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Group I mGluRs and Long-Term Depression: Potential Roles in Addiction?

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Abstract Addiction is an enormous societal problem. A number of recent studies have focused on adaptations at glutamatergic synapses that may play a role in the behavioral responses to drugs of abuse. These studies have largely focused on NMDA receptor-dependent forms of synaptic plasticity such as NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD). A growing body of evidence, however, suggests that metabotropic glutamate receptors (mGluRs) also play important roles in the behavioral responses to drugs of abuse and participate in producing synaptic plasticity at glutamate synapses. In this review, we focus first on the evidence supporting a role for mGluRs in addiction and then on the properties of mGluR-dependent forms of synaptic plasticity, focusing in particular on Gq-linked receptor-induced LTD.

Keywords Addiction · Group I mGluRs · Long-term depression

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Addiction creates an international health and financial burden of massive proportions. Increasingly, addiction is viewed as a pathological coopting of learning-related mechanisms within classical learning-related brain regions, but also more importantly, within circuits considered key to dopamine-based reward sensation models. Recent years have seen an increase in the discovery of targets and actions of addictive drugs beyond dopamine and its receptors. This growing body of research has uncovered several mechanisms by which drugs of abuse can alter excitatory synaptic transmission in multiple brain areas [60, 128, 129]. In particular, many substances of abuse alter NMDA-receptor (NMDAR) dependent synaptic plasticity in brain regions involved in memory and reward. It is intuitively obvious that such long-term changes in synaptic communication in key circuits would likely lead to changes in behaviors associated with reward. Thus, it is hypothesized that long-lasting alterations at glutamatergic synapses in reward-related nuclei underlie aspects of the persistence of addiction. Whereas strong evidence points to a role for NMDAR-dependent plasticity, it is important to note (1) that the mechanisms by which drugs of abuse regulate this plasticity remain unclear and (2) that NMDAR-independent forms of glutamatergic synaptic plasticity exist that could play equally important roles. In this review, we will focus on one particular form of NMDAR-independent plasticity, group I metabotropic glutamate receptor (mGluR)-dependent long-term depression (LTD). We will describe the state of research on mechanisms underlying LTD produced by these receptors, then focus on the regulation of this plasticity by drugs of abuse. Finally, we will speculate on potential pathophysiological relevance of these findings.

Glutamatergic Synapses undergo NMDAR-dependent Synaptic Plasticity in Response to Drugs of Abuse

Glutamate is the major fast excitatory neurotransmitter in the CNS where it acts through binding to different classes of ligand-gated ion channels, including the AMPA, NMDA and kainate classes, and G protein coupled mGluRs [14, 26, 50]. Activation of AMPA receptors (AMPARs), comprised of a tetrameric assembly of different combinations of GluR1-4, provides the primary means of generation of excitatory postsynaptic potentials (EPSPs) at glutamatergic synapses. Persistent alterations of the efficacy of this AMPAR-mediated synaptic transmission, as produced by NMDAR activation in long-term potentiation (LTP) and LTD, have been suggested to play important roles in reward-related responses to substances of abuse, and perhaps to addiction [60, 128].

Although a common theme of substances of abuse from psychostimulants to alcohol is their regulation, either directly or indirectly, of monoaminergic signaling, there is a large body of evidence suggesting that an important consequence of perturbation of this signaling is to produce drug/alcohol-induced alterations in glutamatergic synaptic plasticity [11, 36, 75, 102, 118, 122]. These studies have focused primarily on glutamate synapses in regions critical to reward-related responding, such as the nucleus accumbens (NAc) and ventral tegmental area (VTA), but also other regions involved in memory formation, particularly the hippocampus [119]. Dopamine-containing VTA neurons project heavily into the NAc among other regions, and this projection is thought to be a key contributor to dopamine-dependent reward mechanisms.

To date, psychostimulants have been shown to produce two primary modifications of NMDAR-mediated plasticity in these two regions. First, a single i.p. administration of a number of substances of abuse appears to both produce NMDAR-dependent LTP in vivo [75, 122], and to regulate the subsequent induction of NMDAR-LTP in vitro in dopaminergic neurons of the VTA [75, 122]. Second, multiple exposures to psychostimulants, which have no further effect on LTP in the VTA [15] promote NMDAR-dependent LTD at NAc glutamate synapses after subsequent cocaine challenge [118]. Both of these modifications are thought to be of some importance in the behavioral responses to drugs of abuse, although their direct relationship to addiction remains unclear.

Group I mGluRs and Addiction

Whereas evidence supports the idea that NMDAR-dependent modifications in AMPAR-mediated glutamatergic transmission play important roles in behavioral responses to drugs of abuse, a large literature also suggests that group I mGluRs play a similarly critical role. There are eight mGluRs that are divided into three groups based on pharmacology, similarities in coupling mechanisms, and sequence homology [96]. Group I receptors (mGluR1 and mGluR5) are linked primarily to Gq, whereas group II and group III mGluRs are coupled to Gi/o.

