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Metabotropic Glutamate Receptor-Mediated Long-Term Depression: Molecular Mechanisms

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***Abstract*——The ability to modify synaptic transmission between neurons is a fundamental process of the nervous system that is involved in development, learning, and disease. Thus, synaptic plasticity is the ability to bidirectionally modify transmission, where long-term potentiation and long-term depression (LTD) represent the best characterized forms of plasticity. In the hippocampus, two main forms of LTD coexist that are mediated by activation of either *N*-methyl-D-aspartic acid receptors (NMDARs) or metabotropic glutamate receptors (mGluRs). Compared with NMDAR-LTD, mGluR-LTD is less well understood, but recent advances have started to delineate the underlying mechanisms. mGluR-LTD at CA3:CA1 synapses in the hippocampus can be induced either by synaptic stimulation or by bath application of the group I selective agonist (*R*,*S*)-3,5-dihydroxyphenylglycine. Multiple signaling mechanisms have been implicated in mGluR-LTD, illustrating the complexity of this form of plasticity. This review provides an overview of recent studies investigating the molecular mechanisms underlying hippocampal mGluR-LTD. It highlights the role of key molecular components and signaling pathways that are involved in the induction and expression of mGluR-LTD and considers how the different signaling pathways may work together to elicit a persistent reduction in synaptic transmission.**

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I. Introduction

The vast majority of excitatory neurotransmission is mediated by the amino acid glutamate, which acts on ionotropic and metabotropic receptors throughout the central nervous system. Ionotropic glutamate receptors (iGluRs) consist of NMDA,[1] AMPA, and kainate receptors and act as ligand-gated ion channels mediating fast excitatory neurotransmission (Dingledine et al., 1999). Metabotropic glutamate receptors (mGluRs) are coupled to GTP-binding proteins that link the receptors to downstream signaling pathways (Sladeczek et al., 1985; Nicoletti et al., 1986). The family of mGluRs comprises eight different subtypes (mGluR1–8; now $mGlu_{1-8}$ receptors according to the International Union of Pharmacology classification; Foord et al., 2005) classified into three groups on the basis of sequence similarities, pharmacological properties, and intracellular signal transduction mechanisms (Nakanishi, 1992; Conn and Pin, 1997). Group I includes $mGlu_1$ and $mGlu_5$ receptors, which couple to G_q and activate phospholipase C (PLC) (Ferraguti et al., 2008). In group II ($mGlu_2$, $mGlu_3$) and group III ($mGlu_4$, $mGlu_6$, Glu_7, and $mGlu_8$), receptors couple to G_i/G_o and inhibit adenylyl cyclase (Conn and Pin, 1997; Gerber et al., 2007).

Synaptic plasticity is the strengthening or weakening of synapses in response to different activity patterns. This involves specific changes in cellular activity within complex neural networks; together, these encode distinct memory traces (Bruel-Jungerman et al., 2007). The two main types of synaptic plasticity involve either a long-lasting decrease [long-term depression (LTD)] or increase [long-term potentiation (LTP)] in synaptic efficiency (Citri and Malenka, 2008). A well studied form of hippocampal synaptic plasticity is NMDAR-mediated LTP (Bliss and Collingridge, 1993), which has attracted significantly more attention than the involvement of mGluRs in LTP (Bashir et al., 1993a; Bortolotto and Collingridge, 1993). Like LTP, LTD is also predominantly mediated by activation of synaptic NMDARs (NMDAR-LTD) (Dudek and Bear 1992; Mulkey and Malenka 1992) or by mGluRs (mGluR-LTD) (Bashir et al., 1993a; Oliet et al., 1997; Bellone et al., 2008) at hippocampal CA3:CA1 synapses. In addition to synaptic stimulation protocols, selective pharmacological agonists are extensively used for the induction of NMDAR-LTD and mGluR-LTD. Robust hippocampal NMDAR-LTD (Lee et al., 1998) and mGluR-LTD (Overstreet et al., 1997; Palmer et al., 1997; Fitzjohn et al., 1999; Schnabel et al., 1999a) can be induced by bath application of NMDA and agonists of group I mGluRs, respectively.

Other forms of LTD can also be induced in the hippocampus and other brain areas that are independent of NMDAR and mGluR activation (Berretta and Cherubini, 1998). Furthermore, LTD regulation can be dependent on nonglutamatergic receptors such as adenosine receptors (de Mendonça et al., 1997; Kemp and Bashir, 1997), adrenergic receptors, and muscarinic receptors (Kirkwood et al., 1999). In addition, LTD can be induced by insulin at CA3:CA1 synapses of the hippocampus (Huang et al., 2004a). mGluR-LTD of both excitatory and inhibitory transmission can also be induced in a variety of brain regions (Bellone et al., 2008). However, this review focuses only on group I mGluR-mediated LTD of glutamatergic transmission at the CA3:CA1 synapse in the hippocampus. It will describe how synaptic or pharmacological stimulation can induce mGluR-LTD and subsequently outline the molecular mechanisms underlying mGluR-LTD induction and expression.

II. Long-Term Depression

LTD is a long-lasting decrease in the efficacy and strength of synaptic transmission. This phenomenon was first observed as *heterosynaptic depression* in which a reversible reduction of synaptic response in a nonstimulated pathway resulted after inducing LTP in a separate pathway in the CA1 region in vitro (Lynch et al., 1977). Heterosynaptic LTD was also observed in vivo in the dentate gyrus indicating that the phenomenon could be applied to different brain areas (Levy and Steward, 1979). *Depotentiation* is the reversal of LTP and can be induced by low-frequency stimulation (LFS). Further-

[1] Abbreviations: 12(S)-HPETE, 12(*S*)-hydroperoxyeicosa-5*Z*,8*Z*,10*E*,14*Z*-tetraenoic acid; 4E-BP, eIF4E-binding protein; 5′TOP, 5′-terminal oligopyrimidine; AA, arachidonic acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, AMPA receptor; ATF2, activating transcription factor 2; BAPTA, 1,2-bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CREB, cAMP response element-binding; DHPG, (*R*,*S*)-3,5-dihydroxyphenyl-glycine; eCB, endocannabinoid; eEF, eukaryotic translation elongation factor; eEF2K, eukaryotic translation elongation factor 2 kinase; EF1A, elongation factor 1A; eIF4, eukaryotic initiation factor 4; EPSC, excitatory postsynaptic current; ERK, extracellular signal-regulated kinase; FMRP, fragile X mental retardation protein; FXS, fragile X syndrome; GDI, guanine nucleotide dissociation inhibitor; GRIP, glutamate receptor interacting protein; iGluR, ionotropic glutamate receptor; IP_3, inositol triphosphate; JNK, Jun N-terminal kinase; KN-62, 4-[(2*S*)-2-[(5-isoquinolinylsulfonyl)methylamino]-3-oxo-3-(4-phenyl-1-piperazinyl)propyl]phenylisoquinolinesulfonic acid ester; KO, knockout; LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; LY341495, (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid; LY367385, (*S*)-(+)-α-amino-4-carboxy-2-methylbenzeneacetic acid; MAP1B, microtubule-associated protein 1B; MAPK, mitogen activated protein kinase; MCPG, α-methyl-4-carboxyphenylglycine; MEK, MAP kinase or ERK kinase; mGluR, metabotropic glutamate receptor; Mnk1, MAPK-interacting kinase 1; mTOR, mammalian target of the rapamycin; NCS, neuronal Ca^{2+} sensor; NF-κB, nuclear factor-κB; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; NP, neuronal pentraxin; NPR, neuronal pentraxin receptor; PI3K, phosphoinositide 3-kinase; PICK, protein interacting with C kinase; PKC, protein kinase C; PLA_2, phospholipase A_2; PLC, phospholipase C; PP-LFS, paired-pulse LFS; PSD, postsynaptic density; PTK, protein tyrosine kinase; PTP, protein tyrosine phosphatase; Rab5, ras in the brain protein 5; Rap1, repressor activator protein 1; RSK1, ribosomal S6 kinase-1; S6K, S6 kinase; STEP, striatal-enriched tyrosine phosphatase; TACE, tumor necrosis factor-α-converting enzyme.

more, depotentiation was the first case of homosynaptic depression observed in the hippocampus (i.e., synaptic depression induced only at synapses receiving stimulation) (Staubli and Lynch, 1990; Fujii et al., 1991; Bashir and Collingridge, 1994; O'Dell and Kandel, 1994). De novo LTD is the depression of basal synaptic transmission, which was first observed at CA3:CA1 synapses as a result of improvements in LFS protocols (Dudek and Bear, 1992; Mulkey and Malenka, 1992). Homosynaptic LTD could also be induced at synapses of other brain regions, such as the perirhinal cortex (Ziakopoulos et al., 1999; Cho et al., 2000), amygdala (Wang and Gean, 1999), cerebellum (Ito et al., 1982), and striatum (Calabresi et al., 1992). This raised the possibility that the synaptic phenomena observed in the hippocampus might be similar to synaptic regulatory mechanisms in other brain regions.

III. Metabotropic Glutamate Receptor-Mediated Long-Term Depression

mGluR-mediated LTD was first characterized at parallel fiber-Purkinje cell synapses of the cerebellum (Ito et al., 1982; Kano and Kato, 1987; Ito, 1989). It is dependent on an increase in intracellular Ca^{2+} and activation of postsynaptic group I mGluRs, specifically $mGlu_1$ receptors (Linden et al., 1991; Aiba et al., 1994; Shigemoto et al., 1994). mGluRs were first shown to mediate hippocampal LTD induction when depotentiation at CA1 synapses was blocked by the group I/II antagonist α-methyl-4-carboxyphenylglycine (MCPG) (Bashir et al., 1993b; Bashir and Collingridge, 1994; Schoepp et al., 1999). A key property of mGluR-LTD in the hippocampus is that it is NMDAR-independent (Kemp and Bashir, 2001; Bashir, 2003). LTD induction by either mGluR or NMDAR activation is not mutually exclusive, meaning that one form of LTD does not occlude the other (Oliet et al., 1997; Palmer et al., 1997; Fitzjohn et al., 1999; Huber et al., 2001). This indicates that the two forms of LTD use different induction mechanisms. However, it should be noted that in some areas, such as the amygdala and perirhinal cortex, synergistic NMDAR and mGluR activation is required for LTD (Wang and Gean, 1999; Cho et al., 2000).

