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Review

# Plasticity of Inhibition

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Until recently, the study of plasticity of neural circuits focused almost exclusively on potentiation and depression at excitatory synapses on principal cells. Other elements in the neural circuitry, such as inhibitory synapses on principal cells and the synapses recruiting interneurons, were assumed to be relatively inflexible, as befits a role of inhibition in maintaining stable levels and accurate timing of neuronal activity. It is now evident that inhibition is highly plastic, with multiple underlying cellular mechanisms. This Review considers these recent developments, focusing mainly on functional and structural changes in GABAergic inhibition of principal cells and long-term plasticity of glutamateric recruitment of inhibitory interneurons in the mammalian forebrain. A major challenge is to identify the adaptive roles of these different forms of plasticity, taking into account the roles of inhibition in the regulation of excitability, generation of population oscillations, and precise timing of neuronal firing.

## Introduction

Activity-dependent plasticity of neurotransmission is central to memory encoding and also plays a key role in the development of the nervous system. Persistent changes in communication among neurons also probably represent both adaptive and maladaptive responses to many forms of injury to the CNS. Plasticity in all its forms is thus inextricably intertwined with almost all aspects of brain function. Until recently, most efforts to understand the cellular and molecular mechanisms of plasticity of neurotransmission in the CNS were overwhelmingly directed at long-term potentiation (LTP) of excitatory synapses on pyramidal neurons and, to a much lesser extent, long-term depression (LTD) in pyramidal neurons and at parallel fiber synapses on cerebellar Purkinje cells. Plasticity of inhibition has received less attention. Although progress in one or the other aspect of this topic has recently been reviewed (Castillo et al., 2011; Kullmann and Lamsa, 2011; Luscher et al., 2011), this article has a broader scope: to consider the diversity of inhibitory plasticity in the context of circuit development and function.

The most obvious impediment to understanding inhibitory plasticity is the diversity of interneurons, loosely defined as locally projecting cells that release GABA from their terminals. Even classifying interneurons as exclusively inhibitory is problematic, because GABA can depolarize targets early in development (Ben-Ari et al., 2007), and axo-axonic synapses may even retain this ability into adulthood (Szabadics et al., 2006). Although a definitive taxonomy of interneurons is still some way off, recent advances in identifying the time and birthplace of GABAergic neurons in the ganglionic eminences, and the transcription factors that are active early on, are helping to classify them (Ascoli et al., 2008). It remains to be determined to what extent they exist as discrete nonoverlapping types, as opposed to unique outcomes of combinatorial transcription factor expression and stochastic interactions as they migrate through the cortical mantle.

A further obstacle to the study of plasticity of inhibition is that interneurons themselves are innervated by both excitatory and inhibitory synapses. Ultimately, changes in inhibitory signaling must be considered from the point of view of information processing and storage. We will start by examining the different types of plasticity reported at GABAergic synapses on principal cells and synapses recruiting interneurons before asking how they might impact on circuit computations and contribute to disease.

## Retrograde Signaling at Inhibitory Synapses

Several robust forms of plasticity of GABAergic signaling are elicited by postsynaptic activity, imposed experimentally by current injection or stimulation of excitatory afferents converging on the target neuron. Direct depolarization of principal cells elicits a robust, albeit transient depression of GABA release from a subset of presynaptic interneurons, which has been named depolarization-mediated suppression of inhibition (DSI). DSI was first reported in cerebellar Purkinje cells and hippocampal pyramidal neurons (Llano et al., 1991; Pitler and Alger, 1992) and has since been observed in many other regions of the CNS. According to the generally accepted model, the endocannabinoid (eCB) 2-arachidonoylglycerol (2-AG) is synthesized in principal neurons and diffuses to activate presynaptic G protein-coupled CB1 receptors, leading to a temporary depression of evoked and spontaneous GABA release (Kreitzer and Regehr, 2001; Ohno-Shosaku et al., 2001; Wilson and Nicoll, 2001) (comprehensively reviewed in Kano et al., 2009). Although postsynaptic $Ca^{2+}$ entry via voltage-dependent $Ca^{2+}$ channels and NMDA receptors is a robust stimulus for the synthesis of 2-AG by diacylglycerol lipase, this can also be stimulated by activation of phospholipase C by muscarinic M1/M3 or group I metabotropic glutamate receptors (Figure 1).

Some complexities in the cellular processing of 2-AG continue to receive attention (Alger, 2012). For example, an alternative model proposes that, under some conditions, nitric oxide can act as a retrograde factor triggering eCB production in the presynaptic terminal itself (Makara et al., 2007).