Whereas a growing literature indicates that multiple mGluR subtypes may to some degree regulate and/or mediate aspects of drug-related behavior, group I mGluRs appear to play a particularly critical role. Multiple studies indicate a role for group I mGluRs and associated proteins in cocaine-related behaviors [5, 19, 48, 53, 113, 132]. Most profoundly, mGluR5-null mutant mice are insensitive to the locomotor-stimulating and rewarding properties of cocaine [19]. Consistent with this phenotype, the mGluR5 specific antagonists, MPEP and MTEP, attenuate cocaine-mediated behaviors [61], including cue-induced relapse to cocaine seeking [5, 19, 48]. These antagonists also disrupt reinforcing properties of alcohol [76]. In addition, expression levels of Homer proteins, which are involved in linking group I mGluRs to the postsynaptic density (PSD) [28], are modified by in vivo cocaine administration [53, 113, 115, 132], and targeted deletion of either Homer1 or Homer2 results in an increase in sensitivity to cocaine similar to animals withdrawn from cocaine [117]. Furthermore, targeted deletion of Homer2 disrupts ethanol-induced locomotor sensitization and conditioned place preference [116]. Szumlinski et al. suggest that the similarities in cocaine-related behaviors in Homer knockout mice to the effects of chronic cocaine treatment in wildtype animals implicate decreases in Homer as a key neuronal adaptation involved in regulating addiction to cocaine [116]. Furthermore, it is suggested that decreases in Homer 1b/c expression leads to reduced function of group I mGluRs after repeated exposures to cocaine [112].

Group I mGluRs and Synaptic Plasticity

Clearly, there are multiple mechanisms through which signaling by or disruption of signaling by group I mGluRs could regulate behavioral responses to substances of abuse. In this review, we will focus on group I mGluR-dependent synaptic plasticity, particularly within reward-relevant circuitry. Group I mGluRs play complicated, in some cases paradoxical, roles in synaptic plasticity. Activation of these receptors in several brain regions plays an important role in facilitating the induction of NMDAR-dependent LTP and LTD. In contrast, activation of these receptors in some of these same regions can also elicit a novel form of NMDAR-independent LTD [12, 35, 57, 58, 67, 90, 92, 93]. In this review, we will first discuss in detail the mechanisms thought to underlie group I mGluR LTD, focusing primarily on hippocampal and basal ganglia structures. We will then more

briefly discuss evidence suggesting a role of these same receptors in the facilitation of NMDAR-dependent LTP.

Cerebellar mGluR LTD

Our knowledge of the mechanisms underlying LTD has advanced greatly because of the seminal work describing in vivo LTD in the cerebellum of decerebrate rabbits [63]. Early experiments in cultured Purkinje neurons demonstrated the involvement of a postsynaptic mGluR in the induction of LTD induced by focal application of glutamate [74]. Although Linden et al. were limited by the pharmacological agents available at the time, their analysis nonetheless demonstrated a role for depolarization of the postsynaptic cell, extracellular calcium, and Gq-coupled mGluRs [74]. Subsequent genetic experiments and experiments with mGluR1 blocking antibodies confirmed that the receptor mediating this LTD is mGluR1 [2, 62, 107]. A number of experiments have gone on to suggest that activation of mGluR1 in Purkinje neurons recruits protein kinase Cα (PKCα), which then phosphorylates the AMPAR subunit GluR2 at serine-880 [22, 130], and results in the clathrin-mediated endocytosis of the AMPAR [125], in part mediated by interaction with protein interacting with C-kinase 1 (PICK 1) [110].

Group I mGluR LTD-Chemical Induction in area CA1 of Hippocampus

Although an appreciation for mGluR-dependent forms of LTD began to be formed in the mid-1990s from studies primarily in the hippocampus and cerebellum, the specific appreciation of the roles of group I mGluRs in both LTD induction and regulation of NMDAR-dependent LTP did not really begin until a few years later with the development of key tools, including the group I mGluR specific agonist dihydroxyphenylglycine (DHPG), group I mGluR antagonists such as the mGluR5 antagonist MPEP and the mGluR1 antagonist LY367385, and mice with targeted deletions of mGluR1 and mGluR5. In a series of studies in the mid- to late-1990s, the Collingridge lab demonstrated that brief application of DHPG could elicit an LTD (DHPG-LTD) of glutamatergic transmission in area CA1 of the hippocampus [46, 93]. In these early studies, it was shown that DHPG-LTD consisted of two forms of plasticity; one an indirect LTD induced by group I mGluR-mediated regulation of NMDARs and another that occurred independently of NMDARs [46, 93]. This NMDAR-independent form of DHPG-LTD was subsequently observed by several other labs working in area CA1 [32, 39, 51, 54, 55, 58, 87, 100, 126, 131].