A. Synaptically Induced Metabotropic Glutamate Receptor-Mediated Long-Term Depression

Synaptically induced mGluR-LTD can be evoked in adult brain slices using paired-pulse LFS (PP-LFS) comprising 900 pairs of stimuli delivered at 1 Hz with 50-ms intervals (Kemp and Bashir, 1999, 2001; Huber et al., 2000). Paired-pulse stimulation may facilitate mGluR activation at extrasynaptic sites (Citri and Malenka, 2008). Although the mGluR antagonist MCPG and the group I mGluR antagonist 7-hydroxyiminocyclopropan-[*b*]chromen-1*a*-carboxylic acid ethyl ester (CPCCOEt) can block synaptically induced LTD, initial studies showed this only occurs if the AMPA/kainate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) is also applied (Kemp and Bashir, 1999). It was also demonstrated that LTD could not be blocked by 6-cyano-7-nitroquinoxaline-2,3-dione or MCPG alone (Kemp and Bashir, 1999). However, a separate study using animals on postnatal days 21 to 28 indicated that only mGluR activation was required for PP-LFS-induced LTD (Huber et al., 2000), and in subsequent studies using adult animals, PP-LFS-induced LTD can also be blocked by mGluR antagonists alone (Moult et al., 2008). Other studies using broad-spectrum mGluR antagonists also highlighted the role of mGluRs in synaptically induced LTD in the CA1 region (Bolshakov and Siegelbaum, 1994; Oliet et al., 1997; Otani and Connor, 1998; Faas et al., 2002). Furthermore, application of the $mGlu_5$ receptor specific antagonist 2-methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP) indicated that LTD induction was $mGlu_5$ receptor dependent (Bolshakov et al., 2000; Faas et al., 2002). The conclusions drawn from studies investigating the role of group I mGluRs in CA1 synaptic plasticity can differ because of the various specificities of subunit antagonists and differences in the durations of in vitro and in vivo experiments. To clarify the specific roles of group I mGluR isoforms in regulating late phases of hippocampal LTD, the effects of $mGlu_1$ and $mGlu_5$ receptor antagonism on synaptic plasticity were monitored over a prolonged period in vitro (Neyman and Manahan-Vaughan, 2008). It is noteworthy that $mGlu_5$ receptors convert short-term depression into LTD, indicating that this subunit is necessary to mediate the late-phase of this form of synaptic plasticity.

Compared with NMDAR-LTD, the expression mechanisms underlying synaptically induced mGluR-LTD are poorly understood. It has been proposed that PP-LFS is dependent on protein synthesis and is blocked by inhibitors of translation but not transcription (Huber et al., 2000). The role of the $mGlu_5$ receptor in mediating short-term depression facilitation to LTD is also dependent on protein synthesis (Neyman and Manahan-Vaughan, 2008). However, a more recent study suggested that synaptically induced mGluR-LTD in adult CA1 is independent of protein synthesis (Moult et al., 2008). PP-LFS may also involve activation of the mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), which facilitates regulation of protein synthesis (Gallagher et al., 2004). Furthermore, the effects of PP-LFS is blocked by inhibitors of both p38 MAPK and protein tyrosine phosphatases (PTPs), suggesting that these signaling cascades may also be fundamental (Moult et al., 2008). Although it is generally accepted that mGluR-LTD induction is dependent on PTPs, the involvement of protein synthesis, ERK, and p38 MAPK in synaptically induced mGluR-LTD remains unclear, and further studies are necessary to resolve any underlying controversies.

*B. Agonist-Induced (*R,S*)-3,5-Dihydroxyphenylglycine-Mediated Long-Term Depression*

Broad spectrum mGluR agonists (±)-1-aminocyclopentane-*trans*-1,3-dicarboxylic acid (ACPD) (Schoepp et al., 1999) and quisqualate can be used to pharmacologically induce mGluR-LTD (Bolshakov and Siegelbaum, 1994, 1995; Overstreet et al., 1997) as can the group I-specific agonist (*R*,*S*)-3,5-dihydroxyphenylglycine (DHPG) (Schoepp et al., 1999) and the selective $mGlu_5$ receptor agonist (*R*,*S*)-2-chloro-5-hydroxyphenylglycine (CHPG) (Palmer et al., 1997; Fitzjohn et al., 1999; Huber et al., 2000, 2001). Moreover, in the CA1 region, DHPG-LTD is not induced in the presence of the broad spectrum mGluR antagonists LY341495 and MCPG (Fitzjohn et al., 1998; Huber et al., 2000) or after application of the $mGlu_5$ receptor specific antagonist 2-methyl-6-(phenylethynyl)pyridine hydrochloride (Faas et al., 2002). It is noteworthy that the $mGlu_1$ receptor-specific antagonists 7-hydroxyiminocyclopropan[*b*]chromen-1*a*-carboxylic acid ethyl ester (Faas et al., 2002) and LY367385 generally has no effect on the long-term phase, although the short-term phase is reduced (Fitzjohn et al., 1999; Huang et al., 2004). The absence of DHPG-LTD in $mGlu_5$ receptor knockout (KO) mice further highlights the prominent role of $mGlu_5$ receptor in LTD induction in the CA1 region of the hippocampus (Huber et al., 2001). mGluR-LTD involves sustained activation of $mGlu_5$ receptor, supported by the fact that broad spectrum mGluR antagonists reverse DHPG-LTD several hours after induction (Palmer et al., 1997; Fitzjohn et al., 1999; Watabe et al., 2002; Huang and Hsu, 2006). However, one study has suggested that activation of either $mGlu_1$ or $mGlu_5$ receptor is not sufficient to induce DHPG-LTD, even though LTD is abolished in $mGlu_5$ receptor KO mice (Volk et al., 2006). In summary, the results from pharmacological experiments and receptor KO mice indicate that DHPG-LTD depends predominantly on $mGlu_5$ receptor activation, although the $mGlu_1$ receptor may partly contribute to LTD induction.

DHPG is commonly used for characterizing the induction and expression mechanisms underlying hippocampal mGluR-LTD (Palmer et al., 1997; Huber et al., 2000; Rouach and Nicoll, 2003; Tan et al., 2003; Gallagher et al., 2004; Huang et al., 2004b). Using pharmacological compounds for LTD induction greatly maximizes synaptic stimulation. This is ideal for investigating biochemical mechanisms underlying synaptic plasticity. For in vitro adult hippocampal slice preparation, DHPG-LTD is usually induced using an extracellular medium that is Mg^{2+}-free or contains the $GABA_A$ receptor antagonist picrotoxin (Palmer et al., 1997). Under these conditions, mGluR-LTD is not prevented by application of the NMDAR antagonist D-2-amino-5-phosphonopentanoate (AP-5). The addition of picrotoxin removes any influence from inhibitory neurotransmission at GABAergic synapses. Thus, the overall excitability of the slice is increased, which lowers the threshold for induction of DHPG-LTD (Palmer et al., 1997). It is likely that DHPG-LTD and PP-LFS-induced LTD involve similar expression mechanisms, because the two forms of LTD occlude each other (Huber et al., 2001). Furthermore, it is evident that induction of both DHPG-LTD and PP-LFS-induced LTD employ similar signaling cascades involving MAPKs and PTPs (Rush et al., 2002; Huang et al., 2004b; Moult et al., 2008). This corroborates the concept that DHPG-LTD is a good experimental model for the investigation of molecular and cellular mechanisms underlying synaptically induced mGluR-LTD.

IV. Induction and Expression Mechanisms of Metabotropic Glutamate Receptor-Mediated Long-Term Depression

A. Ca^{2+} Independence and Activation of Kinases

mGluRs are members of the family C G-protein-coupled receptors, which includes $GABA_B$ receptors, the calcium-sensing receptor and a selection of taste, pheromone, and olfactory receptors based on structural similarities (Hermans and Challiss, 2001). mGluRs function as G-protein-coupled receptors in that agonist-induced or constitutive receptor activity leads to G-protein activation by promoting the exchange of GTP to GDP (Hermans and Challiss, 2001). This results in modulation of receptor-protein interactions and activation of distinct second messenger cascades. Group I mGluRs preferentially mediate PLC activation, which leads to diacylglycerol production via an increase in inositol triphosphate (IP_3) (Schoepp and Conn, 1993; Schoepp et al., 1994; Toms et al., 1995). Protein kinase C (PKC) activation and Ca^{2+} release from intracellular stores is stimulated by diacylglycerol and IP_3, respectively (Pin and Duvoisin, 1995).