CB1 receptors are abundantly expressed by a subset of cholecystokinin (CCK)-positive cells, including non-fast-spiking

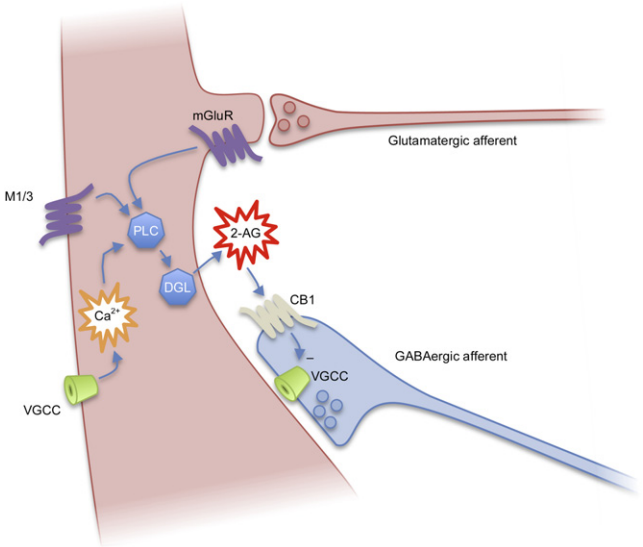


**Figure 1. Endocannabinoid-Mediated Retrograde Signaling at GABAergic Synapses**

Synthesis of the endocannabinoid 2-AG by the phospholipase Cβ (PLC)-diacylglycerol lipase (DGL) pathway can be triggered by $Ca^{2+}$ influx via voltage-gated $Ca^{2+}$ channels (VGCCs) but also by activation of $G_{q/11}$-coupled muscarinic M1/M3 or group I mGluRs via a cascade involving inositol trisphosphate receptors. 2-AG is thought to depress GABA release by inhibiting presynaptic VGCCs and is degraded by monoacylglycerol lipase. The alternative endocannabinoid anandamide has been implicated in retrograde signaling at some synapses and is mainly broken down by fatty acid amyl hydrolase. iLTD can be triggered by activity at nearby excitatory synapses together with firing of GABAergic terminals. Its effector mechanisms involve presynaptic RIM1α and calcineurin at GABAergic terminals. Other retrograde messengers reported at inhibitory synapses include BDNF, nitric oxide, and glutamate, although most of these trigger an increase in GABA release.

basket cells (Katona et al., 1999). In the hippocampus, DSI is robustly elicited at synapses made by these cells on pyramidal neurons. Synapses made by Schaffer collateral-associated interneurons, which also express CCK, appear to be less susceptible to DSI (Lee et al., 2010). CB1 receptor agonists mimic these effects, suggesting presynaptic differences among the CCK-positive interneuron types (Lee et al., 2010). The postsynaptic neuron is also important in DSI induction, with reliable DSI produced between CCK-positive basket cells in the hippocampus (Ali, 2007), but not at CB1 receptor-positive synapses onto layer 2/3 cortical GABAergic interneurons, despite CB1 receptor agonists depressing GABA release (Lemtiri-Chlieh and Levine, 2007; Galarreta et al., 2008). This suggests that some interneurons lack the ability to synthesize eCBs. In the hypoglossal nucleus, DSI of glycinergic inhibition to principal cells has been reported, suggesting that it is not confined to GABAergic synapses (Mukhtarov et al., 2005).

Although DSI generally lasts less than 5 min, eCBs have also been implicated in LTD of GABAergic inhibitory transmission (''iLTD''). In the lateral amygdala, low-frequency stimulation at 1 Hz, designed to release glutamate at synapses on the target neuron, was followed by a persistent depression of inhibitory transmission, which was sensitive to blocking either mGluR1 or CB1 receptors (Marsicano et al., 2002). The effect was potentiated by blocking anandamide degradation, implying that this eCB, rather than 2-AG, is involved (Azad et al., 2004). In contrast, iLTD in hippocampal pyramidal neurons is sensitive to blocking diacylglycerol lipase (Chevaleyre and Castillo, 2003), implicating 2-AG. Roles for presynaptic adenylate cyclase, inhibited by the $\alpha_{i/o}$ limb of the CB1 signaling cascade, and for the active zone protein RIM1α, discriminate iLTD from DSI (Chevaleyre et al., 2007).