Elucidation of the relative involvement of the two group I mGluRs, mGluR1 and mGluR5, in CA1 DHPG-LTD has proven surprisingly difficult. Huber et al. demonstrated that DHPG-LTD in CA1 was absent in mGluR5 knockout mice, clearly indicating involvement of this subtype [58]. Furthermore, Huang and Hsu reported that DHPG-LTD in CA1 was completely blocked by the noncompetitive selective mGluR5 antagonist MPEP, whereas the competitive selective mGluR1 antagonist LY367385 was without effect [54]. Faas et al. also reported that MPEP blocked DHPG-LTD in CA1; however, in addition, they found that the mGluR1 antagonists LY367385 and CPCCOEt strongly reduced an early component of the DHPG-LTD, and mildly reduced the later component as well [32]. Along these lines, Hou and Klann demonstrated that coapplication of MPEP and LY367385 was required to abolish DHPG-LTD in mouse CA1 [51]. Finally, in a recent report, Huber and colleagues comprehensively addressed this issue, utilizing both mGluR1 and mGluR5 knockouts, rats and mice, along with multiple antagonists [124]. They found that in wild-type CA1, blockade of DHPG-LTD induction required antagonism of both mGluR5 and mGluR1. Curiously, as previously reported, DHPG-LTD was completely absent in the mGluR5 knockout mouse, adding to a body of evidence suggesting that mGluR1 and mGluR5 are interregulated [95, 124]. DHPG-LTD was partially, but not completely, reduced in the mGluR1 knockout mouse relative to wild-type. A possible explanation for the variance of the relative contribution of mGluRs 1 and 5 to DHPG-LTD could be age (and perhaps species) differences in the mechanism of chemically-induced mGluR1/5 LTD. This will be reviewed in greater detail in subsequent sections.

Group I mGluR LTD-Synaptic Induction Studies Suggest Multiple Forms

Whereas DHPG application induces LTD at a variety of synapses across a variety of ages of animals, synaptic induction of group I mGluR LTD has been somewhat inconsistent because of apparent age- and nucleus-dependent differences in LTD mechanisms. mGluR LTD was first reported in the hippocampus in 1994 when Bolshakov and Siegelbaum discovered that pairing 5 Hz stimulation with depolarization of the postsynaptic cell could result in NMDAR-independent, mGluR-dependent LTD [12]. As observed in the cerebellum, they found that mGluR LTD in the hippocampus is dependent on depolarization of the postsynaptic cell, likely to allow for the requisite increase in postsynaptic calcium. Similar results were subsequently reported [90]. It is interesting to note that synaptic mGluR LTD induction is dependent upon the activation of group I mGluRs, a threshold level of synaptic inhibition via

$GABA_A$ receptors, and postsynaptic activation of PKC [12, 90].

A general consensus has emerged that at the CA3-CA1 synapse, group I mGluR LTD is more readily induced in slices from very young mice (i.e. in the Bolshakov and Siegelbaum study) compared to older mice. However, with alternate stimulation paradigms, it has been proposed that group I mGluR LTD can be elicited in slices from older animals. For example, group I mGluR-dependent LTD was observed in adult animals by using paired-pulse low frequency stimulation (PP-LFS) [67]. Several lines of evidence suggest that the group I mGluR LTD elicited in young animals is mechanistically distinct from that elicited in older animals (see below). In addition, as discussed below, other studies in the visual cortex and hippocampus have provided evidence that Gq receptor activation by other neurotransmitters can also elicit mechanistically similar forms of LTD and may contribute to the LTD induced by some afferent stimulation protocols (see below) [21]. Furthermore, contrary to previous reports, the Huber lab recently reported that neither mGluR1 nor mGluR5 specific antagonists could block LTD elicited by such stimulation paradigms, and the LTD persisted in mGluR1 and mGluR5 knockout mice [124]. Only a broad-spectrum mGluR antagonist was capable of inhibiting this LTD [124].

Patterned afferent stimulation has also been utilized to induce group I mGluR LTD in regions involved in reward- and addiction-related behaviors. In particular, in the dorsal striatum, high-frequency afferent stimulation, which would produce LTP in hippocampal slice preparations, induces a group I mGluR-dependent LTD [111]. Consistent with the findings in the hippocampus and cerebellum, postsynaptic depolarization appears to be required for this LTD as well. It is interesting to note that similar patterns of stimulation in the nucleus accumbens have been reported to produce LTD that is regulated by group II mGluRs [97], whereas lower frequency stimulation (13 Hz) produces LTD that depends on group I mGluR activation [36]. More studies will be required to determine the mechanisms involved in this differential recruitment of mGluR subtypes. Finally, in another area of the brain involved in reward-related behavior, a region of the extended amygdala known as the bed nucleus of the stria terminalis (BNST), application of DHPG produces robust LTD [43].

In summary, it appears that whereas group I mGluR LTD can be reliably induced at many synapses pharmacologically through DHPG application, afferent stimulation produces variable results. An interesting possibility to consider is that group I mGluRs are typically thought to be localized at multiple sites outside the glutamatergic synapse, and thus may also be sensitive to nonsynaptic sources of glutamate, such as that released from astrocytes through multiple mechanisms [6, 47]. In addition, it is possible that activation of nonglutamatergic Gq-linked receptors may also play important roles in the induction of similar forms of LTD, as discussed below.

Gq-linked Acetylcholine and Adrenergic Receptors and LTD

Although far fewer experiments have investigated the possibility of LTD induced by Gq-coupled receptors of other neurotransmitter families, it was recognized early on that disrupting both cholinergic and adrenergic inputs into the visual cortex (vCTX) interfered with LTD induced by ocular deprivation [8]. Subsequently, it was shown that LTD could be induced at glutamatergic synapses in the vCTX by the activation of muscarinic M1 acetylcholine receptors (AChRs) or α_1-adrenergic receptors (ARs) (agonist application in conjunction with a paired-pulse protocol) in an input-specific and NMDAR-dependent manner [68]. More recently, in the same region it has been established that low-frequency stimulation (1 Hz 15 min) induces LTD that can only be blocked by simultaneous coapplication of antagonists to mGluR5, M1-AChRs, and α_1-ARs during the induction protocol [21]. Conversely, M1-AChR activation in the perirhinal cortex induces a long-lasting depression (although not LTD as it can be reversed by subsequent antagonist application) that is independent of NMDAR activation and concurrent stimulation [81].