Although mGluR-LTD is mediated by $mGlu_5$ receptor, it is completely Ca^{2+}-independent, because DHPG-LTD induction is not prevented by the intracellular Ca^{2+} chelator BAPTA and does not depend on extracellular Ca^{2+} (Fitzjohn et al., 2001). In addition, DHPG-LTD induction does not require presynaptic stimulation (Fitzjohn et al., 1999). Furthermore, it was demonstrated that Ca^{2+} release from intracellular stores was not necessary for DHPG-LTD induction because intracellular Ca^{2+} depletion had no effect (Schnabel et al., 1999a; Fitzjohn et al., 2001). In fact, DHPG-LTD may induce a decrease in the intracellular Ca^{2+} levels of the presynaptic cell (Watabe et al., 2002). It is known that Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII) has an important role in LTP induction, hence it may be down-regulated during LTD. Consistent with this hypothesis, DHPG-LTD at CA3:CA1 synapses is enhanced in the presence of the CaMKII antagonist KN-62 (Schnabel et al., 1999b). Although mGluR-LTD in the hippocampus is Ca^{2+}-independent, this is not universally true for other brain areas. For example, it has recently been discovered that in the perirhinal cortex, mGluR-LTD in-

duction is dependent on interactions between the neuronal Ca^{2+} sensor protein (NCS-1) and protein interacting with C kinase (PICK1) (Jo et al., 2008). The NCS-1–PICK1 complex associates with PKC near the plasma membrane, which could facilitate AMPAR endocytosis via phosphorylation of the GluA2 AMPAR subunit (the new International Union of Pharmacology iGluR subunit nomenclature is used in this review; see Collingridge et al., 2009). Furthermore, at cerebellar parallel fiber-stellate cell synapses, mGluR and $GABA_BR$ activation stimulates a decrease in Ca^{2+}-permeable AMPARs (Kelly et al., 2009). This form of plasticity is therefore dependent upon a switch of AMPAR subunit composition initiated by both excitatory and inhibitory inputs and an increase in intracellular Ca^{2+}.

DHPG-LTD induction does not require PKC or protein kinase A activation (Schnabel et al., 1999a, 2001). In contrast, synaptically induced LTD in the CA1 may be dependent on PKC activation under some (Bolshakov and Siegelbaum, 1994; Oliet et al., 1997) but not all (Moult et al., 2008) circumstances. PKC may mediate a decrease in synaptic transmission by stimulating MAPK cascades (Ferraguti et al., 1999), activating phospholipase D (Boss and Conn, 1992; Pellegrini-Giampietro et al., 1996) or phospholipase A_2 (PLA_2) (Aramori and Nakanishi, 1992), or modulating cation channel activity (Sharon et al., 1997).

It can therefore be concluded that group I mGluR-LTD induction in the hippocampus is Ca^{2+}-independent and does not involve the typical intracellular signaling cascade that is normally associated with group I mGluR activation. The molecular mechanisms are thought to differ substantially between different brain regions as demonstrated by the fact that LTD induction is Ca^{2+}-dependent in both the perirhinal cortex and the cerebellum. Although DHPG-LTD and synaptically induced LTD in the CA1 share common molecular mechanisms, it should be kept in mind that some differences do exist.

B. Coupling of Group I Metabotropic Glutamate Receptors to G-Proteins and Scaffolding and Regulatory Proteins

mGluR-LTD induction is also dependent on G-protein activation, specifically involving signaling cascades coupled to the $G\alpha_q$ subunit. Both synaptically induced LTD and DHPG-LTD in the CA1 region were prevented in $G\alpha_q$ KO mice (Kleppisch et al., 2001). Although activation of group I mGluRs typically involves a G-protein coupled Ca^{2+}-dependent PLC-IP_3 signaling pathway, other Ca^{2+}-independent cascades may also be activated (Pin and Duvoisin, 1995; Wang et al., 2007). These may be mediated by scaffolding proteins such as Homer, which brings multiprotein signaling complexes in close proximity to group I mGluRs (Brakeman et al., 1997; Xiao et al., 1998; Sheng and Kim, 2002; Wang et al., 2007). For example, Homer 1b/c may couple $mGlu_5$ receptor activation to the Ca^{2+}-independent ERK signaling cascade (Mao et al., 2005). This may involve association of $mGlu_5$ receptor with the epidermal growth factor receptor tyrosine kinase (Peavy et al., 2001) and activation of Src nonreceptor tyrosine kinases (Luttrell et al., 1997). To support this theory, it has recently been shown that mGluR-LTD in the CA1 of the hippocampus is dependent on mGluR C-terminal interactions with Homer (Ronesi and Huber, 2008).

In addition to Homers, several other proteins have been identified that interact with group I mGluRs and are involved in receptor trafficking and attachment to the cytoskeleton (Kitano et al., 2002; Enz, 2007; Francesconi et al., 2009a,b). For example, caveolin-1, an adaptor protein that associates with lipid rafts and the main protein of caveolae, binds to and colocalizes with group I mGluRs (Francesconi et al., 2009b). The interaction with caveolin-1 affects the rate of constitutive $mGlu_{1/5}$ internalization, thereby regulating the level of receptor expression at the cell surface. Furthermore, association with caveolin-1 regulates mGluR-dependent phosphorylation/activation of ERK-MAPK (Francesconi et al., 2009b), which is required for mGluR-LTD in the hippocampus (Gallagher et al., 2004). It has been proposed that calmodulin (CaM) binding stabilizes $mGlu_5$ receptor surface expression (Lee et al., 2008). This interaction is modulated by PKC-mediated phosphorylation of the intracellular C terminus of $mGlu_5$ at serine 901 after receptor stimulation. Ser901 phosphorylation inhibits $mGlu_5$ binding to CaM, which leads to reduced $mGlu_5$ receptor surface expression (Lee et al., 2008). The role of protein phosphorylation of mGluRs in the regulation of protein-protein interactions, G-protein coupling, and receptor trafficking and desensitization has been reviewed recently (Kim et al., 2008).

Although the precise functional significance of these protein interactions in mGluR-LTD is not clear, it is generally accepted that they provide additional regulatory mechanisms that are independent of and sometimes synergistic with the typical G-protein-coupled second messenger pathways and connect mGluR-mediated signaling to other receptors and signaling cascades (for review, see Enz, 2007).

C. Metabotropic Glutamate Receptor-Mediated Long-Term Depression Signaling Pathways

1. Mitogen-Activated Protein Kinase Signaling Cascades. It has been demonstrated that mGluR-LTD involves all three MAPK subclasses: p38 MAPK (Rush et al., 2002; Huang et al., 2004b; Moult et al., 2008), Jun N-terminal kinase (JNK) (Li et al., 2007b), and ERK (Gallagher et al., 2004) (Figs. 1 and 2). It has been implied that mGluR-LTD induction involves the repressor activator protein 1 (Rap1)–MAPK kinase 3/6–p38 MAPK cascade in the CA1 region (Huang et al., 2004b). The pathway is coupled to endocytotic machineries and is thought to stimulate AMPAR internalization downstream of $mGlu_5$ receptor activation (Fig. 1). Ras and Rap are important GTPases

