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Presynaptic long-term depression mediated by $G_{i/o}$-coupled receptors

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Abstract

Long-term depression (LTD) of the efficacy of synaptic transmission is now recognized as an important mechanism for regulation of information storage and control of actions, as well as synapse, neuron, and circuit development. Studies of LTD mechanisms have focused mainly on postsynaptic AMPA receptor trafficking. However, the focus has now expanded to include presynaptically expressed plasticity; the predominant form being initiated by presynaptically expressed $G_{i/o}$-coupled metabotropic receptor ($G_{i/o}$-GPCR) activation. Several forms of LTD involving activation of different presynaptic $G_{i/o}$-GPCRs as a “common pathway” are described. Here, we review the literature on presynaptic $G_{i/o}$-GPCR-mediated LTD, discuss known mechanisms, gaps in our knowledge, and evaluate if all $G_{i/o}$-GPCR are capable of inducing presynaptic LTD.

Keywords

Long-term synaptic plasticity; $G_{i/o}$-GPCR; Synaptic inhibition; Presynaptic plasticity; Neurotransmitter release; Vesicle release machinery; Plasticity mechanisms

Defining LTD

It is increasingly clear that long-term depression of synaptic transmission (LTD) is critical to shaping lasting changes in circuit function, learning, memory, and behavior. LTD is often thought of as a mechanism that weakens synaptic strength (Glossary) [1]. However it is a common misconception that LTD is “forgetting” and long-term potentiation (LTP) is “memory.” Several studies now indicate that LTD supports various forms of learning [2–4].

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LTD may function as a signal/noise filter, as the strongest afferent inputs would have the most influence on postsynaptic neuronal output. LTD may thus increase the amount of convergent input required to generate output from a particular circuit element. It is conceivable that if both presynaptically-expressed LTD and postsynaptically-expressed LTP exist at the same synapse, the earliest response to a burst of afferent inputs would be augmented relative to subsequent responses. Therefore, LTD contributes to frequency filtering at synapses that are critical for encoding novel behaviors or memories.

In contrast to short-term depression (STD; Fig. 1a), which by definition lasts for only seconds to minutes, LTD persists for tens of minutes or more (Box 1, Fig. 1b). Operational definitions of what constitutes LTD vary, however. The more liberal definition of LTD is any suppression that persists over time and may or may not be reversed by a receptor antagonist. Here, we refer to LTD that is reversible by application of receptor antagonists after LTD is established as “labile” LTD (Fig. 1c). There are a few reasons suppression can endure yet be reversible, including persistent neurotransmitter release, persistent receptor binding, or poor agonist clearance. Indeed, extracellular levels of neuromodulators can reach levels that tonically activate receptors [5, 6]. Receptor conformational states may also play a role in the reversibility of LTD [7]. A more stringent definition of LTD is a persistent depression that is not reversible by application of receptor antagonists after LTD is established, which we refer to as “static” LTD (Fig. 1d).

Box 1

Presynaptic Gi/o-GPCR STD versus LTD: binary states or two ends of a continuum?

Many factors may determine if a particular presynaptic $G_{i/o}$-GPCR mediates LTD. It is not as simple as a $G_{i/o}$-GPCR belonging to a specific structural class. For example, class A/rhodopsin GPCRs, such as CB1R, 5-HT1bR, and the opioid receptors and the class C/glutamate GPCRs, the group II/III mGluRs [10], can induce LTD following activation. Even within classes there appears to be divergence; activation of certain presynaptic $G_{i/o}$-GPCRs, such as CB1R, is known to induce either STD or LTD, depending on the induction protocol that is delivered [100].

The level of activity in the presynaptic terminal appears to be important for the transition from STD to LTD, at least at some synapses. At GABAergic synapses in hippocampus and striatum and at corticostriatal synapses in dorsal striatum, decreasing presynaptic activity with TTX determines whether CB1R activation induces STD or LTD [24, 43, 101]. However, for 5-HT1bR, application of an agonist in the presence of TTX does result in corticostriatal LTD [87]. Furthermore, the level of presynaptic activity at inhibitory synapses in the hilar region of the dentate gyrus does not affect eCB-LTD expression [102]. These functional differences also occur across synapses. In contrast to the effect of CB1R agonist on excitatory synapses on to striatal MSNs in TTX, a CB1R agonist depresses inhibitory synapses on to MSNs in TTX, but this depression is reversed by application of a CB1R antagonist [43]. This apparent difference across synapse types then suggests what dictates the expression of STD versus LTD is a combination of the particular presynaptic $G_{i/o}$-GPCR and the complement of downstream effectors that are

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expressed in a particular presynaptic terminal. Are the mechanisms underlying STD and LTD dissociable? Possibly at some synapses STD is solely mediated by presynaptic VDCC blockade, whereas LTD results from extended agonist binding or activation of a high number of receptors, along with presynaptic terminal activation, leading to long-term maintenance of synaptic depression involving AC inhibition, de novo local protein synthesis, and other intra-terminal Ca^{2+} signaling mechanisms. It is also possible that presynaptic VDCC blockade, downstream of AC inhibition, may also contribute to protein synthesis necessary for LTD maintenance. As we have discussed, there are multiple examples of presynaptic $G_{i/o}$-GPCRs that can induce LTD, and some that induce STD. Experimental evidence suggests that synaptic depression is more complicated than this binary (either LTD or STD) picture would suggest. Perhaps it could be better described as a continuum, from STD to LTD, encompassing reversible labile and irreversible, likely protein synthesis-dependent static LTD. Is a synapse that undergoes LTD forever depressed? It would not be unreasonable to think that even these forms of LTD could be reversed via engagement of mechanisms that are as yet undiscovered.