Both cholinergic and adrenergic innervation have been implicated in hippocampal-dependent memory formation. LTD induced by the activation of M1-AChRs and α_1-ARs has now been described in the hippocampus where, like the vCTX, it is dependent on NMDARs and is input-specific [103, 104], unlike mGluR LTD in the same region. Intriguingly, septal lesions that disrupt cholinergic innervation in the hippocampus prevent the induction of M1-AChR LTD; however, subsequent sympathetic sprouting rescues this LTD [104], suggesting that in the face of neurodegeneration the brain attempts to maintain the capacity for this plasticity in the hippocampus. Evidence from the Kirkwood lab also supports the notion that this LTD may be an important mechanism of plasticity in a healthy aging brain. They have observed that expression of Gq-mediated LTD in learning unimpaired aged rats (24 months) is greater than that of young rats (6 months) and aged-matched rats with spatial learning impairments [71].

Group I mGluR LTD is Induced Postsynaptically

Immunohistochemical and electrophysiological results reveal group I mGluRs localize and function predominant-

ly postsynaptically, but also presynaptically and on glia [7, 23, 77–79, 99, 108]. From the earliest reports of mGluR LTD, most evidence supports the idea that group I mGluR LTD is induced postsynaptically. In particular, as mentioned above, many synaptic stimulation paradigms for group I mGluR induction require pairing with postsynaptic depolarization [42, 70, 90]. Consistent with this idea, many, but not all studies have reported that group I mGluR LTD is blocked by chelation of postsynaptic calcium by inclusion of BAPTA in the patch pipette [90, 92]. Using this same technique, inclusion of GDPβS or tyrosine phosphatase inhibitors in the patch pipette to disrupt G protein signaling or tyrosine phosphorylation similarly disrupts LTD induction [43, 55, 86]. In addition, in a dendritic preparation of hippocampal slices, mGluR-dependent LTD was shown to depend on local (postsynaptic), rapid protein synthesis [57].

Multiple Maintenance Mechanisms for mGluR LTD

Whereas most evidence points toward the postsynaptic element as the site of induction of group I mGluR LTD, multiple maintenance mechanisms, both presynaptic and postsynaptic, appear to exist. In this section, we will break our description of these mechanisms into two sections: (1) mechanisms of presynaptic maintenance and (2) mechanisms of postsynaptic maintenance. We will also briefly discuss data suggesting a role for constitutive mGluR signaling in group I mGluR LTD.

Presynaptic Maintenance Mechanisms

Early studies, particularly using synaptic induction paradigms in tissues from very young animals, suggested that group I mGluR LTD at the Schaffer collateral (SC)-CA1 synapse is maintained by a decrease in release probability, as this LTD was associated with changes in the coefficient of variance [12] and decreases in the frequency of activity-dependent quantal release recorded in the presence of strontium [90], both traditionally thought of as predictors of presynaptic events. Whereas interpretation of changes in biophysical readouts based on quantal theory during LTD can be complicated by possible postsynaptic "silencing" mechanisms, some of the strongest evidence supporting presynaptic maintenance of group I mGluR LTD was obtained utilizing optical approaches to examine vesicular release. Using FM 1-43, a fluorescent marker taken up by presynaptic boutons, Zakharenko et al. found that group I mGluR activation resulted in a decrease in the rate of FM 1-43 release at CA3-CA1 synapses from p4-p9 rats [133]. They went on to further conclude that a change in the mechanism of vesicular release from a full fusion mode to a "kiss-and-run" mode of release was responsible for the reduction in synaptic efficacy during group I mGluR LTD.

A postsynaptically induced, presynaptically maintained LTD must involve a retrograde signal from the postsynaptic element. Two main candidates (which may well be interrelated) have been suggested, specifically arachidonic acid metabolites and endocannabinoids. Consistent with the proposed hypothesis of postsynaptic induction and presynaptic expression of group I mGluR LTD, it was found that endocannabinoid synthesis can be triggered by activation of group I mGluRs [41]. In the CNS, endocannabinoids are thought to work predominantly through the activation of the CB1 class of cannabinoid receptors, which is concentrated at presynaptic elements [38, 105]. At the adult SC-CA1 synapse, only the transient component of DHPG-LTD was disrupted in the CB1-receptor knockout mouse, suggesting that endocannabinoids do not participate in group I mGluR LTD of excitatory transmission in the hippocampus [100]. To date, however, similar studies have not been reported in the young animal hippocampus.