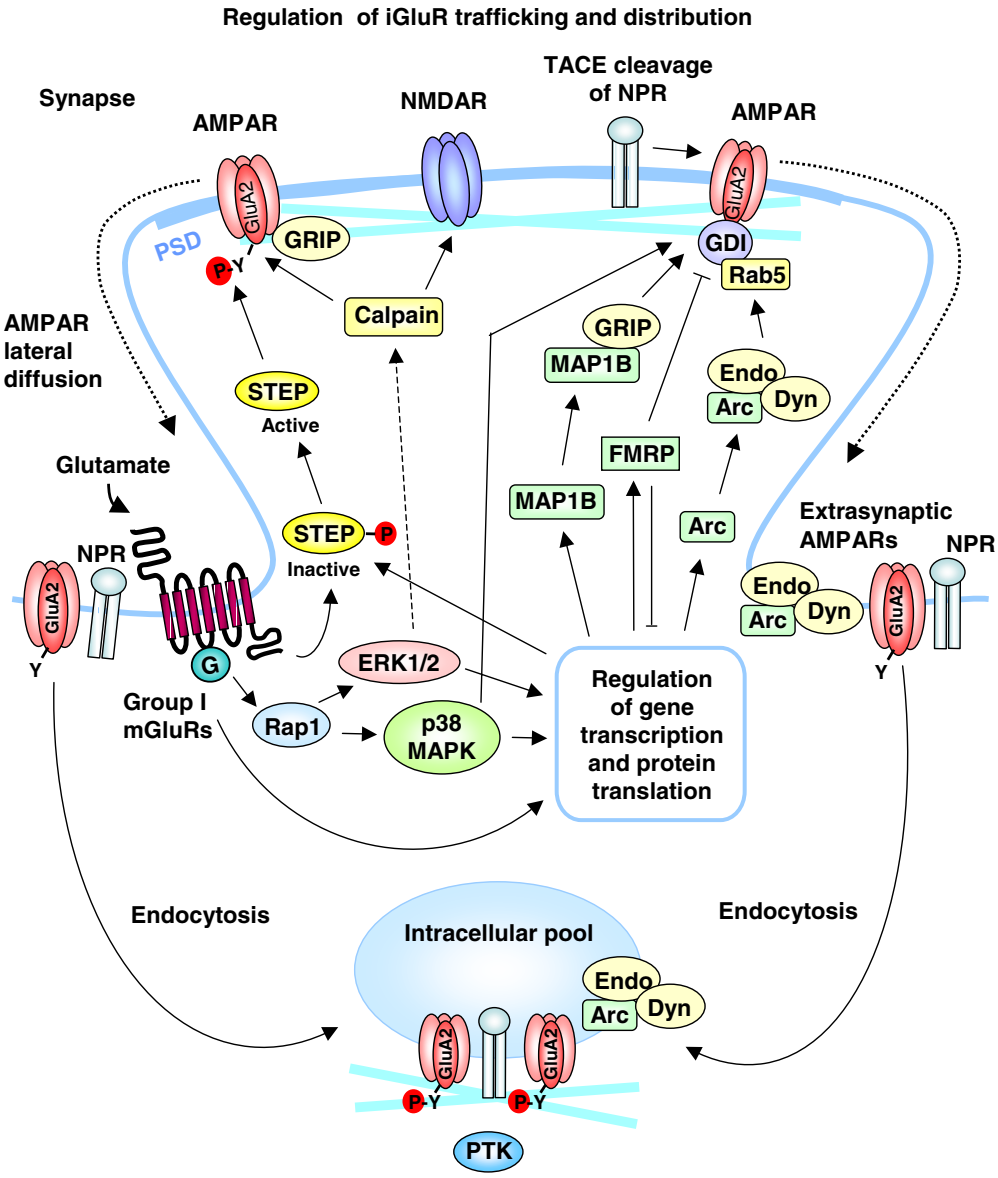

FIG. 1. Schematic model of the molecular mechanisms that regulate ionotropic glutamate receptor distribution during hippocampal mGluR-LTD induction and expression. Activation of group I mGluRs leads to dephosphorylation and activation of STEP, which transiently dephosphorylates tyrosine (Y) residues in GluA2-containing AMPARs at the PSD. This may trigger lateral diffusion of AMPARs to extrasynaptic endocytic zones from which internalization occurs. It is likely that upon internalization, AMPARs are rephosphorylated by PTKs and retained at intracellular compartments until recycled or degraded. In parallel to STEP activation, group I mGluR activation can stimulate ERK1/2 and p38 MAPK signaling pathways via G-protein release and activation of the small GTPase Rap. ERK1/2 activation could stimulate calpain proteolysis of NMDAR and AMPAR subunit C-termini, which facilitates loss of synaptic receptors. Protease involvement is also exemplified by TACE, which cleaves NPR and allows it to cluster with AMPARs and other NPs in endocytic vesicles. Activation of the p38 MAPK signaling pathway stimulates the formation of the GDI-Rab5 complex, which also mediates AMPAR endocytosis. mGluR-LTD involves regulation of gene transcription and protein translation via the activation of signaling pathways such as p38 MAPK and ERK. Protein synthesis up-regulated includes STEP, FMRP, Arc/Arg3.1, and MAP1B, which are all involved in regulation of AMPAR internalization. After synthesis, FMRP is rapidly degraded such that it can no longer inhibit translation of specific mRNAs such as Arc/Arg3.1 and can no longer down-regulate AMPAR endocytosis. Arc/Arg3.1 forms a complex with endophilin2/3 (Endo) and dynamin (Dyn), which facilitates AMPAR internalization. MAP1B also promotes receptor endocytosis by sequestering the scaffolding protein GRIP away from the PSD such that AMPAR synaptic stabilization is reduced. The dotted line corresponds to a postulated pathway involved in mGluR-LTD, solid arrows relate to confirmed molecular mechanisms that promote AMPAR internalization, and the inhibitory arrows refer to pathways that are down-regulating protein synthesis or receptor endocytosis. Figure is based on data described in Zhang et al. (2008) and Gladding et al. (2009).

that control AMPAR trafficking at synapses and are regulated by activators, guanine-nucleotide exchange factors and inactivators, and GTPase-activating proteins (Zhu et al., 2002). It is thought that upon $mGlu_5$ receptor activation, Rap1 and sequentially MAPK kinase 3/6 are activated by the release of G$\beta\gamma$ subunits. This leads to p38 MAPK activation, which promotes AMPAR internalization via the formation of the GDI-Rab5 complex (Cavalli et al., 2001) (Fig. 1). The formation of clathrin-coated vesicles is dependent on specific endocytotic machinery containing the GDI-Rab5 complex (McLauchlan et al., 1998). mGluR-LTD induction in the dentate gyrus is also thought to depend on p38 MAPK and PKC activation, which may also involve the tumor necrosis factor-recep-

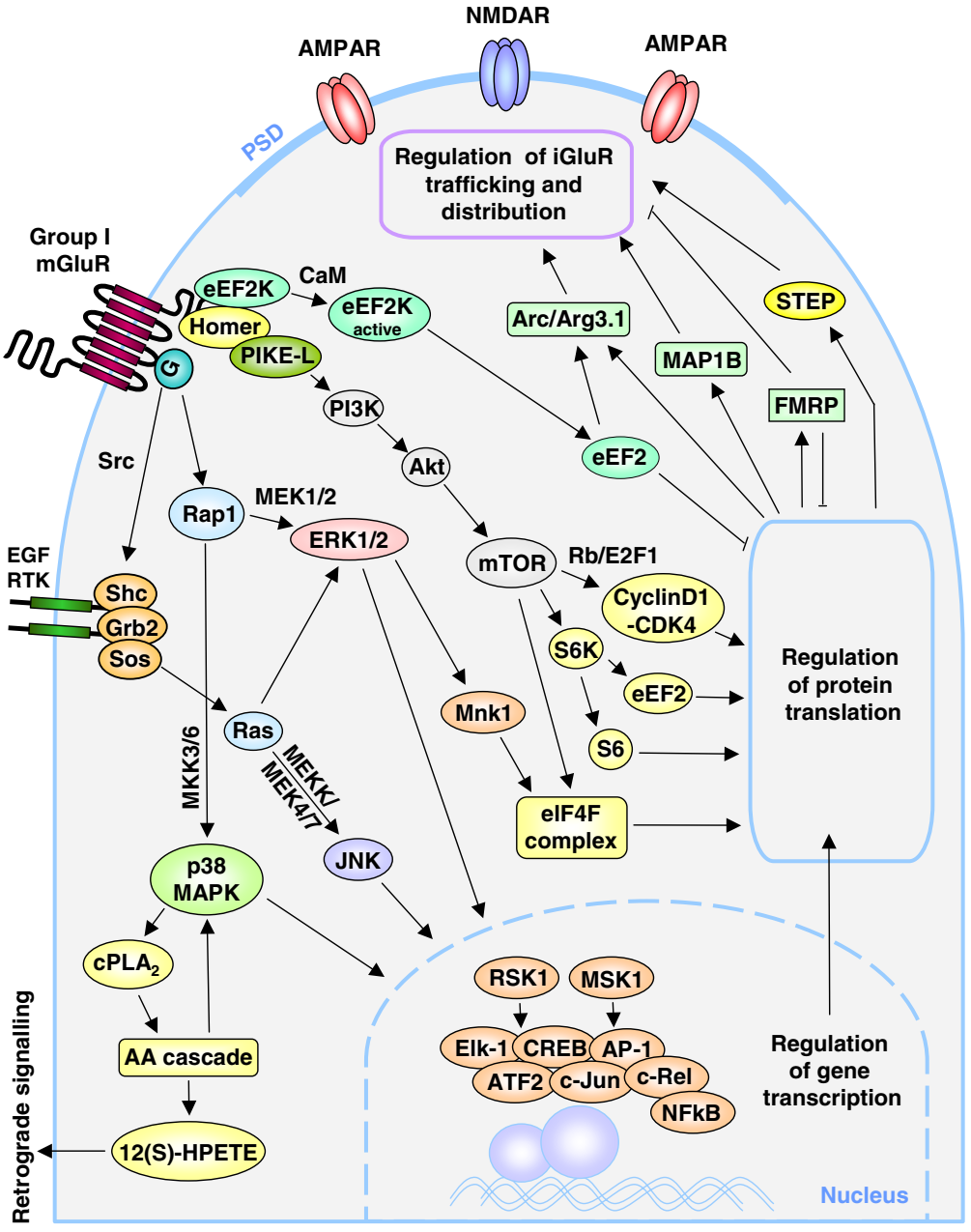

FIG. 2. Schematic model of molecular mechanisms underlying regulation of gene transcription and protein translation during mGluR-LTD in postsynaptic neurons of hippocampal CA3-CA1 synapses. Group I mGluR stimulation can activate the epidermal growth factor receptor tyrosine kinase (RTK) via G-protein release, which activates the nonreceptor tyrosine kinase Src. Recruitment of the Shc-Grb2-Sos complex stimulates the small GTPase Ras, which leads to activation of ERK1/2 and JNK MAPK signaling cascades. ERK1/2 and p38 MAPK can also be stimulated by G-protein release via the small GTPase Rap1 through the mitogen-activated protein kinase kinases MKK3/6 and MEK1/2, respectively. Stimulation of ERK1/2, JNK, and p38 MAPK signaling cascades leads to activation of the transcription factors Elk-1, CREB, activator protein-1 (AP-1), ATF2, c-Jun, c-Rel, and NF-κB via the kinases RSK1 and mitogen and stress-activated protein kinase-1. p38 MAPK is also linked to activation of the AA cascade of which the 12(*S*)-HPETE metabolite may serve as a retrograde signaling molecule. In addition, ERK1/2 signaling can mediate formation of the translation initiation eIF4F complex necessary for initiating protein synthesis. mGluR-LTD involves activation of the PI3K-Akt-mTOR signaling pathway via interactions with Homer and PI3K enhancer-L (PIKE-L). This can facilitate regulation of protein synthesis by activating S6K, eEF2, the eIF4F complex, and the cyclin1-CD4 complex. Furthermore, mGluR activation leads to dissociation and activation of eEF2K, which phosphorylates eEF2. Activated eEF2 prevents global protein translation but facilitates up-regulation of Arc/Arg3.1 synthesis, which is involved in AMPAR endocytosis. Other proteins synthesized during mGluR-LTD include STEP, FMRP, and MAP1B, which may also regulate AMPAR synaptic trafficking.

tor 1 (Rush et al., 2002; Wang et al., 2007). Although several studies have shown a role for p38 MAPK in mGluR-LTD, one study reported that ERK, but not p38 MAPK, is required for the induction and regulation of synaptic protein synthesis (Gallagher et al., 2004) (Fig. 2). The reason for this discrepancy is unclear but may indicate that mGluR activation can couple to different signaling mechanisms dependent on the experimental conditions.

ERK activation may be triggered by $mGlu_5$ receptor activation by a similar cascade involving Rap1 and mitogen-activated protein/ERK kinase (MAPK/MEK)

(Morozov et al., 2003). This leads to activation of the downstream effector ribosomal S6 kinase-1 (RSK1), which is known to be a key regulator of neuronal protein synthesis in response to synaptic activity (Angenstein et al., 1998). The ERK/MAPK signaling cascade is also linked to regulation of *m*-calpain, an isoform of the large calpain subunit (Perrin and Huttenlocher, 2002). It is thought that in addition to phosphorylation, calpain-mediated truncation of iGluR C-terminal tails is important in mediating synaptic plasticity (Guttmann et al., 2001). Although it has not been directly shown, mGluR-LTD may involve a decrease in AMPAR-mediated synaptic transmission as a result of an increase in AMPAR calpain proteolysis (Fig. 1). High NMDA concentrations lead to an increase in GluA1 proteolytic cleavage, which is differentially regulated by GluA1 phosphorylation by CaMKII and protein phosphatases 1 and 2A (Yuen et al., 2007). It has also been demonstrated that GluA1 phosphorylation by Fyn decreases calpain-mediated proteolysis (Rong et al., 2001). Thus, changes in AMPAR phosphorylation may mediate ERK-activated calpain proteolysis during mGluR-LTD, although this has yet to be demonstrated.