Mechanistically, LTD can be placed into two categories: those with presynaptic and those with postsynaptic expression mechanisms. Postsynaptically-expressed LTD generally involves the removal of receptor proteins, such as AMPA receptors, from the postsynaptic membrane, resulting in reduced transmission. These mechanisms are reviewed elsewhere [8]. Presynaptic LTD is expressed through various mechanisms including presynaptic NMDA receptor (NMDAR) activation [9] or activation of select presynaptically-localized metabotropic receptors that couple to $G_{i/o}$ G proteins ($G_{i/o}$-GPCRs). This review focuses on this latter, presynaptic $G_{i/o}$-GPCR-dependent form of LTD. Furthermore, we discuss a wide range of receptors that mediate presynaptic LTD and explore the general principle that activation of any presynaptic $G_{i/o}$-GPCR is capable of inducing LTD.

GPCRs and presynaptic LTD

GPCRs are a diverse family of metabotropic receptors that signal through associated heterotrimeric G proteins and scaffolding proteins. G proteins exist in complexes consisting of a G_{α} subunit and a $G_{\beta\gamma}$ dimer pair of subunits. Receptor activation induces these G protein subunits to couple to numerous effector proteins, allowing a single receptor to modulate diverse cellular processes.

G_{α} subunits are divided into four classes. $G_{\alpha s}$ stimulates adenylyl cyclase (AC), $G_{\alpha i}$ inhibits AC, $G_{\alpha q/11}$ activates phospholipases and subsequently intracellular Ca^{2+} levels, whereas $G_{\alpha 12/13}$ operates through more complex pathways [10]. Specific GPCRs are referred to as coupling to a specific G_{α} class, but this preferred coupling is mutable [10]. $G_{\beta\gamma}$ protein subunits couple to ion channels such as voltage dependent Ca^{2+} channels (Cav2, VDCCs) and the G protein-coupled Kir3 class of potassium channels (GIRKs) [11]. $G_{\beta\gamma}$ also directly interacts with vesicular fusion machinery (consisting of SNARE, Ca^{2+} sensing and regulatory proteins) [11] as well as kinases, phospholipases, and even AC [12]. Scaffolding proteins such as beta-arrestin unite GPCRs with other signaling proteins such as kinases that provide additional routes for GPCRs to influence cellular function [10].

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Activation of presynaptic $G_{i/o}$-GPCRs produces a decrease in synaptic efficacy through inhibition of neurotransmitter release. Table 1 lists the effectors through which $G_{i/o}$-GPCRs exert their control of neurotransmission. Fig. 2 details how some of these effectors may induce LTD subsequent to receptor activation.

Ca^{2+} influx from VDCCs or release from internal stores influences vesicular release as well as Ca^{2+}-sensitive signal transduction pathways that influence synaptic plasticity. The sensitivity of the release machinery in a particular synapse to Ca^{2+} and/or the degree to which receptors couple to VDCCs confers synapse-specific effects of receptor mediated, Ca^{2+}-dependent regulation of neurotransmitter release [13, 14]. $G_{i/o}$-GPCRs regulate presynaptic Ca^{2+} levels by inhibiting VDCCs. Blocking VDCCs often disrupts LTD [15–21], but this may be due to reduced Ca^{2+}-sensitive protein function rather than direct involvement of VDCC inhibition in LTD expression. Indeed, Ca^{2+} activates proteins, such as calmodulin and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which may play important roles in presynaptic LTD expression [22, 23]. The Ca^{2+} sensitive phosphatase calcineurin can contribute to LTD, but this appears to be synapse-specific [24, 25].

$G_{i/o}$-GPCR-induced LTD with mechanisms downstream of VDCC activation is likely due to an effect on vesicular release machinery. Many signaling pathways engaged by $G_{i/o}$-GPCRs converge on these proteins. Presynaptic $G_{i/o}$-GPCRs negatively couple to AC, attenuating cAMP-protein kinase A (PKA) signaling [26], which influences release machinery function and indirectly modulates VDCCs [21, 27–30]. Kinases, such as protein kinase C (PKC) [31–34], diacylglycerol kinase (DGK) [35], and mitogen-activated protein kinase (MAPK) might have a role in presynaptic $G_{i/o}$-GPCR-mediated LTD [36]. Presynaptic NMDARs may also play a role in GPCR-mediated presynaptic LTD, albeit in a supporting role [31, 37–39]. Nitric oxide (NO) signaling can intersect with GPCR-mediated LTD through NO-signaling pathway-mediated Ca^{2+} release from presynaptic internal stores and subsequent activation of Ca^{2+}-sensitive LTD mediators. Protein kinase G (PKG)-mediatedphosphorylation of release machinery may also contribute to these forms of LTD [40–42]. While these mechanisms can be recruited for presynaptic LTD induction, the maintenance of this form of LTD requires long-lasting changes at axon terminals possibly accomplished by alterations in protein translation or posttranslational modification. Presynaptic protein synthesis plays a role in presynaptic LTD maintenance at some synapses [43–45], but not at others [16, 46].