Use of pharmacological tools and genetic manipulations has provided evidence for a role of arachidonic acid metabolites, more specifically the 12-lipoxygenase metabolite of arachidonic acid, 12(*S*)-hydroxyeicosa-5Z,8Z,10E,14Z-tetraenoic acid (HETE), in inducing group I mGluR LTD in the hippocampus. Direct application of this metabolite mimicked and occluded mGluR5-dependent LTD at these synapses, mGluR5-dependent LTD in the hippocampus is absent in mice lacking the "leukocyte type" 12-lipoxygenase, and group I mGluR LTD-inducing stimuli promote 12-lipoxygenase activity [33]. These authors suggest a potential downstream target of 12-lipoxygenase is p38 kinase. Indeed, inhibitors of p38 MAP kinase block this form of LTD [13]. p38 kinase, like ERK, is a member of the MAP kinase family and has been implicated in group I mGluR LTD. For instance, in the dentate gyrus, group I mGluR LTD is dependent on p38 kinase signaling [101] and in area CA1 of the hippocampus, activation of group I mGluRs results in AMPAR endocytosis, which will be discussed in greater detail in a subsequent section and is dependent on p38 kinase signaling.

At about the same time these discoveries were being made in the hippocampus, work by the Lovinger laboratory and subsequently the Manzoni laboratory suggested that group I mGluR LTD in the dorsal and ventral striatum was also postsynaptically induced and presynaptically maintained, again suggesting the requirement of a retrograde signal. As evidence that this LTD is presynaptically maintained, it was shown that this LTD occurs coincident with an increase in paired-pulse ratios (PPR) of evoked synaptic responses and also a decrease in the frequency of quantal events recorded in strontium [20, 40]. They found that high-frequency synaptic stimulation resulted in a lasting depression of AMPAR currents that was group I mGluR-dependent

[98, 111]. In a series of experiments, Gerdeman et al. demonstrated that group I mGluR-dependent LTD in the striatum was absent in CB1R knockout mice and slices pretreated with a selective CB1R antagonist [42]. Furthermore, this LTD was blocked when the endocannabinoid transporter blocker AM404 was included in the patch pipette, consistent with the idea that endocannabinoids are synthesized and released from the postsynaptic cell in an activity-dependent manner. In addition, loading the postsynaptic cell with anandamide, an endocannabinoid, resulted in the depression of synaptic transmission and an enhanced probability of release that was blocked by preincubation with the CB1R antagonist SR141716 [42]. This implicates a diffusion of anandamide from the postsynaptic cell to the presynaptic CB1R. Group I mGluR LTD in the ventral striatum was also reported to be dependent on endocannabinoid signaling [98].

Whereas synaptic induction of group I mGluR LTD can be readily elicited at corticostriatal terminals, curiously DHPG-induced LTD is more difficult to elicit. Recent data illustrate that the successful induction of DHPG-LTD in the striatum depends on the membrane potential of the postsynaptic medium spiny neurons [70]. In vivo, the membrane potential of these neurons normally oscillates between an "up" state and a "down" state ranging from approximately −50 mV to approximately −70 mV, respectively. Kreitzer and Malenka provide evidence that DHPG-LTD is enabled under conditions most consistent with the "up" state [70].

Postsynaptic Maintenance Mechanisms for Group I mGluR LTD

Another major maintenance mechanism for group I mGluR LTD, particularly in more mature animal hippocampus, is the regulation of postsynaptic AMPAR trafficking. As mentioned above, much work has been done characterizing removal of AMPARs from cerebellar synapses upon mGluR1 activation via PKC/clathrin-mediated endocytosis of GluR2/3 containing AMPARs [62]. For instance, immunohistochemical studies suggest that the expression of mGluR LTD of excitatory transmission in cultured neurons or hippocampal slices requires internalization of postsynaptic AMPARs [54, 55, 86, 87, 109, 131]. Furthermore, Snyder et al. also report a removal of NMDAR subtype NR1 from the cell surface after activation of group I mGluRs [109].

An interesting feature of these studies is that in many of them, parallel to the decreases in surface AMPAR expression, decreases were observed in miniature excitatory postsynaptic current (mEPSC) frequency after group I mGluR activation. Changes in mEPSC frequency are traditionally viewed as a consequence of a decrease in presynaptic probability of glutamate release from synaptic vesicles. However, complete removal of AMPARs from a subset of synapses would have the same electrophysiological signature. Moult et al. were able to rescue group I mGluR-induced changes in mEPSC frequency by preventing postsynaptic actin depolymerization with jasplakinolide and therefore preventing endocytosis or by blocking tyrosine phosphatases specifically in the postsynaptic cell [86]. Furthermore, Xiao et al. blocked group I mGluR LTD via dynamin-mediated endocytosis by inclusion of a peptide designed to disrupt interaction of dynamin with amphiphysin and therefore clathrin-mediated endocytosis of AMPARs [131].

Group I mGluR-dependent AMPAR internalization may be developmentally regulated. Nosyreva and Huber [87] characterized a developmental switch of group I mGluR LTD in the hippocampus. As reported by others, they observed that this LTD appears to be presynaptically maintained and not associated with alterations in surface AMPAR expression in young animals, but switches to a postsynaptically maintained form that is associated with AMPAR redistribution in older animals.