It is evident that JNK is also required for LTD induction under some conditions, because both PP-LFS and DHPG-LTD were impaired in the CA1 region of JNK KO mice (Li et al., 2007b) (Figs. 1 and 2). In wild-type mice, DHPG-LTD results in an increase in the phosphorylation levels of the JNK1 substrates activating transcription factor 2 (ATF2) and c-Jun. Expression of the c-*Jun* gene is mediated by ATF2 and c-Jun transcription factors that combine together to form heterodimers (van Dam et al., 1995). However, in this study there was no change in c-*Jun* expression levels, indicating that post-translational modifications rather than mRNA transcription were necessary for mediating DHPG-LTD (Li et al., 2007b). A further study supports a role of c-Jun in mGluR-LTD expression in neurons (Yang et al., 2006). Activator protein-1 mediated gene expression is facilitated by a process that involves dimerization of c-Jun and Fos (Schwarzschild et al., 1997; Yang et al., 2006).

It is evident, therefore, that the MAPK signaling cascades are important for the induction and expression of mGluR-mediated LTD in the hippocampus. The p38 MAPK cascade links mGluR activation to AMPAR internalization via its coupling to endocytotic machineries. ERK can modulate neuronal protein synthesis but may also facilitate a decrease in AMPAR-mediated synaptic transmission by triggering calpain-mediated GluA1 proteolysis. JNK is also involved in the expression of mGluR-LTD by activating specific transcription factors via changes in post-translational modifications.

2. Protein Tyrosine Phosphatases. In contrast to NMDAR-LTD, mGluR-LTD does not involve serine/threonine phosphatases (Schnabel et al., 2001; Harris et al., 2004). However, it is clear that mGluR-LTD induction is dependent on activation of postsynaptic PTPs (Moult et al., 2002, 2006; Huang and Hsu, 2006; Zhang et al., 2008; Gladding et al., 2009) (Fig. 1). There is controversy regarding whether transient (Moult et al., 2002, 2006) or persistent (Huang and Hsu, 2006) PTP activation is required. This may be due to differences in experimental design. It is evident that the AMPAR GluA2 subunit, but not GluA1 or GluA3, is tyrosine dephosphorylated during mGluR-LTD (Moult et al., 2006; Gladding et al., 2009). Furthermore, AMPAR tyrosine dephosphorylation is specific to mGluR-LTD, because only GluA1 serine dephosphorylation was observed during NMDA-LTD (Gladding et al., 2009). Regulation of tyrosine phosphorylation is likely to modulate AMPAR interactions with scaffolding and effector proteins, which subsequently alters receptor stability at the synapse. It is evident that mGluR-LTD involves internalization of surface iGluRs (Snyder et al., 2001; Xiao et al., 2001; Huang et al., 2004b; Waung et al., 2008; Zhang et al., 2008; Gladding et al., 2009) and that tyrosine dephosphorylation of the GluA2 subunit triggers the endocytosis of surface AMPARs (Gladding et al., 2009). Upon DHPG application, the rate of AMPAR endocytosis is increased, and the tyrosine phosphorylation of surface but not intracellular AMPARs is reduced. Hence, it is postulated that tyrosine dephosphorylation of surface AMPARs initiates their redistribution away from the synapse via lateral diffusion and internalization. AMPARs are subsequently rephosphorylated and held at intracellular compartments, perhaps by enhanced interactions with scaffolding proteins such as glutamate receptor interacting protein (GRIP) (Gladding et al., 2009).

It has recently been discovered that the PTP that dephosphorylates the GluA2 subunit during mGluR-LTD is the striatal-enriched tyrosine phosphatase (STEP) (Zhang et al., 2008). mGluR activation leads to elevated STEP expression via activation of both MAPK and phosphoinositide-3-kinase (PI3K) pathways. Increased expression and activation of STEP induces AMPAR endocytosis via tyrosine dephosphorylation of the GluA2 subunit (Zhang et al., 2008). Although ERK1/2 stimulates STEP translation, STEP can also dephosphorylate and inactivate ERK1/2 in addition to p38 MAPK (Muñoz et al., 2003; Paul et al., 2003). Because ERK1/2 and p38 MAPK signaling cascades are involved in mGluR-LTD induction (Rush et al., 2002; Gallagher et al., 2004; Huang et al., 2004b; Moult et al., 2008), STEP activation may be regulated by a feedback mechanism (Zhang et al., 2008). It is noteworthy that it has been shown that STEP activity is increased in transgenic mouse models of Alzheimer's disease (Chin et al., 2005; Snyder et al., 2005), raising the possibility that mGluR-LTD may be abnormal in these mice, although this has yet to be tested.

Although PTK inhibitors have no significant effect on DHPG-LTD, they do prevent the block mediated by PTP inhibitors (Moult et al., 2006). A similar effect of PTK inhibitors have been observed with regard to NMDAR-

LTD (Coussens et al., 2000). It is possible that mGluR-LTD requires the activation of two parallel independent pathways (Moult et al., 2006, 2008). The first may involve PTP-mediated dephosphorylation of AMPARs, whereas the second is dependent on a separate signaling pathway, such as the p38 MAPK cascade (Rush et al., 2002; Huang et al., 2004b; Moult et al., 2008). Whereas PTP activation is required for LTD induction, a parallel pathway may mediate LTD expression by modulating AMPAR trafficking. Parallel activation of p38 MAPK may induce AMPAR internalization by stimulating the formation of the GDI-Rab5 complex involved in clathrin-dependent endocytosis (Rush et al., 2002; Huang et al., 2004b; Moult et al., 2008). PTP inhibition favors PTK phosphorylation of AMPARs and prevents mGluR-LTD induction (Moult et al., 2006, 2008). PTK inhibition does not facilitate LTD induction because it is also necessary to activate the parallel pathway. PTK inhibitors may reverse the effect of PTP inhibitors, because PTK activation is required for the PTP inhibitor block.

In summary, mGluR-LTD induction in the hippocampus is dependent on the activation of PTPs, specifically STEP, which dephosphorylates the GluA2 subunit of surface-expressed AMPARs and triggers receptor lateral diffusion and internalization. This occurs in parallel with a pathway involving p38 MAPK, which mediates the clathrin-dependent endocytosis of AMPARs that is necessary for expression of mGluR-LTD.

3. Proteases. Induction of mGluR-LTD in the hippocampus can be mediated by a member of the group S8A serine proteases namely subtilisin (MacGregor et al., 2007). A novel *Aspergillus* spp. S8A serine protease, cadeprin (CA1-depressing protein), has also been discovered that similarly induces long-lasting depression of CA1 neuronal transmission. The LTD mediated by both subtilisin and cadeprin is dependent on specific activation of group I mGluRs because there is no effect of NMDAR or adenosine receptor inhibitors on LTD induction (MacGregor et al., 2007). mGluR-LTD also involves cleavage of the neuronal pentraxin receptor (NPR) by the matrix metalloprotease tumor necrosis factor-α-converting enzyme (TACE) (Cho et al., 2008) (Fig. 1). Although matrix metalloproteases have important roles in neuronal development and remodelling and in neuronal precursor cell migration (Del Bigio et al., 1999; Ethell and Ethell, 2007), they are also necessary for mediating hippocampal LTP (Tomimatsu et al., 2002; Nagy et al., 2006). NPR, neuronal pentraxin 1, and neuronal-activity-regulated pentraxin form an extracellular scaffolding complex at excitatory synapses, where it associates with AMPARs and mediates synapse formation (Goodman et al., 1996; Tsui et al., 1996; O'Brien et al., 1999; Xu et al., 2003). Bimodulatory regulation of NPs is mediated by the C-terminal and N-terminal domains that regulate AMPAR association and NP self-clustering, respectively (Xu et al., 2003). mGluR stimulation leads to activation of TACE, which cleaves the NPR transmembrane domain. The cleaved NPR remains associated with neuronal-activity-regulated pentraxin and neuronal pentraxin 1 but is subsequently internalized via its incorporation into endosomes with clustered AMPARs.

Although AMPAR tyrosine dephosphorylation can trigger receptor distribution away from the synapse (Gladding et al., 2009), NPR cleavage may also mediate internalization by facilitating the formation of AMPAR-containing endosomes (Cho et al., 2008). It is evident that NPs regulate AMPAR clustering depending on the developmental stage, in that AMPARs are anchored at synapses during synaptogenesis but are captured at endocytic sites during depression of synaptic transmission. Synaptic Arc/Arg3.1 translation is increased upon mGluR stimulation, which may also mediate AMPAR endocytosis (Waung et al., 2008) (Fig. 1). It is postulated that TACE-mediated NPR cleavage is important for induction of mGluR-LTD, whereas LTD expression may be maintained by elevated Arc/Arg3.1 synthesis (Cho et al., 2008). Together, the collected activities of the serine proteases cadeprin and subtilisin, the Ca^{2+}-activated protease calpain and the matrix metalloprotease TACE are important for facilitating mGluR-LTD induction and expression.

