances LTD produced by subthreshold low frequency stimulation, whereas in control conditions the same stimulation protocol is ineffective at inducing LTD. The Ab-mediated enhancement of subthreshold LTD is blocked by the application of a group I-mGluR inhibitor, suggesting it may share mechanisms with mGluR-LTD (Shankar *et al.* 2008; Li *et al.* 2009). In the dentate gyrus Ab also facilitates mGluR-LTD and importantly this is dependent on the activation of p38 (Chen *et al.* 2013). Also, the prolonged exposure of cultured hippocampal slices to Ab occludes mGluR-LTD and the proposed mechanism underlying this change is that Ab exposure initially promotes the phosphorylation and endocytosis of AMPARs which leads to occluded mGluR-LTD at the later time point (Hsieh *et al.* 2006). This Ab-mediated internalization of AMPARs is hypothesized to contribute to the loss of synapses that is observed in Alzheimer's disease (Shankar and Walsh 2009).

Supporting this hypothesis is the finding that expression of an AMPAR mutant that prevents the mGluR-LTD-dependent endocytosis of AMPAR also prevents the morphological changes and loss of dendritic spines observed after prolonged Ab exposure (Hsieh *et al.* 2006). The proteins that mediate mGluR-dependent activation of the MAPK cascade leading to AMPAR internalization could therefore be potential therapeutic targets in Alzheimer's disease.

Other signaling molecules that are involved in mGluR- LTD have been implicated in Alzheimer's disease. These include Arc/Arg3.1 (Dorostkar and Herms 2012), which is required for activity-dependent production of Ab (Wu *et al.* 2011). The deletion of Arc/Arg3.1 reduces Ab load in AD transgenic mice and this effect is because Arc/Arg3.1 regulates the trafficking of amyloid precursor protein as well as directly binding to presenilin-1, which is a c secretase required for the production of Ab. It is hypothesized that Arc/Arg3.1 plays a role in the activity driven production of Ab because it increases the association between amyloid precursor protein and presenilin-1 (Wu *et al.* 2011).

The activation of the MAPK pathways, especially the p38 cascade, have strong links to neurodegeneration (Munoz and Ammit 2010; Corrêa and Eales 2012). Ab exposure stimulates the activation of the p38 pathway *in vitro* (Pyo *et al.* 1998; Jin *et al.* 2005; Corrêa and Eales 2012). In addition to this p38 is up-regulated in human AD brains (Hensley *et al.*1999) and in an AD mouse model (Savage *et al.* 2002). The role of ERK1/2 in Alzheimer's disease is not yet as clear and there have been reports of it being both up-regulated (Pyo *et al.* 1998; Pei *et al.* 2002) and down-regulated by Ab exposure (Jin *et al.* 2005). The inhibition of ERK1/2 or p38 has had success in reducing cognitive impairments in AD model mice (Munoz *et al.* 2007; Ashabi *et al.* 2012). This could be because the inhibition of p38 prevents the increased endocytosis of AMPARs on exposure of endogenous Ab and therefore rescues the impairment of LTP (Wang *et al.* 2004; Nomura *et al.* 2012). The over-activation of this pathway is significant as p38 activation has been shown to play a role in the hyperphosporylation of tau, which results in neurofibrillary tangles, a hall mark of Alzheimer's (Lauretti and Pratico 2015). Preventing the up-regulation of MAPK pathways could be a therapeutic strategy to delay the cognitive impairments observed in AD.

The increased production of Ab stimulates the activation and proliferation of microglia in Alzheimer's disease (Meda *et al.* 1995) which in turn causes an increase in the release of neuroinflammatory factors such as TNFa (Combs *et al.* 2001). The release of TNFa has been shown to enhance the exocytosis of AMPARs (Stellwagen *et al.* 2005). Therefore, hypothetically the increase in TNFa production during Alzheimer's could be linked to AMPAR internalization possibly via mGluR–LTD (Hogg *et al.* in press). The inhibition of the p38 cascade prevents the Ab-mediated increase in the production of inflammatory factors and this could be another beneficial effect of therapeutically targeting p38 (Bachstetter *et al.* 2011). Although direct evidence for proinflammatory factors regulating mGluR-LTD is lacking, there are recent studies that highlight neuroinflammation as an interesting area to develop therapeutic intervention in cognitive decline in Alzheimer's (Tobinick *et al.* 2006; Shi *et al.* 2011).

Until recently specific drugs to target single isoforms of MAPKs were not available but a small peptide inhibitor of p38a has now been developed, MW01-18-150SRM, and administration of this peptide rescued the spatial memory deficits seen in a transgenic Alzheimer's disease model (Roy *et al.* 2015). There have also been advances in the development of specific MK2 inhibitors which may also be a good target for the inhibition of the p38 cascade, as targeting proteins downstream of p38 offer the advantage of reducing unwanted side effects by inhibiting only one and not all the p38 effector proteins (Duraisamy *et al.* 2008). The targeting of mGluR5 has also been proposed as a possible therapeutic target in AD (Kumar *et al.* 2015).