Postsynaptic maintenance of group I mGluR LTD appears to occur in other brain regions in addition to the hippocampus and cerebellum. To study potential redistribution, in addition to traditional biochemical approaches such as biotinylation experiments, more recent studies have taken advantage of specific electrophysiological signatures of AMPARs composed of different subunit combinations. For instance, incorporation of GluR2 into an AMPAR, as occurs most commonly, prevents inward rectification of current passing through the receptor. Strong rectification occurs, however, in AMPARs lacking GluR2. In the VTA, activation of mGluR1 either by high-frequency stimulation or DHPG induces a postsynaptic calcium-dependent LTD [9]. This mGluR LTD results in a decrease in inward rectification of AMPAR currents, suggesting a reduction in the relative contribution of GluR2-less AMPARs to EPSCs. Furthermore, this LTD occludes joro spider toxin-induced depression of AMPAR-mediated synaptic transmission. This toxin blocks non-GluR2 containing AMPARs. In total, these results suggest a change in AMPAR subunit composition from GluR1 to GluR2 containing AMPARs [9].

A Role for Constitutive mGluR Signaling in Group I mGluR LTD

An unusual feature of group I mGluR LTD in the hippocampus that has been reported in several studies is that mGluR antagonists applied after the induction of LTD can inhibit LTD maintenance, and that this inhibition is reversible [35, 93, 124, 126]. Multiple labs have shown that broad-spectrum mGluR antagonists, such as MCPG or LY341495 at high concentration, are capable of reversibly blocking maintenance of LTD evoked by DHPG [35, 93, 126]. As with the pharmacology of induction, however,

results with more specific antagonists are less consistent. For example, whereas Huang and Hsu find that the mGluR5 antagonist MPEP mimics these actions [54], Huber and colleagues found that the mGluR1 antagonist LY367385 was able to reversibly inhibit LTD maintenance whereas MPEP was not [124].

At present, the mechanisms underlying this apparent constitutive mGluR activity and its role in DHPG-LTD are not clear. In a very interesting recent study, Huang and Hsu [54] provide data suggesting that constitutive activity of mGluR5 in the hippocampus is necessary to maintain altered surface expression of AMPARs, as administration of the mGluR antagonist MCPG after DHPG reversed both tyrosine phosphorylation and AMPAR surface expression back to basal levels, whereas in parallel experiments where MCPG was subsequently washed out, normal LTD levels of altered tyrosine phosphorylation and reduced surface AMPAR expression were observed. Paralleling these studies, they observed that tyrosine phosphatase inhibitors could mimic the effects of MCPG when applied after DHPG [54]. Thus, mGluR5-dependent control of tyrosine phosphorylation may play an important constitutive role [86]. In future studies, it will be important to determine whether the constitutive activity of mGluRs reflects altered agonist availability [6, 47], for example through nonsynaptic sources as mentioned above or whether this reflects alterations in intrinsic mGluR signaling [94].

Group I mGluR LTD-Signal Transduction in Induction

Given that group I mGluRs couple through Gq to activation of phospholipase C, it is not surprising that PKC is implicated in hippocampal group I mGluR LTD [90]. Cerebellar LTD can be induced by activation of mGluR1 resulting in the PKC-mediated expression of LTD [49, 74]. Further work in the dentate gyrus suggests that pharmacological inhibition of PKA or PKC attenuates group I mGluR LTD [56, 101]. However, antagonism of both PKA and PKC block group I mGluR LTD in this region [56].

It is interesting to note that it has been shown in some instances that the PKA and PKC pathways converge at the level of the mitogen-activated protein kinase MAPK/ERK pathway [1, 114]. This signaling cascade may function as a coincidence detector, integrating and amplifying transient neurochemical signals and converting them into persistent modifications of neuronal function at the biochemical, functional, and behavioral levels. Consistent with this, the ERK pathway plays a crucial role in a variety of cell regulatory events [18], including long-term synaptic changes and behavior [1, 84, 91]. By preventing activation of ERK by inhibiting the upstream kinase MEK, the induction of several forms of NMDAR-dependent LTP and LTD are blocked throughout synapses of the hippocampus and the amygdala (for review see Sweatt [114]). Of particular interest, NMDAR-independent forms of LTD are also blocked by MEK inhibitors. In particular, group I mGluR LTD in the PFC, hippocampus, cerebellum, and the BNST is dependent on ERK activation [39, 43, 66].