Presynaptic $G_{i/o}$-GPCRs implicated in LTD

Group II and III mGluRs

LTD mediated by the group II mGluRs, mGluR2 and mGluR3, was first identified at mossy fiber (MF)-area CA3 hippocampal synapses [47] and has since been found in many brain regions. For example, mGluR2/3 agonists induce LTD (mGluR2/3-LTD) in nucleus accumbens (NAc), prefrontal cortex, and substantia nigra pars reticulata [21, 48, 49], among others. mGluR2/3-LTD may be achieved via modulation of cAMP-PKA signaling. Maintaining high cAMP levels prevents mGluR2/3-LTD induction at MF-CA3 synapses and PKA inhibition is occlusive of mGluR2/3-LTD [47]. PKA inhibition similarly occludes mGluR2/3-LTD in basolateral amygdala [50]. mGluR2/3-LTD at excitatory synapses onto medium spiny neurons (MSNs) in the NAc is also dependent upon cAMP-PKA signaling

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[21]. Interestingly, this LTD can be occluded by blockade of P/Q-type presynaptic VDCCs, suggesting an interaction between suppression of PKA activity and VDCC inhibition, as previously reported [21, 51].

NMDARs may serve a supporting role for mGluR2/3-LTD. In dentate gyrus mGluR2-LTD is partially sensitive to NMDAR antagonists and is completely blocked by both PKA and PKC inhibitors [31]. The fact that this LTD is not completely ablated in the presence of NMDAR antagonists suggests that NMDARs are not of critical importance. However, it is possible that NMDARs are downregulated along with VDCCs to ultimately result in some forms of $G_{i/o}$-GPCR initiated LTD.

mGluR2/3 can target SNAP25, a SNARE protein. Botulinum toxin A treatment cleaves SNAP25 and disrupts mGluR2/3-LTD at hippocampal CA3-CA1 synapses [52]. Saturation of LTD occludes this toxin's effect, which is not prevented by increasing Ca^{2+} levels. Sequestration of $G_{\beta\gamma}$ with C-terminal SNAP25 peptide fragment infused presynaptically into CA3 neurons prevents LTD induction. This blocking peptide only slightly reduced Ca^{2+} transients, thus this LTD pathway occurs independently of Ca^{2+} and is likely due to a direct action of G proteins on SNAP25 or other components of the interacting release machinery [52].

Activation of the group III mGluR7 receptor, another presynaptically-localized $G_{i/o}$-GPCR, by L-AP4 or high frequency stimulation (HFS) also induces LTD (mGluR7-LTD). Interestingly, mGluR7-LTD at excitatory synapses onto CA3 hippocampal interneurons requires postsynaptic Ca^{2+} entry through AMPA receptors. Thus, a retrograde signaling molecule cannot be ruled out that may act in concert with mGluR7 activation to induce LTD [53]. HFS of MF synapses onto CA3 stratum lucidum interneurons induces presynaptic mGluR7-LTD, but only in slices not previously exposed to mGluR7 agonist [33]. This mechanism functions through inhibition of P/Q-type VDCC inhibition, as P/Q-channel inhibition occludes mGluR7-LTD [54]. Consistent with these findings, Ca^{2+} transients in the filopodial extensions of mGluR7-LTD-sensitive MF boutons are persistently depressed following LTD induction by HFS [54]. This indicates that a lasting inhibition of Ca^{2+} influx through presynaptic P/Q-channels, rather than a transient inhibition of influx triggering a downstream signaling event, may be a necessary feature of presynaptic $G_{i/o}$-GPCR mediated LTD.

The cAMP pathway is recruited upstream of P/Q channel inhibition [55, 56]. Following activation, mGluR7 is internalized, which induces a switch in cAMP production. mGluR7 internalization allows HFS to activate AC and PKA, resulting in LTP of neurotransmitter release. Thus, mGluR7 acts as a state-dependent switch of bidirectional plasticity. mGluR7 acts similarly at glutamatergic synapses on magnocellular neurosecretory cells (MNCs) in the paraventricular nucleus of the hypothalamus (PVN), although its activation only induces STD at these synapses [3]. Further investigation is necessary to determine if other presynaptic $G_{i/o}$-GPCRs are capable of this function.

The kinase activation profile during presynaptic mGluR-dependent LTD is not limited to PKA. At MF-stratum lucidum interneuron synapses (in CA3), presynaptic mGluR7

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activation results in PKC- but not PKA-mediated LTD [33]. Priming synapses with PKC activation using the phorbol ester PMA lowers the threshold for LTD induction at Schaffer collateral (SC)-CA1 hippocampal synapses [34]. In addition to mGluR activation in CA3, CaMKII activation is also required for presynaptic LTD of MF synapses [22, 57]. In neonatal mice, presynaptic DGKi plays a role in mGluR2/3-LTD at SC-CA1 synapses and PKC inhibition restores mGluR2/3-LTD that was lost in DGKi KO mice [35]. mGluR2/3-LTD in the striatum is unaffected by cAMP-PKA pathway modulation but is partially blocked by MAPK kinase1/2 inhibitors suggesting the importance of the MAPK signaling pathway [36]. However, it is unclear whether this MAPK activity dependence is localized to the presynaptic terminal.

CB1 receptor

The first hint that activation of the presynaptically-expressed $G_{i/o}$-coupled type 1 cannabinoid receptor (CB1R) might induce LTD came from a study of glutamatergic transmission from parallel fibers onto cerebellar Purkinje cells. A CB1R agonist induced a persistent, but reversible depression of transmission (CB1R-LTD) [58]. Following the discovery of pharmacologically-induced CB1R-LTD, HFS-induced-LTD of glutamatergic transmission on to MSNs in the dorsal striatum (corticostriatal synapses) was demonstrated to occur via presynaptic CB1R activation, providing the first evidence that this form of LTD is inducible by an endocannabinoid (eCB) [59]. Shortly thereafter moderate-frequency stimulation-induced eCB-LTD was discovered at cortical inputs to MSNs in NAc [60]. eCB-dependent LTD is now known to be inducible at striatal GABAergic synapses and in many other brain regions [3, 61–64]. In contrast to mGluR2/3-LTD, where the putative source of the endogenous agonist resulting in LTD is the presynaptic terminal itself, the source of eCBs is most likely the postsynaptic neuron [65].