Final remarks

In the last decade considerable progress has been made in understanding the role of MAPK cascades in regulating the induction and maintenance of mGluR-LTD. Proteins down- stream of mGluR-MAPK activation are likely to play a critical and specific role in mGluR-LTD and its associated forms of learning and memory. Therefore, the characterization of these effectors may reveal novel therapeutic targets to slow down cognitive impairments observed in natural aging and diseases. To develop novel and specific targets with reduced side effects, further fundamental research is required to map the precise proteins downstream of the individual MAPK cascades as well as the potential cross talk between these cascades as they orchestrate mGluR-LTD (Fig. 2).

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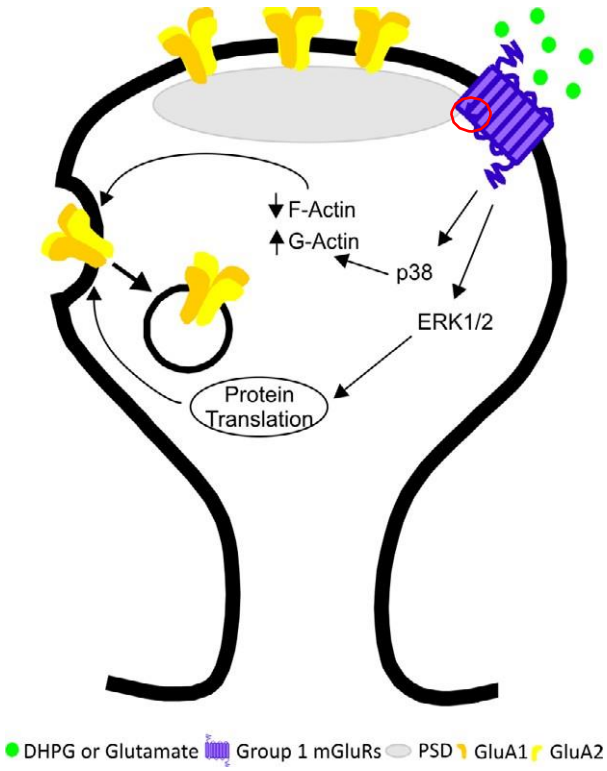

mGluR-LTD is a form of synaptic plasticity that impacts on memory formation. In the hippocampus mitogen-activated protein kinases (MAPKs) have been found to be important in mGluR-LTD. In this 60th anniversary special issue article, we review the independent and complementary roles of two classes of MAPK, p38 and ERK1/2 and link this to the aberrant mGluR-LTD that has an important role in diseases.

***Abbreviations used*:** (F)-actin, filamentous actin; (G)-actin, globular actin; AD, Alzheimer's disease; AMPAR, a-amino-3-hydroxy-5-methyl- 4-isoxazolepropionic acid receptors; APP, amyloid precursor protein; Arc/Arg3.1, activity-regulated cytoskeleton associated protein; Arp2/3, actin related protein 2 and 3; ASD, autism spectrum disorders; Ab, amyloid beta; DHPG, (RS)- or (S)-3,5-dihydroxyphenylglycine; DKO, double knockout; eEFs, eukaryotic elongation factors; eIFs, eukaryotic initiation factors; eRFs, eukaryotic release factors; ERK1/2, extracellular signal-regulated kinase 1/2; FMR1, fragile mental retardation 1; FMRP, fragile mental retardation protein; GFP, green fluorescent protein; IEGs, immediate early genes; JNK, Jun N-terminal kinases; KO, knockout; LIMK, LIM kinase; LTD, long-term depression; LTP, long-term potentiation; MAP1B, microtubule-associated protein 1B; MAPK, mitogen activated protein kinase; mEPSCs, miniature excitatory postsy- naptic currents; mGluR, metabotropic glutamate receptor; MK2/3, mitogen-activated protein kinase-activated protein kinases 2 and 3; Mnk1, MAPK interacting protein kinase 1; MSK1, mitogen and stress activated protein kinase 1; mTOR, mammalian target of rapamycin; NMDAR, *N*-methyl-D-aspartate receptors; OPHN1, oligophrenin-1; PAK, p-21 activated kinase; PP-LFS, paired-pulse low frequency stimulation; Rac1, Ras-related C3 botulinum toxin substrate 1; SEP, super-ecliptic pHluorin; SRE, serum-response-element; SRF, serum response factor; STEP, striatal enriched protein phosphatase; TNFa, tumor necrosis factor alpha; TSC1/2, tuberous sclerosis 1/2.