This brief summary of CB1 receptor-mediated plasticity of inhibition focuses exclusively on activity-dependent eCB signaling. Signaling by eCBs may also be tonically active. For example, a CB1 antagonist was shown to increase GABA release from a subset of hippocampal CCK-positive interneurons (Losonczy et al., 2004), and similar results have been reported in the hypothalamus (Oliet et al., 2007). These reports raise the possibility that CB1 receptor-mediated control of GABA release can be modulated up or down. However, most of the available CB1 antagonists act as inverse agonists (Kirilly et al., 2012). The observation that these compounds can increase GABA release could therefore be explained as relief from constitutive G protein-coupled receptor activity and therefore falls short of demonstrating basal occupancy of CB1 receptors by continued synthesis of eCBs.

Several other retrograde factors have been reported to modulate GABA release and lead to long-term changes in inhibitory transmission. In the ventral tegmental area, nitric oxide can be synthesized in response to high-frequency stimulation of glutamatergic afferents innervating dopaminergic cells. Nitric oxide in this system appears to trigger LTP of GABAergic transmission (Nugent et al., 2007). This phenomenon coexists with eCB-mediated iLTD in the same dopaminergic neurons (Pan et al., 2008), and these long-term changes in GABAergic signaling are modulated by drugs of abuse and D2 dopamine receptors (Nugent et al., 2007; Pan et al., 2008).

In the neonatal hippocampus, high-frequency stimulation of afferent fibers can lead to a presynaptic form of LTD of GABAergic transmission (McLean et al., 1996). The induction of this phenomenon has been attributed to $GABA_A$ receptor-mediated depolarization, leading to NMDA receptor-mediated $Ca^{2+}$ influx. Interestingly, the same conditioning stimuli resulted in LTP when NMDA receptors were blocked (Caillard et al., 1999), suggesting that different forms of plasticity can coexist. A possible mediator for LTP induction is BDNF, which can be released in an activity-dependent manner from dendrites (Kuczewski et al., 2008) and plays a role in strengthening GABAergic synapses early in development (Gubellini et al., 2005; Inagaki et al., 2008; Sivakumaran et al., 2009; Peng et al., 2010). Chronic application of BDNF to cultured neurons increases both the size and the number of GABAergic terminals (Bolton et al., 2000; Palizvan et al., 2004). Later in development, BDNF has been reported to depress GABA release (Frerking et al., 1998), and it has also been implicated in postsynaptic plasticity of $GABA_A$ receptors (see below).

Fast-spiking (FS) interneurons are thought not to express CB1 receptors. Nevertheless, trains of backpropagating action potentials in layer 2/3 pyramidal neurons in the neocortex can depress GABA release transiently at synapses made by such interneurons (Zilberter, 2000). It has been suggested that glutamate, packaged into dendritic vesicles by vGLUT3, is released

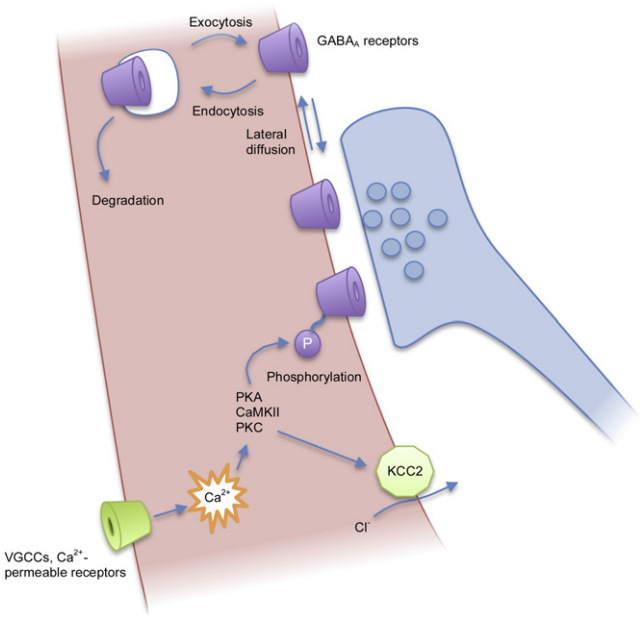


**Figure 2. Mechanisms Underlying Changes in GABA$_A$ Receptor Function**

The trafficking, lateral mobility, and phosphorylation of GABA$_A$ receptors all vary with neuronal activity, with multiple kinases implicated, resulting in either increases or decreases in GABAergic currents. Epilepsy is also associated with changes in the subunit composition of GABA receptors. The $Cl^-$ equilibrium potential can also be altered in an activity-dependent manner, principally by changes in function or trafficking of the transporter KCC2.

in an activity-dependent manner from pyramidal cell dendrites to act on presynaptic mGluRs (Harkany et al., 2004). Glutamate also acts as a retrograde factor in the induction of a transient increase in GABA release from interneuron terminals triggered by trains of action potentials in Purkinje cells, although in this case, presynaptic NMDA receptors were implicated on pharmacological grounds (Duguid et al., 2007).