CB1R-LTD of glutamatergic transmission in midbrain dopamine neurons involves presynaptic inhibition of PKA [66]. Experiments in NAc and hippocampus indicate that manipulating AC function and cAMP levels prevent induction of CB1R-LTD [20, 28]. However, postsynaptic AC5 appears to have important roles in eCB-LTD induction at glutamatergic synapses onto striatal MSNs [67]. Thus, it will be important to separate pre- and postsynaptic AC roles, at least at these synapses.

As with other $G_{i/o}$-GPCRs, activation of CB1R directly inhibits VDCCs, but according to studies in single neurons this inhibition does not persist following removal of a CB1R agonist [68, 69]. Indirect CB1R-VDCC interactions through cAMP-PKA may also be involved in LTD. For example, the irreversible phase of eCB-LTD in NAc depends on the cAMP-PKA cascade and ultimately suppression of P/Q-type VDCCs [20], much like what was found with amphetamine-induced eCB-LTD in the amygdala [19]. In the lateral amygdala, CB1R mediates LTD through PKA modulation of N-type VDCCs, but this may be an indirect effect [27].

CB1R coupling to potassium channels may play some role in LTD. Glutamatergic transmission onto MSNs of the NAc is depressed by application of a CB1R agonist, and this depression is reversible by a CB1R antagonist [70]. This reversible form of CB1R-dependent synaptic depression is not mediated by the cAMP-PKA cascade, but instead by

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potassium channel activation. Potassium channel blockers also prevent CB1R-mediated LTD at hippocampal SC-CA1 synapses [71], in the lateral amygdala [72] and synaptic depression (not-necessarily LTD) at cerebellar parallel fiber-Purkinje cell synapses [73]. Moreover, activation of GIRKs produces STD that can prevent the induction of CB1R-dependent LTD at some synapses [27] and may play a role in CB1R-dependent LTD induction at others [72]. In addition to presynaptic VDCC and potassium channels, some evidence exists to support a role for presynaptic NMDARs as downstream targets of CB1R activation [37, 74], as well as NO at striatal synapses [40, 75, 76].

PKA inhibition appears to be critical for CB1R-LTD. But what is downstream of this? A potential PKA target is the release machinery-associated protein RIM1α [30, 77]. CB1R-LTD is absent in RIM1α null mice and PKA inhibition fails to induce LTD in these mice as well [28]. Interestingly, CB1R agonist application induces STD at these synapses rather than LTD. RIM1α deletion also prevents a CB1R-mediated component of LTD at glutamatergic synapses in NAc [78]. RIM1α interacts with RAB3, and both are predominantly presynaptic proteins associated with release machinery at inhibitory terminals [30]. The RAB3B null mouse has normal basal neurotransmission but has greatly reduced inhibitory LTD in CA1and lacks LTD at MF-CA3 synapses [43, 70, 79]. Phosphorylation of RIM1α induces LTP at cerebellar parallel fiber-Purkinje cell synapses [80], thus it is possible that dephosphorylation allows for LTD to occur. The protein phosphatase calcineurin has been implicated in CB1R-LTD at hippocampal GABAergic synapses, and this protein could also contribute to presynaptic dephosphorylation needed for LTD expression [24].

Opioid and neuropeptide receptors

Opioid receptor mediated-LTD (OP-LTD) was first identified in the PVN [81]. Kappa opioid receptor (KOR) activation induces LTD (KOP-LTD) of excitatory inputs to MNCs. Dynorphin is somatodendritically released from vasopressin MNCs to act on presynaptic KORs. Here, KOP-LTD is gated by the presynaptic modulation of glutamate release by eCB signaling [82]. GABAergic synapses onto paraventricular neuroendocrine cells also undergo LTD when moderate frequency stimulation is paired with postsynaptic depolarization in slices treated with cortisol or in slices made from previously stressed animals [83]. This LTD, which is induced by retrograde opioid signaling on to presynaptic mu opioid receptors (MORs) (MOP-LTD), is reversed by an antagonist chase.

In hippocampus area CA2, HFS of the SC pathway produces presynaptically expressed LTD of parvalbumin positive interneuron-pyramidal cell synapses that is not blocked by MOR or CB1R antagonists, but is blocked by delta opioid receptor (DOR) antagonists [84]. This DOR-mediated LTD (DOP-LTD) is also induced by moderate frequency stimulation and by DOR receptor agonists. DOR agonist effects are mutually occlusive with HFS-induced LTD. DOP-LTD is not present in CA1 as DOR activation there only produces STD.

OP-LTD also occurs in the dorsal striatum, mediated by DOR, KOR, and MOR [85]. Both exogenously applied and endogenously released opioid peptides produce LTD of excitatory inputs on to MSNs. Opioid receptor antagonists fail to reverse depression elicited by activation of each receptor. The OP-LTD mediated by activation of each receptor is dissociable from the others. Whereas MOP-LTD and DOP-LTD are clearly presynaptically

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expressed, KOP-LTD appears to have a presynaptic component, but is not unequivocally presynaptic. MOP-LTD is mutually occlusive with CB1R-LTD, whereas DOP-LTD is additive with both MOP- and CB1R-LTD, suggesting synapse-specificity or parallel routes of LTD induction.

Neuropeptide Y (NPY) application causes a persistent decrease in excitatory transmission in the suprachiasmatic nucleus [86]. However, NPY also causes a lasting depression of postsynaptic Ca^{2+} levels. Therefore, the mechanisms underlying NPY-LTD require clarification. NPY-LTD is not dependent on NMDARs, L- or N-type VDCCs, but is dependent on $G_{i/o}$ proteins. Since NPY1 and NPY2 receptors were ruled out, the exact identity of the NPY receptor that produces the NPY-LTD remains a mystery. However, the other NPY receptors NPY4 and NPY5 are also $G_{i/o}$-coupled.