The ERK signaling cascade is a key cellular regulatory signal that acts to acutely regulate the function of proteins such as potassium channel subunits, but more commonly at both the level of transcriptional and translational control. Work from the Bear, Huber and Klann labs suggest group I mGluR LTD in the hippocampus and cortex can have a protein synthesis-dependent component [52, 57, 58]. This suggests a possible pathway downstream of group I mGluR activation potentially through ERK-induced protein synthesis, which results in a dampening of AMPAR-mediated signaling in adult hippocampus. The synthesis of multiple postsynaptic proteins can be induced by group I mGluR activation, including the AMPAR subunits GluR1 and GluR2 as well as PSD-95 [65, 120]. However, it is unclear how increased expression of these subunits would result in depression of excitatory transmission. It is interesting to note that activation of group I mGluRs results in the increased expression of fragile X mental retardation protein (FMRP) as well [52]. FMRP is an interesting RNA binding protein that is thought to suppress translation of its RNA targets. FMRP mRNA is transcribed in response to stimuli including group I mGluR activation [3]. Curiously, DHPG-LTD is enhanced in FMR1 knockout mice, and the LTD observed in these knockouts does not apparently require protein synthesis [52, 59] or ERK activity. Protein synthesis and AMPAR internalization are increased in neurons from Fmr1 KO mice [52, 59]. Recent work from the Klann lab demonstrates that DHPG-induced increases in FMRP levels are followed by rapid ubiquitination and degradation of this protein. Furthermore, they found that pretreatment of hippocampal slices with proteasome inhibitors disrupted the induction of DHPG-LTD [52]. In total, these studies suggest that a complicated interaction exists between mRNA binding proteins, protein synthesis, and degradation in regulating group I mGluR-induced LTD. It should be noted that whereas protein synthesis is necessary for group I mGluR LTD in adult hippocampus, like Fmr1 KO mice [88], neonatal rats exhibit protein synthesis-independent mGluR LTD [87]. mGluR5-LTD in the BNST of adult mice is also insensitive to protein synthesis inhibitors further suggesting multiple pathways in mediating mGluR LTD (Grueter and Winder, unpublished findings). Thus, these data are most consistent with a model where translational processes modulate rather than mediate

group I mGluR LTD. Clearly, additional studies will be necessary to determine the substrates involved in this regulation.

In addition to the ERK pathway, electrophysiological and biochemical evidence indicate a parallel regulation of DHPG-LTD in the hippocampus by the phosphoinositide 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway [51]. Hou and Klann found that application of DHPG recruited the phosphorylation of multiple signaling proteins in this cascade, and that DHPG-LTD was blocked by PI3K inhibitors [51]. As with the FMRP studies, at present, it is unclear what downstream substrates are regulated by these signaling processes to control LTD.

As we have discussed, evidence suggests that a number of ser/thr kinases play key roles in the induction of group I mGluR LTD. This stands in contrast to NMDAR-dependent LTD, which critically depends on ser/thr phosphatase activation [127]. Available evidence suggests that mGluR LTD does not depend on ser/thr phosphatase activity [90], although recent studies have proposed a role for protein phosphatase 2 A in group I mGluR-dependent ERK activation [80]. In CA1 hippocampal pyramidal cells of juvenile rats, loading of postsynaptic cells with the protein phosphatase inhibitor microcystin LR had no effect on mGluR LTD [90].

Whereas ser/thr phosphatases may not be involved, tyrosine phosphatases do appear to contribute to or modulate induction of group I mGluR LTD [85]. In addition, a recent study in the hippocampus suggests protein tyrosine phosphatases, but not serine/threonine phosphatases 1 or 2 A, are involved in the expression of DHPG-induced LTD [54]. This DHPG-induced LTD is accompanied by changes in tyrosine phosphorylation levels of GluR2, but not GluR1, and a decrease in GluR2 and GluR1 surface expression [54, 86].

In summary, it appears that at least two major forms of group I mGluR-initiated LTD exist. All appear to be initiated by postsynaptic group I mGluR activation. Group I mGluR LTD in the young hippocampus, in the striatum, and in the cerebellum, appears to involve presynaptic maintenance via the recruitment of a retrograde messenger. In the young hippocampus, the strongest evidence points to this messenger being HETE, although it is possible that this HETE contributes to endocannabinoid production. In the striatum, evidence is strongest for an endocannabinoid. In both cases, the retrograde messenger acts presynaptically to regulate glutamate release probability and may also alter release mechanisms. Another major form of group I mGluR LTD is maintained postsynaptically, most likely via the internalization of specific populations of AMPARs. This form of LTD is regulated by a complex series of interactions between multiple kinases, tyrosine phosphatases, mRNA binding proteins, and the proteasome system.

Group I mGluRs and LTP

In addition to the multiple mechanisms through which group I mGluRs depress excitatory transmission, strong evidence suggests that these receptors can facilitate the induction of NMDAR-dependent LTP. Significant controversy has existed through the years as to the degree to which mGluRs mediate versus modulate LTP, and the reader is referred to several reviews on the subject [4, 24, 44]. Regardless, it is clear that in a variety of contexts, targeted deletion of mGluR5 or antagonists of this receptor can reduce the degree of NMDAR LTP achieved [34, 37, 45, 64, 72]. Consistent with this idea, application of DHPG to hippocampal slices promotes a number of biochemical processes thought to facilitate and/or underlie LTP. These include increasing the phosphorylation state of GluR1 at Ser845 and Ser831, activation of ERK, and increased synthesis of AMPA receptor subunits and PSD -95 [25, 65].

What purpose might the dual roles in LTD induction and LTP facilitation serve? Although clearly more experiments are needed, a picture emerges where perhaps group I mGluR activation “resets” glutamatergic synapses. That is, whereas the LTD mechanisms described above would promote the removal of synaptic AMPARs, mGluR5-induced enhancement of Ser845 phosphorylation of GluR1 would result in enhanced extrasynaptic expression of AMPARs ready for insertion into the synapse [17, 31, 89].

Group I mGluR LTD is Altered by Drugs of Abuse

As mentioned above, there is substantial evidence for a role of group I mGluRs in addiction-related behaviors. The role of group I mGluRs and the mechanisms involved in the changes in mGluR function after in vivo administration are just beginning to be uncovered. The following section discusses the changes in group I mGluR function in brain regions involved in addiction, primarily in response to psychostimulants and Delta 9-tetrahydrocannabinol (Δ-THC), the active component of marijuana.