4. Endocannabinoids. Endocannabinoids (eCBs) are thought to act as a retrograde signal, because upon postsynaptic depolarization and mGluR stimulation, they are released into the synaptic cleft (Chevaleyre et al., 2006). They subsequently diffuse across the cleft to presynaptic afferents, where synaptic transmission is generally reduced (Kreitzer, 2005). The eCB receptor subtype CB1R is expressed in several brain areas, including the hippocampus, cerebellum, amygdala, and cerebral cortex (Chevaleyre et al., 2006), and its activation leads to a reduction in the probability of neurotransmitter release (Alger, 2002). DHPG-LTD of excitatory transmission is not believed to involve eCB production, although the short-term depression seen during DHPG application is reduced by CB1 receptor antagonism (Rouach and Nicoll, 2003). In contrast, LTD at inhibitory synapses on CA1 pyramidal neurons is dependent on mGluR-stimulated eCB production (for review, see Chevaleyre et al., 2006).

5. Phosphoinositide 3-kinase–Akt–Mammalian Target of the Rapamycin Signaling. It has been proposed that hippocampal group I mGluR activation is coupled to protein synthesis (Huber et al., 2000) via the PI3K-Akt-mammalian target of the rapamycin (mTOR) signaling pathway (Hou and Klann, 2004) (Fig. 2). mGluRs may be coupled to the PI3K cascade via interactions with Homer and the cytoplasmic GTPase PI3K enhancer-L (Rong et al., 2003). Formation of the mGluR-Homer-PI3K enhancer complex is necessary to stimulate translation of 5′TOP containing mRNAs via activation of the PI3K pathway (Ronesi and Huber, 2008). It is believed that both the PI3K-Akt-mTOR and the ERK-MEK pathways mediate cap-dependent translation during mGluR-LTD

(Banko et al., 2006). mGluR-LTD triggers an increase in the formation and binding of the eukaryotic initiation factor 4F (eIF4F) complex to the mRNA 5′TOP sequence. This is dependent on binding of eIF4E and eIF4G to the complex, which is regulated by phosphorylation of eIF4E-binding protein (4E-BP). mGluR activation facilitates the binding of eIF4E to eIF4G by phosphorylating 4E-BP2 and preventing eIF4E inhibition. Furthermore, initiation of mRNA translation is dependent on phosphorylation of eIF4E by Mnk1 (Gingras et al., 1999), which is also regulated by the ERK-MEK signaling cascade (Banko et al., 2006). Translational events can additionally be modulated by mTOR-mediated phosphorylation of ribosomal protein S6 via activation and phosphorylation of S6 kinase (S6K) (Dufner and Thomas 1999; Gingras et al., 2001) (Fig. 2). It has recently been discovered that mGluR stimulation increases the phosphorylation of both S6 and S6K and that this is dependent on activation of all three PI3K, mTOR, and ERK signaling cascades (Antion et al., 2008a).

Cyclins and cyclin-dependent kinases (CDKs) are not only involved in cell cycle control (Li et al., 2007a) but also have diverse roles in the regulation of basal transcription (Rickert et al., 1996), apoptosis (Crumrine et al., 1994), and synaptic plasticity (Richter, 2001). Several signaling molecules such as Rho (Welsh et al., 2001), JNK (Zhang et al., 2005), NF-κB (Guttridge et al., 1999) and the PI3K/AKT/mTOR/p70S6K1 pathway (Gao et al., 2003, 2004) mediate the regulation of the expression and translocation of the cyclinD1-CDK4 complex in the hippocampus. It is postulated that mGluR-LTD activates the PI3K/AKT/mTOR cascade, which stimulates the cyclinD1-CDK4 complex via the retinoblastoma (Rb)/E2F1 pathway leading to modulation of protein synthesis (Li et al., 2007a) (Fig. 2).

In parallel with the ERK-MEK pathway, the PI3K-Akt-mTOR signaling cascade is therefore essential for triggering cap-dependent translation during mGluR-LTD. This is done by facilitating the formation of the translation initiation eIF4F complex by mediating the activation of both S6 and SK6 and by stimulating the formation of the cyclinD1-CD4 complex, all of which are important for modulation of protein synthesis.

D. Regulation of Gene Expression

It is evident that mGluR-LTD involves regulation of gene expression via MAPK-mediated modulation of specific transcription factors under some experimental conditions (Fig. 2). DHPG-LTD involves ERK-mediated activation of the E-26-specific (ETS) domain transcription factor Elk-1, which is a tertiary complex factor (Wang et al., 2004; Mao et al., 2005). ERK can also activate cAMP response element-binding (CREB), which, with Elk-1, facilitates expression of the gene c-*Fos* (Mao et al., 2005). After mGluR activation, ERK may modulate CREB expression via the activation of RSK1 (Xing et al., 1998; Frödin and Gammeltoft, 1999; Gallagher et al., 2004) and mitogen and stress-activated protein kinase-1 kinases (Arthur and Cohen, 2000). ERK is not localized solely to the nucleus but is also active in dendrites such that translation and transcription can be regulated in close proximity to synapses (Kelleher et al., 2004a,b).

NF-κB is a further transcription factor that is activated in mGluR-LTD via PI3K, Ras, and p38 MAPK signaling pathways (O'Riordan et al., 2006). The NF-κB transcription factor C-Rel is specifically required for long-term maintenance of hippocampal mGluR-LTD. Although previous studies have indicated that mGluR-LTD involves translational rather than transcriptional regulation, this may be because synaptic changes were monitored at an early phase (<90 min) rather than at a late phase (2–3 h) of LTD (Huber et al., 2000; O'Riordan et al., 2006). In contrast to other transcription factors, NF-κB was the first to be synaptically localized (Korner et al., 1989) and upon synaptic activation is rapidly trafficked from the synapse to the nucleus (Meberg et al., 1996; Wellmann et al., 2001; Meffert et al., 2003). In mGluR-LTD stabilization, NF-κB may act as a signal messenger to facilitate an increase in specific gene expression in response to synaptic activity (O'Riordan et al., 2006).

In summary, regulation of specific gene expression during mGluR-LTD is dependent on activation of MAPK and PI3K signaling pathways, which leads to modulation of transcription factors such as NF-κB, Elk-1, and CREB. These transcription factors are not restricted to the nucleus, meaning that rapid synaptic modulation of gene transcription can be mediated in response to mGluR activation.

E. Identity of Newly Synthesized Proteins

There is much evidence to suggest that mGluR-LTD is dependent on rapid dendritic protein synthesis (Huber et al., 2000, 2001; Hou and Klann, 2004; Park et al., 2008; Waung et al., 2008; Zhang et al., 2008), although mGluR-LTD may also be protein synthesis independent (Fig. 2). Indeed, it has been shown that protein synthesis initiation is regulated by mGluR interactions with Homer (Ronesi and Huber, 2008). Protein synthesis may be important for either promoting AMPAR endocytosis or by producing a retrograde signaling molecule that is able to regulate presynaptic neurotransmitter release. To facilitate rapid modulation of synaptic transmission, key mediator proteins can be synthesized in close proximity to the synapse (Sutton and Schuman, 2006). mRNA-protein complexes can therefore be transported along the dendrite via interactions with microtubule filaments in the cytoskeleton. Indeed, group I mGluR activation mediates increased translation of AMPAR subunit mRNA in nearby regions of the dendrite (Grooms et al., 2006). In response to mGluR-LTD induction, local translation facilitates rapid protein recruitment to the synapse such that synaptic transmission can be efficiently modulated. Use of specific pharmacological

agents and KO mice may aid the identification of proteins involved in mGluR-LTD. For example, 4E-BP2 KO mice have increased mGluR-LTD indicating that 4E-BP2 has an important role in negatively regulating synaptic activity (Banko et al., 2006). 4E-BP2 is phosphorylated by the PI3K-Akt-mTOR pathway, which facilitates formation of the eIF4F translation initiation complex (Gingras et al., 1999). Modulation of 4E-BP2 phosphorylation is therefore important for regulation of translation during mGluR-LTD (Banko et al., 2006).

It is known that STEP is the PTP that tyrosine-dephosphorylates the AMPAR GluA2 subunit and mediates AMPAR endocytosis (Zhang et al., 2008). This study specifically showed that mGluR activation facilitates an increase in STEP translation in synaptosomes via activation of MAPK and PI3K pathways. This is consistent with previous reports demonstrating that dendritic protein synthesis is regulated by stimulation of both signaling pathways (Wang and Tiedge, 2004). Because STEP is quickly degraded after mGluR activation, it is postulated that de novo synthesis of STEP is required upon LTD induction (Zhang et al., 2008).

Interactions with the postsynaptic density (PSD) 95/disc-large/zona occludens (PDZ) domain-containing proteins GRIP, AMPAR binding protein, and PICK1 are important for modulating AMPAR stabilization at the synapse. DHPG-LTD involves tyrosine dephosphorylation of the AMPAR GluA2 subunit (Moult et al., 2006; Zhang et al., 2008, Gladding et al., 2009). This may induce surface AMPAR mobilization via modulation of GRIP/AMPAR binding protein and PICK1 interactions. Indeed, it has been reported that DHPG-stimulated AMPAR endocytosis is dependent on disruption of GRIP-GluA2 binding (Davidkova and Carroll, 2007). In addition, DHPG stimulates an increase in microtubule-associated protein 1B (MAP1B) synthesis, which binds to GRIP1 and promotes AMPAR internalization (Davidkova and Carroll, 2007) (Fig. 1). MAP1B is highly expressed outside the synapse, indicating that MAP1B-GRIP1 interactions may facilitate AMPAR endocytosis by sequestering GRIP away from the PSD. MAP1B translation is dependent on inhibition of eukaryotic translation elongation factor 2 (eEF2) kinase, which results in increased activation of eEF2 (Ryazanov and Davydova, 1989; Redpath et al., 1993). This is particularly interesting because eEF2 kinase inhibition is mediated by mTOR and p70 S6 kinase (Wang et al., 2001; Browne and Proud, 2004), which are thought to be involved in mGluR-LTD (Hou and Klann, 2004; Banko et al., 2006).