5-HT1b receptor

Activation of the presynaptic serotonin 5-HT1bR with exogenous 5-HT, endogenous 5-HT, (secondary to application of a selective 5-HT reuptake inhibitor) or the 5-HT1bR-specific agonist CP93129, induces LTD of corticostriatal neurotransmission in dorsal striatum [87]. This 5-HT-LTD is AC-cAMP-dependent and is not reversible. 5-HT-LTD is mutually occlusive with eCB-LTD, indicating that both 5-HT1bR and CB1R co-express on corticostriatal terminals. In addition, 5-HT-LTD mediated by 5-HT1bR is also present at dorsal striatal GABAergic terminals and in the NAc [2, 29, 87]. 5-HT-LTD in NAc is sensitive to protein kinase inhibitors [29]. Interestingly, in this same study the authors found evidence that was suggestive of increased phosphorylation of release machinery following in vivo cocaine exposure that prevented the induction of 5-HT-LTD [29]. 5-HT-LTD mediated by 5-HT1bR in NAc is also induced by presynaptic oxytocin receptor activation on inputs from the dorsal raphe nucleus, and appears to be a critical component of socially conditioned place preference [2].

A1 adenosine and purinergic receptors

Data from in vivo studies and reduced preparations indicate that synapses in many brain regions are subjected to tonic, low-level presynaptic A1 adenosine receptor (A1R)-mediated synaptic depression due to ambient levels of adenosine [88, 89]. A1R activation often results in STD, however, a more recent report investigating hippocampal CA3-CA1 synapses of morphine-dependent rats showed that theta (5 Hz)-burst stimulation results in LTD only in morphine dependent animals. This LTD is blocked by an A1R-specific antagonist or an NMDAR antagonist, but not both [90]. In addition, in cerebellar slices delivery of a train of 5 electrical pulses at 100 Hz, paired with postsynaptic depolarization, results in LTD of parallel fiber-Purkinje cell transmission that is largely blocked by an A1R antagonist [91].

Activation of P2Y1 receptors produces presynaptic NMDAR-independent LTD in cultured hippocampal neuron pairs and in hippocampal area CA1 [15]. Receptor activation via endogenous release of ATP from optogenetically stimulated astrocytes, or by exogenous application of ATP or a P2Y agonist, induces this form of plasticity. These effects are blocked by a P2Y1 antagonist and the astrocytic-stimulated LTD is occluded by electrical stimulation-induced LTD.

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Manifold control

Given the number of known presynaptic $G_{i/o}$-GPCRs involved in LTD and the potential for more (Table 2), it is quite possible that a given presynaptic terminal may be under the control of multiple $G_{i/o}$-GPCRs. At the corticostriatal synapse alone, GABABR, 5-HT1bR, CB1R, D2R, A1R, mGluR2, H3 histamine receptor (H3R), M4 muscarinic receptor (M4R), DOR, and MOR are at least known to be expressed. Fig. 3 conceptualizes three possible interactions of different presynaptic $G_{i/o}$-GPCRs expressed on the same terminal. First, it is clear that at some synapses, LTD induced by different receptors is mutually occlusive [85, 87, 92]. It is therefore possible that presynaptic LTD operates via a common pathway with a "winner-take-all" process such that the modulator that manages to induce LTD prevents others from doing so (Fig. 3a). A possible mechanistic example comes from heterologous CB1R expression in superior cervical ganglion neurons. CB1R sequesters $G_{i/o}$ G proteins such that it prevents other endogenously expressed $G_{i/o}$-coupled receptors from inhibiting VGCCs, but mGluR2 expression had no effect on these receptors [93]. However, evidence that this sort of sequestration occurs in native presynaptic terminals is currently lacking. Second, it is conceivable that full activation of two $G_{i/o}$-GPCRs on the same terminal could operate in parallel through distinct pathways to produce an additive effect on LTD induction (Fig. 3b), although this has not been demonstrated experimentally to our knowledge. Third, despite full activation, some $G_{i/o}$-GPCRs do not induce LTD on their own, but facilitate the ability of other receptors to induce LTD possibly through enhancing inhibition of the cAMP-PKA pathway [41, 94, 95] (Fig. 3c). A variant of this possibility may be that simultaneous, but insufficient activation of two $G_{i/o}$-GPCRs on the same terminal is capable of summating to sufficiently induce LTD.

Slice electrophysiology only provides one piece of evidence for interactions between given presynaptic $G_{i/o}$-GPCRs, and is not necessarily an accurate reflection of how the system is actually functioning in vivo. To advance our understanding of how coordination and competition between multiple $G_{i/o}$-GPCRs contributes to learning and memory, it will be important to understand the context specific patterning of neurotransmission amongst differentially excitable dendritic arbor subregions on a given neuron.

It is evident that much more work is needed to clarify the role of known $G_{i/o}$-GPCR contributors to LTD in vitro and in vivo, and to investigate the potential for other receptors in this class to modulate synaptic transmission at different central synapses (Box 2). Given the wide ranging and powerful effect of presynaptic $G_{i/o}$-GPCR activation on LTD, it is not surprising that many of these receptors are involved in pathophysiology and are current therapeutic targets for a host of neuropsychiatric disorders ranging from anxiety and depression, to addiction, to Parkinson's disease [96–99]. Induction of LTD may well be one desirable consequence of such therapeutic receptor targeting. Tapping into this powerful neurotransmitter release control system using circuit-specific tools could represent a fruitful strategy for the development of future neurotherapeutics. Furthermore, clarifying the role of individual receptors and the interactions between receptors in presynaptic LTD will further our understanding of how these receptors shape learning, memory, and behavior.