In the VTA, it was recently reported that a single in vivo exposure to cocaine enhanced mGluR1-mediated LTD [10]. The authors attributed this result to a cocaine-induced switch in AMPAR subunit composition from basal GluR2 to GluR2-lacking receptors at these synapses. It is interesting to note that this shift in AMPAR composition is reversed in vitro by mGluR1 activation and in vivo by administration of a systemically active mGluR1 positive allosteric modulator.

Downstream of the VTA, repeated in vivo administration of cocaine can cause a lasting NMDAR-dependent depression of excitatory synaptic transmission in the NAc [106, 118]. With only a single in vivo exposure to cocaine or Δ-THC, however, group I mGluR-dependent LTD in the NAc

is attenuated [36, 83]. The cocaine mediated effects on group I mGluR LTD are transient in that they recover to control levels at 1 week postcocaine exposure. The block of group I mGluR LTD in the NAc is attributed to a reduction in surface expression of mGluR5 [36]. Consequently, after repeated exposures to Δ-THC, NAc LTD recovers to control values [82]. Further experiments demonstrate an uncoupling of CB1R function whereas the authors attribute the recovery of LTD with compensation by group II mGluRs [82].

Another brain region innervated by the VTA that receives similar inputs as the NAc is the BNST. The BNST is uniquely situated to integrate the flow of information from the higher processing regions of the brain to the stress and reward pathways [69]. Consistent with its anatomical positioning, behavioral studies have shown that the BNST is involved in stress-induced relapse to cocaine seeking [29, 30, 73]. Similar to the VTA, in vivo cocaine administration induces an enhancement of AMPA/NMDA ratios in the ventral BNST [27]. In another part of the BNST, the dorsal BNST, activation of mGluR5 by application of DHPG induces LTD [43]. In contrast to the NAc, group I mGluR LTD in the BNST is not dependent on endocannabinoid signaling and is not altered by a single in vivo exposure to cocaine [43]. However, both contingent and noncontingent cocaine administration over repeated sessions attenuates this group I mGluR LTD when assayed 24 h after the last exposure [43]. It is interesting to note that as in the hippocampus, group I mGluR LTD in the BNST is ERK-dependent, however, DHPG-LTD in the BNST is heavily dependent on the ERK1 isoform [43]. Immunohistochemical studies indicate activation (as indicated by increased phosphorylation) of ERK after administration of a multitude of drugs of abuse in the BNST and other regions associated with reward responses [123]. This drug-induced ERK activation in the BNST is dependent on D1-like receptors, as it is blocked by preinjection with the D1-dopamine receptor antagonist SCH23390. This data suggests the possibility of converging pathways of the DA system and group I mGluRs at the level of ERK in the BNST.

A potential target for the interaction of group I mGluRs and alterations in synaptic efficacy after administration of drugs of abuse is the scaffolding protein Homer [112]. Homer proteins are part of the scaffolding at postsynaptic densities and link group I mGluRs with proteins in the PSD. Homers also link these receptors to intracellular calcium stores via IP3 receptors and other scaffolding proteins such as Shank [16]. It is suggested that Homer proteins may regulate the expression and function of group I mGluRs at multiple levels including targeting, surface expression, clustering, physical linkage to other synaptic and subsynaptic complexes, and modulation of constitutive activity [131]. Homer proteins have also been shown to form complexes with Shank proteins, which act as scaffolding proteins, and link group I mGluRs with other proteins in postsynaptic densities, such as Dynamin2, an important molecule indicated in endocytosis and AMPAR-glutamate receptor interacting protein (GRIP) complexes [121]. As mentioned above, mice with targeted deletions of Homer isoforms display disrupted behavioral responses to drugs of abuse. Furthermore, administration of drugs of abuse can alter the expression levels of Homer isoforms [53, 112, 115].

Clearly, in vivo cocaine administration produces dramatic changes in excitatory synapses in reward circuitry. It is now critical to begin addressing the physiological significance of these alterations. A larger question for the field of plasticity in general is the physiological significance of LTD evoked by Gq-linked receptors, particularly group I mGluRs. Whereas it is clear that these receptors play important roles in many aspects of neural function and behavior, it is currently less clear whether the forms of LTD described in this review are engaged in vivo in a meaningful way. This is a critical direction for future research in this area.

Conclusion

Historically, the dopaminergic system has been the primary focus of addiction research. The long-lasting behavioral modifications elicited by drugs of abuse suggest a cellular substrate such as glutamatergic plasticity mechanisms may be a strong candidate underlying these effects. As this review suggests, in addition to NMDAR-dependent plasticity, evidence for group I mGluR LTD as a mediator of addiction is emerging. As the field develops, mGluR1 and mGluR5, as well as there downstream effectors may prove to be important therapeutic targets for treating addiction-related behaviors. Whereas the few studies of demonstrating changes in group I mGluR mediated synaptic plasticity induced by drugs of abuse have focused on the early components of drug abuse, much work remains in determining the role of these receptors during the various stages of addiction.

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