mGluR-LTD may involve synthesis of the cytoplasmic fragile X mental retardation protein (FMRP), which is found to be expressed in neuronal dendrites (Feng et al., 1997; Weiler et al., 1997) (Fig. 2). FMRP forms a protein complex with polyribosomes at specific mRNA sites and acts as a negative regulator of mRNA translation (Jin and Warren, 2003). A role for FMRP was indicated in mGluR-LTD when FMRP expression levels were enhanced upon mGluR activation (Weiler et al., 1997). Furthermore, hippocampal slices from *Fmr1*-KO mice showed increased mGluR-LTD (Huber et al., 2002), indicating that FMRP is important for modulation of protein synthesis upon synaptic activation. In contrast to wild-type mice, the LTD in *Fmr1*-KO mice is independent of protein synthesis and activation of the ERK signaling cascade (Huber et al., 2002; Koekkoek et al., 2005; Hou et al., 2006; Nosyreva and Huber, 2006). Protein translation independence is mediated by a reduction in mGluR-Homer interactions such that the PI3K-Akt-mTOR pathway is not activated in the KO mice (Ronesi and Huber, 2008). It is possible that in the absence of FMRP, LTD can still be induced and maintained by pre-existing proteins that can mediate AMPAR endocytosis. In wild-type mice, mGluR-LTD involves a rapid increase in FMRP translation that is subsequently ubiquitinated and degraded (Hou et al., 2006). Degradation of FMRP permits the translation of FMRP-targeted mRNAs and thus provides a dynamic mechanism for regulating protein synthesis during mGluR-LTD.

FMRP can regulate the translation of several mRNAs, and a particularly interesting synaptic target is the adaptor protein PSD-95. mGluR stimulation leads to an increase in PSD-95 translation, which is dependent on regulation by FMRP (Todd et al., 2003). Moreover, it has been confirmed that FMRP mediates stabilization of PSD-95 mRNA through direct interactions with its 3′ untranslated region (Zalfa et al., 2007). This stabilization is enhanced by mGluR activation, implying that FMRP mediates the regulation of key synaptic proteins under both basal and stimulated conditions. FMRP is also thought to regulate the synthesis of other key synaptic players (i.e., AMPAR subunits GluA1/GluA2 and CaMKIIα) upon mGluR activation (Muddashetty et al., 2007). Furthermore, modulation of AMPAR internalization is dependent on negative regulation of protein synthesis by FMRP (Nakamoto et al., 2007). FMRP is therefore crucial for preventing mGluR stimulation leading to excessive AMPAR endocytosis via overactivation of signaling cascades. Patients with fragile X syndrome (FXS) have cognitive deficits that may be due to impairments in synaptic glutamate signaling dependent on key effector and adaptor proteins such as PSD-95 (Bear et al., 2004; Koukoui and Chaudhuri, 2007). Anxiety and epilepsy symptoms are also elevated in patients with FXS and *Fmr1*-KO mice, which could be due to disrupted interactions between mGluRs and the short isoform Homer1a (Penagarikano et al., 2007). Homer1a competes with the longer Homer isoforms for mGluR binding (Xiao et al., 1998; Fagni et al., 2002), which is important for modulation of mGluR-mediated synaptic transmission in the hippocampus (Kammermeier and Worley, 2007). Because Homer1a can protect against induction of epilepsy, anxiety, and pain (Szumlinski et

al., 2006), it is postulated that mGluR interactions with both short and long Homer isoforms are impaired in FXS (Penagarikano et al., 2007).

Other proteins synthesized during hippocampal mGluR-LTD are the ribosomal protein S6 and the 5′TOP-encoded protein elongation factor 1A (EF1A) (Antion et al., 2008a). Although mGluR-LTD involves an increase in the phosphorylation of S6K and S6 via activation of PI3K, mTOR, and ERK signaling pathways, LTD expression and protein synthesis is not dependent on activation of S6Ks. mGluR-LTD was normal or enhanced in the S6K1- and S6K2-KO mice, and there was no reduction in S6 phosphorylation or EF1A synthesis (Antion et al., 2008b). However, in these mice, LTD may be mediated by activation of the remaining S6K or by up-regulation of a different kinase such as Akt (Hou and Klann, 2004; Antion et al., 2008b). It is interesting that mGluR-LTD increases the synthesis of the translation factor EF1A, because it is also up-regulated during late LTP induction (Tsokas et al., 2005). In addition to its role as an elongation factor, it can also facilitate the polymerization of actin-monomers to form F-actin (Liu et al., 2002). Furthermore, EF1A mRNA translation is down-regulated by binding of FMRP (Sung et al., 2003). This is consistent with the hypothesis that mGluR-LTD leads to down-regulation of FMRP, which permits the synthesis of key proteins such as EF1A and S6 necessary for LTD induction. Similar to EF1A, S6 may have an important role in mediating different forms of synaptic plasticity, because an increase in S6 phosphorylation is also detected during LTP and learning (Kelleher et al., 2004b). Upon mGluR activation, S6K may also phosphorylate other substrates in addition to S6, such as eEF2 and eIF4B, which have been implicated in protein synthesis dependent mGluR-LTD (Park et al., 2008). It is evident that mGluR-stimulated protein translation is regulated by several converging signaling pathways that facilitate the regulation of multiple target proteins. For example, the PI3K-Akt-mTOR pathway mediates direct regulation of S6K but also modulates cap-dependent translation by 4E-BP (Banko et al., 2006). Regulation of cap-dependent translation proteins Mnk1, eIF4E, and 4E-BP is also dependent on activation of the MEK-ERK signaling pathway (Banko et al., 2006).

It has recently been discovered that mGluR-LTD involves rapid de novo dendritic synthesis of the immediate-early gene Arc/Arg3.1 via activation of eEF2K and eEF2 (Park et al., 2008) (Fig. 2). Up-regulation of Arc transcription also involves activation of CaMKII, PLC, ERK1/2, and NMDARs but not L-type voltage-gated Ca^{2+} channels (Wang et al., 2009). Arc/Arg3.1 is an important homeostatic regulatory protein involved in modulation of AMPAR-dependent excitability (Shepherd et al., 2006). Arc/Arg3.1 interacts with endophilin 2/3 and dynamin, which are important components of the AMPAR endocytic pathway (Chowdhury et al., 2006) (Fig. 1). Thus, Arc/Arg3.1 synthesis is linked to increased AMPAR endocytosis and down-regulation of AMPAR-mediated synaptic activity upon LTD induction. mGluRs are linked to eEF2K via Homer and eEF2K dissociation is induced upon mGluR stimulation and activation of CaM. Activated dissociated eEF2K subsequently phosphorylates eEF2, which inhibits global mRNA translation (Park et al., 2008). However, phosphorylated eEF2 leads to specific up-regulation of Arc/Arg3.1 synthesis, which results in modulation of AMPAR endocytosis and regulation of cap-dependent and -independent initiation of translation (Pestova et al., 2001).

Under basal conditions, Arc/Arg3.1 translation is negatively regulated by FMRP. Upon mGluR-LTD induction, FMRP is dephosphorylated by PP2A, which reduces its binding to target mRNAs (Narayanan et al., 2007). This facilitates rapid de novo local synthesis of specific mRNAs at close proximity to the synapse. It is evident that activation of eEF2K is a parallel pathway to inhibition of FMRP after mGluR activation (Park et al., 2008). mGluR-LTD is enhanced in *Fmr1*-KO mice but is reduced upon ablation of Arc/Arg3.1 function. Because mGluR-LTD is not completely abolished in the double-KO mice, it suggests that pre-existing Arc/Arg3.1 can partially mediate LTD induction upon stimulation of mGluRs (Park et al., 2008). This is corroborated by a study stating that AMPAR endocytosis can be partly mediated by pre-existing Arc/Arg3.1, but maintenance of elevated internalization is dependent on further de novo synthesis (Waung et al., 2008). Furthermore, this synthesis occurs rapidly in dendrites and not the soma and transport of Arc/Arg3.1 from the soma to the dendrites is not required. mGluR stimulation may increase Arc/Arg3.1 trafficking to the postsynaptic membrane and enhance its interactions with AMPARs and/or key endocytic mediators such as dynamin and endophilin 2/3 (Waung et al., 2008). Although Arc/Arg3.1 can facilitate actin polymerization (Messaoudi et al., 2007), it is unknown whether Arc/Arg3.1 is necessary for mGluR-mediated dendritic remodeling (Vanderklish and Edelman, 2002) and whether this underlies LTD induction. It is clear that Arc/Arg3.1 is important for modulation of AMPAR endocytosis, yet it is likely that this occurs in conjunction with other key processes such as TACE-mediated cleavage of NPR (Cho et al., 2008) and STEP-mediated tyrosine dephosphorylation of the GluA2 subunit (Moult et al., 2006; Zhang et al., 2008; Gladding et al., 2009).

In conclusion, it is highly evident that mGluR-LTD involves the up- and down-regulation of the expression of several proteins that are important for modulation of gene transcription, regulation of actin polymerization, and mediation of AMPAR internalization. FMRP is a big player in regulating protein synthesis because it is itself modulated upon mGluR-LTD induction and is also responsible for regulating the synthesis of key synaptic proteins such as PSD-95, GluA1, GluA2, and CaMKIIα

and also the dendritic immediate-early gene Arc/Arg3.1. This has direct consequences on the regulation of AMPAR endocytosis and actin dynamics that occurs concomitantly with altered synthesis of other regulatory proteins such as STEP and MAP1B. It is therefore clear that the mGluR-LTD induction and expression is dependent on complex interconnected regulatory mechanisms, which finely control the expression levels and localization of several key proteins throughout the LTD time course.