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Box 2

Open questions

Are there more forms of presynaptic $G_{i/o}$-GPCR-mediated LTD to be discovered?

While it is established that certain presynaptic $G_{i/o}$-GPCRs induce LTD, there are many other $G_{i/o}$-GPCRs that may be localized presynaptically and positioned to exert LTD (see Table 2). Evidence for involvement of novel forms of LTD already exists. In rats, H3R activation by histamine produces a persistent decrease in glutamate release onto striatal MSNs [103], and from medial perforant pathway synapses of the dentate gyrus [104]. M2 muscarinic receptor activation in somatosensory cortex results in a lasting depression of glutamate-evoked discharges [105]. Presynaptic M4Rs at corticostriatal terminals might also induce LTD [106]. Finally, in the amygdala, alpha2-adrenoreceptor activation inhibits excitatory transmission on to principal neurons and prevents LTD induction by low frequency stimulation [17]. More work is needed to clearly define the role of these proteins in inducing presynaptic static or labile LTD. Given the number of $G_{i/o}$-GPCRs remaining to be studied, the potential is high for the discovery of more forms of presynaptic $G_{i/o}$-GPCR-mediated LTD.

What determines whether a $G_{i/o}$-GPCR induces labile or static LTD?

Some $G_{i/o}$-GPCRs induce labile LTD at one synapse and static LTD at another. For example MOR activation in hypothalamus produces labile LTD [83] whereas in dorsal striatum it produces static LTD [85]. One hypothesis to explain this diversity is that the efficiency with which the receptor at a particular synapse couples to downstream effectors dictates the persistence of synaptic depression. For instance, eCB-LTD in dorsal striatum is only reversed by a CB1R antagonist applied 1 min, but not 10 min, after induction [107]. There may be a requirement for the receptor to have sufficient time to engage signaling pathways and the efficiency of its coupling may determine the window in which it needs to remain active. Also, a recent report suggests that during LTD induction receptors may become constitutively activated but are still in equilibrium with inactive conformations [7]. Thus an antagonist can “reverse” LTD if it stabilizes LTD-inducing receptors in an inactive conformation. It is possible that upon removal of antagonist the receptors can return to a constitutively active conformation and restore LTD. The presynaptic proteome may also play a role. CB1R-LTD of inhibitory synapses in hippocampus and basolateral amygdala is changed to STD when RIM1α is absent [28]. Perhaps an unknown set of presynaptic proteins performs similar roles in determining whether labile or static LTD is the end result of receptor activation. Much more work is needed to determine why different $G_{i/o}$-GPCRs or the same $G_{i/o}$-GPCRs at different synapses induce differing forms of LTD.

What is the nature and significance of the interaction between multiple $G_{i/o}$-GPCRs at a given presynaptic terminal?

Multiple receptors exist at a given synaptic terminal, so what is the significance of their inevitable interaction? Is there a common pathway for presynaptic $G_{i/o}$-GPCR mediated LTD induction or are there multiple routes to achieve LTD? It is apparent that there are

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many effectors between receptor activation and manifestation of LTD. Are kinase activation, ion channel inhibition, and release machinery interactions all interconnected mechanisms or are there parallel pathways that yield the same end result of LTD? Unraveling this mystery requires a greater understanding of how different presynaptic $G_{i/o}$-GPCRs expressed at the same terminals interact over time to affect synaptic depression and, ultimately, behavior.

Glossary Box

$G_{i/o}$ G protein-coupled receptor ($G_{i/o}$-GPCR)	An inhibitory metabotropic neurotransmitter receptor characterized by its seven transmembrane helical structure and its ability to activate associated heterotrimeric G proteins upon agonist binding. These receptors couple to the $G_{i/o}$ class of G proteins that, when localized presynaptically, allow them to inhibit neurotransmitter release through modulation of adenylyl cyclase and ion channels
Presynaptic long-term depression	Long-term depression (LTD) of synaptic efficacy that results from a reduction in the probability of neurotransmitter release. Presynaptic LTD is distinguished from postsynaptic LTD, which results from reduced responsiveness to neurotransmitter due to a reduction in postsynaptic receptor levels
Short-term depression	Short-term depression (STD) of synaptic efficacy is a form of synaptic plasticity that reduces neurotransmission on a time scale of seconds to minutes

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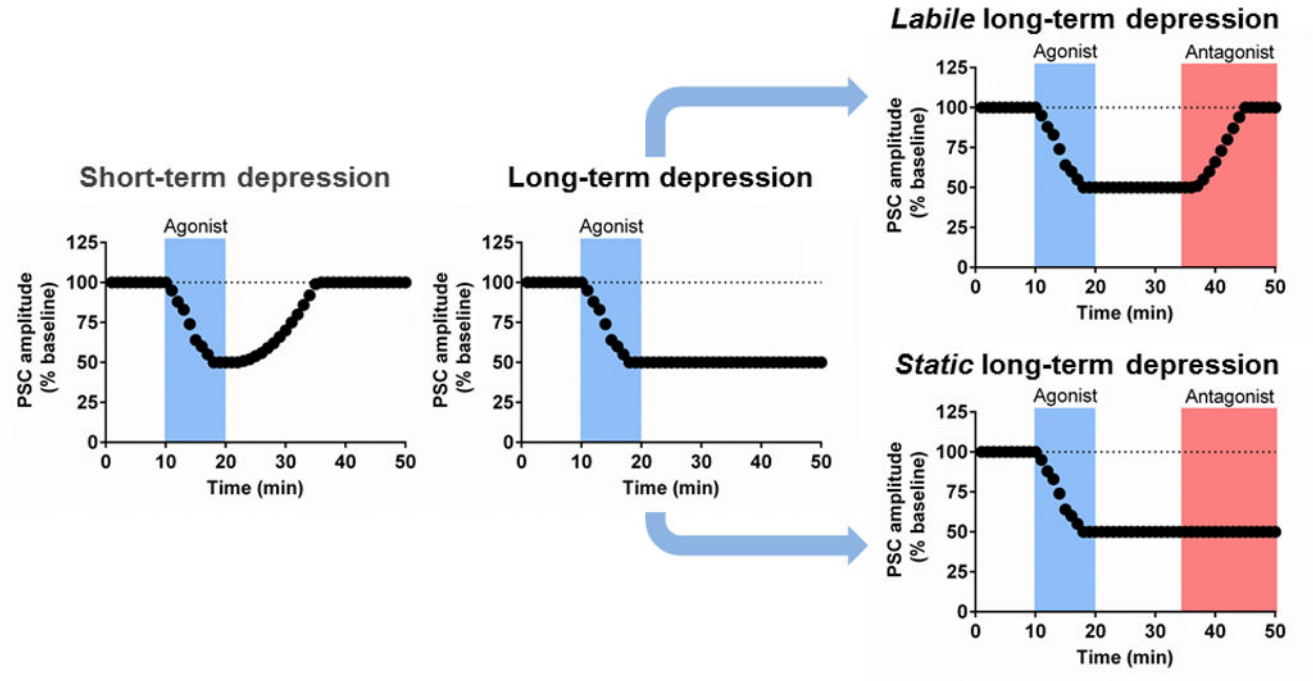

Figure 1. Operational definitions for distinct forms of synaptic depression

(a) Short-term synaptic depression (STD) persists for only as long as the neurotransmitter or agonist is present in the preparation (usually seconds to minutes) and therefore reverses upon washout of receptor agonist or termination of a stimulation induction protocol. (b) Depression that lasts for tens of minutes or longer following termination of receptor agonist application or an induction protocol is defined as long-term depression (LTD). LTD may be further subdivided into two operational definitions; “labile” and “static” LTD. (c) Evidence for labile LTD may be obtained by a chase with a receptor antagonist subsequent to LTD induction, as persistent receptor activation will therefore be blocked and LTD reversed. (d) We refer to the second definition of LTD as “static” LTD. Static LTD does not reverse when a receptor agonist application (or LTD-induction protocol) is followed by a receptor antagonist chase.

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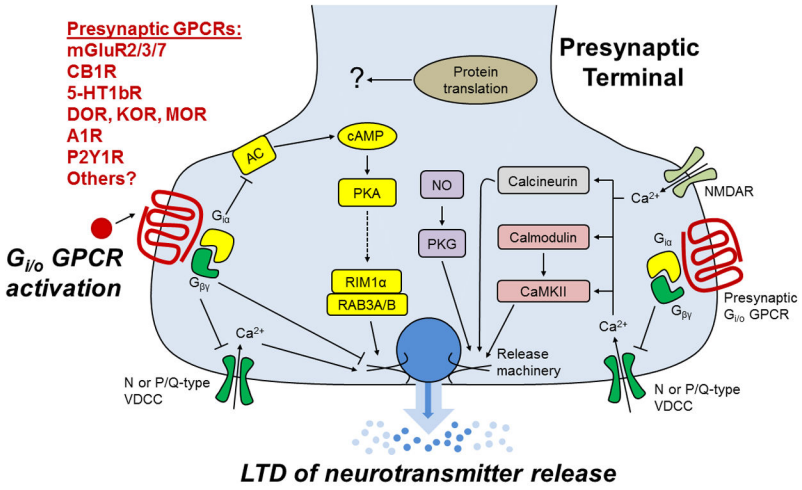

Figure 2. A schematic diagram of the possible mechanisms of presynaptic $G_{i/o}$ coupled GPCR activation-induced LTD

Activation of presynaptic $G_{i/o}$-coupled GPCRs results in the dissociation of the $G_{\alpha i}$ and $G_{\beta\gamma}$ subunits from the receptor complex. $G_{\beta\gamma}$ subunits directly and negatively couple to voltage-dependent Ca^{2+} channels (VDCCs) resulting in reduced Ca^{2+} entry into the presynaptic terminal. Reduced Ca^{2+} influx decreases vesicle fusion and neurotransmitter release probability. In addition, $G_{\beta\gamma}$ may directly inhibit components of the vesicular release machinery (e.g. SNAP25). The $G_{\alpha i}$ subunits negatively couple to adenylyl cyclase (AC) resulting in decreased cAMP levels. A decrease in cAMP levels results in dampened PKA activity, which is associated with reduced functionality of RIM1α. RIM1α complexes with the vesicular proteins RAB3A and RAB3B to enhance neurotransmitter release. Therefore, reduced PKA activity directly or indirectly inhibits this complex's ability to promote neurotransmission. In addition, Ca^{2+} entry through VDCCs or NMDARs activates the presynaptic kinases calmodulin and CaMKII and the protein phosphatase calcineurin. GPCR modulation of presynaptic Ca^{2+} levels likely influences the activity of these proteins, which subsequently alters neurotransmitter release. Although not directly modulated by presynaptic $G_{i/o}$ GPCRs, nitric oxide (NO) signaling intersects with GPCR-mediated signaling to promote LTD. NO signaling results in PKG activation that influences release machinery function. Finally, at some synapses protein translation appears to be a necessary component of LTD maintenance. The mechanisms that engage the protein translation apparatus as well as the proteins that are expressed are currently unknown.