V. Locus of Metabotropic Glutamate Receptor-Mediated Long-Term Depression Expression

There is conflicting evidence regarding the expression mechanism of hippocampal mGluR-LTD in terms of whether it is postsynaptic or presynaptic (Anwyl, 2006). For example, a presynaptic mechanism is suggested by studies showing that mGluR-LTD involves changes in paired-pulse facilitation (Fitzjohn et al., 2001; Watabe et al., 2002; Rouach and Nicoll, 2003; Tan et al., 2003). An increase in the EPSC amplitude coefficient of variation (CV) and a reduction in the frequency of mini-EPSCs is also observed during synaptically induced LTD (Bolshakov and Siegelbaum, 1994) and DHPG-LTD (Fitzjohn et al., 2001; Xiao et al., 2001). It has also been demonstrated that DHPG-LTD involves a decrease in neurotransmitter release, indicated by zinc fluorescence detection of exocytosis (Qian and Noebels, 2006). Negative postsynaptic changes include a lack of alteration in sensitivity to uncaged L-glutamate upon DHPG-LTD induction (Rammes et al., 2003). However, these experiments were performed at relatively low temperatures (22–24°C), which may prevent the detection of postsynaptic changes such as receptor internalization (Snyder et al., 2001; Xiao et al., 2001; Huang et al., 2004b; Waung et al., 2008; Zhang et al., 2008; Gladding et al., 2009).

It is evident that postsynaptic application of endocytotic inhibitors can prevent DHPG-LTD, and it has also been reported in both hippocampal slices and primary hippocampal neurons that internalization of surface iGluRs occurs in response to mGluR activation (Snyder et al., 2001; Xiao et al., 2001; Huang et al., 2004b; Waung et al., 2008; Zhang et al., 2008; Gladding et al., 2009). DHPG-LTD also involves a reduction in the amplitude of mini-EPSCs consistent with a postsynaptic mechanism (Xiao et al., 2001). It is possible that the synaptic mechanisms underlying mGluR-LTD are subject to a developmental switch, which would explain why there are conflicting ideas regarding the expression mechanism (Nosyreva and Huber, 2005). It is proposed that mGluR-LTD is presynaptically expressed in neonatal synapses, because there is no change in surface expression of AMPARs, and it seems to be independent of protein synthesis. During synapse maturation, there is a developmental switch involving mGluR regulation of AMPAR trafficking via the production of new synaptic proteins. At immature synapses, regulation of presynaptic release probability rather than AMPAR internalization may be a more efficient way of depressing transmission at synapses (Nosyreva and Huber, 2005). It has also been reported that there is a developmental change in mGluR-LTD induction mechanisms (Kumar and Foster, 2007), where PTPs are required for DHPG-LTD in young adult rats (5–8 months) but not in aged rats (22–26 months). A recent study of NMDAR-mediated synaptic currents ($EPSCs_{NMDAR}$) in DHPG-LTD found that both depression and LTD are initiated by activation of $mGlu_1$ and $mGlu_5$ receptors but are not dependent on tyrosine kinase or phosphatase activity, and increase in intracellular Ca^{2+}, or protein synthesis (Ireland and Abraham, 2009). Although the mechanism underlying the transient short-term depression is likely to be presynaptic, the LTD is mediated postsynaptically by lateral movement of synaptic NMDARs via actin depolarization (Ireland and Abraham, 2009).

Synaptically induced mGluR-LTD involving postsynaptic induction but presynaptic expression would require a membrane-permeable retrograde signaling molecule to pass from the postsynaptic CA1 neuron to the presynaptic CA3 neuron. A strong candidate is 12(*S*)-hydroperoxyeicosa-5*Z*,8*Z*,10*E*,14*Z*-tetraenoic acid [12(S)-HPETE], a 12-lipoxygenase metabolite of arachidonic acid (AA) (Feinmark et al., 2003). It has been shown that the AA cascade is essential for mGluR-LTD induction and is initiated via the cytosolic PLA_2 enzyme (Bolshakov and Siegelbaum, 1995) (Fig. 2). This is activated by p38 MAPK consistent with previous reports implicating that mGluR-LTD requires p38 MAPK activation (Bolshakov et al., 2000; Rush et al., 2002; Zhu et al., 2002; Huang et al., 2004b; Moult et al., 2008). Long-term plasticity may be maintained by the positive feedback mechanism in which p38 MAPK is also stimulated by the production of AA (Hii et al., 1998; Kalyankrishna and Malik, 2003). However, this pathway implicates that the Ca^{2+}-sensitive cytosolic PLA_2 enzyme is activated upon a rise in postsynaptic Ca^{2+} after mGluR-LTD induction. This is inconsistent with previous evidence indicating that mGluR-LTD is Ca^{2+}-independent, but implies that there may be alternative retrograde signaling molecules that can act in the absence of Ca^{2+}. Potential presynaptic targets of a retrograde signal are voltage-gated ion channels or constituents of the presynaptic release machinery (Fitzsimonds and Poo, 1998; Zakharenko et al., 2002). For example, the presynaptic S-type K^+ channel is activated by 12(S)-HPETE, which leads to inhibition of neurotransmitter release by decreasing Ca^{2+} influx (Feinmark et al., 2003).

Because of conflicting results from studies, it cannot be conclusively stated whether hippocampal mGluR-LTD expression is presynaptic or postsynaptic. Inconsistent results from these studies could be due to differences in experimental design or temperature or to differences in the age of the animal used. It is entirely possible that both presynaptic (neurotransmitter re-

lease) and postsynaptic (AMPAR internalization) expression mechanisms occur. It is generally thought that induction involves the postsynaptic activation of PTPs and other signaling cascades, which could include a retrograde signaling molecule that passes back to the presynaptic neuron. If both pre- and postsynaptic mechanisms do contribute to mGluR-LTD, it may be that they can occur simultaneously or that differing experimental conditions will favor one mechanism over the other. Further work is required to delineate the precise complexities of the induction and expression mechanisms of this form of synaptic plasticity.

VI. The Pathological Significance of Metabotropic Glutamate Receptor-Mediated Long-Term Depression

Investigating the molecular mechanisms underlying hippocampal mGluR-LTD is essential for understanding and treating diseases such as FXS and addiction (Grueter et al., 2007) in which synaptic plasticity abnormalities are displayed. Patients with FXS have cognitive deficits (Bear et al., 2004; Koukoui and Chandhuri, 2007) and also anxiety and epilepsy symptoms, which could be due to impaired synaptic glutamate signaling or to disrupted interactions between mGluRs and interacting proteins such as Homer 1a (Penagarikano et al., 2007). It is therefore crucial to understand how mGluR-LTD occurs in the healthy functioning brain, so as to delineate how this is dysfunctional in FXS. Understanding the molecular mechanisms could facilitate the discovery of effective drug targets that could specifically and efficiently ameliorate the symptoms of this neurodevelopmental disorder. Because the FMRP protein is a translational repressor, in its absence in patients with FXS, there is overexpression of specific mRNAs in response to $mGlu_5$ receptor activation. Therapeutic interventions have arisen from the idea that mGluR signaling could be modulated back to normal levels by pharmacologically blocking or antagonizing the $mGlu_5$ receptor (Dölen and Bear, 2009). Furthermore, in the *Fmr1*-KO mouse model of autism, it has been shown that normal mGluR function and synaptic signaling can be restored by preventing 50% of $mGlu_5$ receptor signaling (Dölen et al., 2007). FXS is the most common cause of autism, and it is hoped that therapeutics for FXS could also benefit autism sufferers. Clinical trials are currently ongoing to investigate whether mGluR targeting drugs are efficient, safe, and specific in improving the symptoms of patients with FXS and/or autism (Dölen and Bear, 2009). It would be most rewarding and beneficial if drugs targeted for one disorder were also effective in pharmacologically treating a related illness.

A recent behavioral study identified that $mGlu_5$ receptor plays a fundamental role in the extinction or reversal of learning. This has raised the intriguing possibility that these receptors provide a potential target for new treatment strategies in processes of maladaptive learning (Xu et al., 2009). Because some psychiatric disorders are associated with unwanted disturbing memories, it could be advantageous to be able to reverse the acquisition of these specific memories such that a healthy lifestyle can be resumed. The development of specific $mGlu_5$ receptor modulatory pharmacological compounds for treatment of FXS, autism, and neuropsychiatric disorders has highlighted the biological and pathological significance of mGluR-LTD in the mammalian brain and why it is crucial to investigate the molecular mechanisms underlying this form of synaptic plasticity.

Conclusions

This review has considered the complexities of the molecular mechanisms underlying mGluR-mediated LTD in the hippocampus. As illustrated in Figs. 1 and 2, regulation of mGluR-dependent synaptic transmission is accomplished by coordinated activation of multiple signaling pathways that collaborate to precisely regulate postsynaptic and presynaptic processes. It is clear that recent studies have broadened our understanding of both the induction and expression mechanisms of this form of synaptic plasticity. Future work will continue to expand our knowledge of key molecules, signaling cascades, and mechanisms required for long-lasting depression of hippocampal mGluR-mediated synaptic transmission. To understand further the complexities of the molecular mechanisms, one needs to investigate in greater detail the role of newly synthesized proteins in the induction and expression of LTD, how individual signaling pathways activated interconnect to form a coordinated network that precisely modulates synaptic activity, and how this form of synaptic plasticity translates into hippocampal learning and memory in a freely moving animal. For example, further investigations could be employed to determine the precise mechanisms underlying PTP-triggered AMPAR internalization. The GluA2 residue that STEP dephosphorylates is unknown; it has not been confirmed that this indeed facilitates AMPAR lateral diffusion before internalization from extrasynaptic endocytotic zones, and the fate of the internalized receptors has not been determined. This is just one example of the many finer details that are missing from what is currently known about the complexities of this molecular mechanism. Further work is also required to eliminate some of the controversies that exist regarding the expression locus or the involvement of protein synthesis or specific signaling pathways.

In conclusion, it cannot be denied that valuable progress has been made to improve our understanding of this form of synaptic plasticity, and our continual ongoing investigative efforts will only be of further benefit to increase our understanding of learning and memory in the normal and dysfunctional brain.

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