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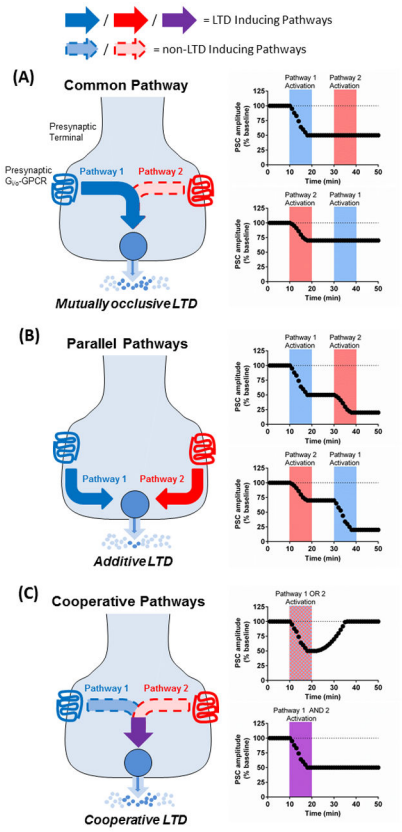

Figure 3. Possible interactions between two $G_{i/o}$-coupled receptors co-expressed on the same presynaptic terminal

(a) Two presynaptic $G_{i/o}$-GPCRs may signal through pathways that converge upon the same downstream effectors to induce LTD. Alternatively the two receptors may signal through pathways that not only converge, but are nearly identical. In either case, the two receptors will compete at some level for access to signaling proteins. The end result of this interaction will be mutually occlusive: LTD expression mediated by one receptor will prevent LTD by the second receptor. (b) A second possible interactive scenario could occur if two receptors operate through independent, non-converging signaling pathways that each achieved the same end result of inducing LTD. In this case LTD induction by one GPCR would be added to during induction by the second GPCR to increase the degree to which the terminal is depressed resulting in greater, additive LTD. (c) A final possible interaction between two presynaptic receptors is cooperation. In this relationship neither receptor is able to induce LTD on its own, but the ability of one receptor to do so is bolstered by signaling from the other. As such, one receptor would be required for LTD induction and the other would serve a facilitating role. In each of these scenarios, the timing of receptor activation would be critical. Coincident receptor activation could be needed for the hypothesized outcomes to occur, or possibly there may be a time window in which the two pathways could still interact.

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Table 1

Coupling of G protein subunits with effectors and the cellular consequences of such interactions.

G protein subunit	Target	Cellular Effect	Effect on Neurotransmission	References
$G_{\alpha i/o}$	Adenylyl cyclase	Inhibition, reduction in cAMP	Inhibition of neurotransmitter release	[26, 108]
$G_{\beta\gamma}$	VDCC inhibition	Reduced I_{Ca}	Reduced neurotransmitter release	[109, 110]
$G_{\beta\gamma}$	K channel activation	Increased I_K, reduced cellular excitability	Reduced neurotransmitter release	[111–113]
$G_{\beta\gamma}$	Vesicular release machinery	Inhibition of vesicular release	Inhibition of neurotransmitter release	[114–116]
$G_{\beta\gamma}$	PLCβ	PKC activation, increase intracellular Ca^{2+}	Inhibition of neurotransmitter release	[117]
$G_{\beta\gamma}$	Adenylyl cyclase	Activation or inhibition, increase or decrease in cAMP	*Inhibition or enhancement of neurotransmitter release*[1]	[26, 108]
$G_{\beta\gamma}$	Kinases: MAPK, βARK, PI3K	Phosphorylation of target proteins	*Inhibition or enhancement of neurotransmitter release*[1]	[118–120]

[1] $G_{\beta\gamma}$-mediated effects on presynaptic-modulation neurotransmission for the indicated effectors remain to be directly demonstrated.

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Table 2

A list of inhibitory $G_{i/o}$-coupled GPCRs that may be presynaptically-expressed and potentially mediate LTD at various synapses throughout the CNS.

Receptor Family	Receptor
Serotonin	5-HT1a
	5-HT1b
	5-HT1d
	5-HT1e
	5-HT1f
	5-HT5a
Acetylcholine	M2
	M4
Adenosine	A1
	A3
Adrenergic	A2a
	A2b
	A2c
Anaphylatoxin	C5a1/CD88
Angiotensin	AT1
	AT2
Apelin	APJ
Cannabinoid	CB1
Chemokine	CCR2
	CCR10
	CXCR4
	CX3CR1
Dopamine	D2
	D3
	D4
Galanin	GAL1
	GAL2
	GAL3
Histamine	H3R
Leukotriene	BLT1
	BLT2
	OXE
	FPR2/AXE
Lysophospholipid	LPA3
	S1P1
	S1P3
	S1P5
MCH	MCH1

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Receptor Family	Receptor
Melatonin	MT1
	MT2
	MT3
Neuropeptides	DOR
	KOR
	MOR
	NOR/ORL-1
	NPFF1
	NPFF2
	NPBW1
	NPBW2
Orexin	OX2
Purinergic	P2Y1
	P2Y12
	P2Y13
Prokineticin	PKR2
Prostanoid	EP3
	DP2
Relaxin	RXFP2
	RXFP3
	RXFP4
Somatostatin	SSTR1
	SSTR2
	SSTR3
	SSTR4
	SSTR5
Ca^{2+} Sensing	CaS
GABA	$GABA_B$
mGluR	mGluR2
	mGluR3
	mGluR4
	mGluR6
	mGluR7
	mGluR8