## Plasticity of GABA$_A$ and Glycine Receptors Triggered by Postsynaptic $Ca^{2+}$

The postsynaptic elements of inhibitory synapses are dynamic structures (Kittler et al., 2000; Lévi et al., 2008), and several signaling cascades involving protein kinases A and C (PKA and PKC), $Ca^{2+}$/calmodulin-dependent kinase II (CamKII), and tyrosine kinases converge on GABA$_A$ receptors to regulate their splicing, subunit composition, trafficking, and phosphorylation (recently reviewed by Vithlani et al., 2011; Figure 2). Several of these cascades are themselves affected by neuronal activity, accounting, for instance, for a potentiation of GABAergic transmission reported in Purkinje cells (Kano et al., 1992). Either depression or potentiation of GABAergic synapses in the deep cerebellar nucleus can be elicited by stimulation of Purkinje cell afferents, which results in direct or rebound depolarization, with the change in synaptic strength dependent on both NMDA receptors and $Ca^{2+}$ channels (Morishita and Sastry, 1996; Aizenman et al., 1998). Similar findings have been reported in the neocortex, where action potentials in layer 5 pyramidal neurons lead to either exo- or endocytosis of GABA receptors (and LTP or LTD of GABAergic signals), with the polarity of plasticity depending on the relative contributions of L- and R-type $Ca^{2+}$ channels (Kurotani et al., 2008).

$Ca^{2+}$-permeable receptors can also trigger plasticity of GABA receptors in the absence of postsynaptic spiking. Thus, in hippocampal neurons in acute brain slices, GABA$_A$ receptor-mediated signaling can be transiently depressed by activation of α7 nicotinic receptors (Wanaverbecq et al., 2007). NMDA receptor activation also affects GABA$_A$ receptor expression in cultured neurons, with bidirectional effects that depend at least in part on the degree of activation of calcineurin (Lu et al., 2000; Marsden et al., 2007, 2010; Bannai et al., 2009; Muir et al., 2010).

Although BDNF has been implicated in retrograde signaling (see above), it also modulates GABA$_A$ receptors, with several studies reporting a rapid decrease in GABAergic currents in cultured neurons (Brünig et al., 2001; Cheng and Yeh, 2003; Jovanovic et al., 2004) or acute brain slices (Tanaka et al., 1997; Mizoguchi et al., 2003).

## Plasticity of Inhibition Dependent on Presynaptic Spiking

The different forms of plasticity of inhibitory receptors outlined above are induced by postsynaptic activity. However, induction of heterosynaptic hippocampal iLTD has been shown to require activity of target presynaptic GABAergic terminals and to depend on calcineurin, providing a potential mechanism to suppress inhibitory inputs coincident with firing of excitatory afferents (Heifets et al., 2008). Another heterosynaptic interaction requiring near-synchronous activity of excitatory and inhibitory afferents was reported in the developing frog optic tectum, where activation of presynaptic NMDA receptors on GABAergic terminals leads to LTD (Lien et al., 2006). In the rodent cerebellar cortex, on the other hand, presynaptic NMDA receptors have been implicated in a long-lasting increase in GABA release (Liu and Lachamp, 2006).

In the visual cortex, LTP of inhibitory synaptic potentials in layer 5 pyramidal neurons can be elicited by high-frequency stimulus trains (Komatsu, 1994). Pairing 50 Hz trains of action potentials in individual fast-spiking neurons with subthreshold depolarization of postsynaptic layer 4 pyramidal neurons elicits a postsynaptically expressed LTP of GABAergic transmission (Maffei et al., 2006). This phenomenon is arguably unexpected because, unlike glutamatergic synapses, GABAergic synapses are not obviously equipped with a mechanism to detect the conjunction of pre- and postsynaptic firing: opening of GABA$_A$ receptors does not on its own lead to major changes in secondary messengers when the reversal potential of the receptor is relatively negative, and GABA$_B$ receptor signaling lacks the temporal and spatial precision usually associated with synapse-specific plasticity.

A quite different form of spike-timing-dependent plasticity (STDP) is mediated by changes in the driving force for $Cl^-$ through GABA$_A$ receptors. In both neuronal cultures and in acute hippocampal slices, the conjunction of presynaptic interneuron and postsynaptic principal cell firing within a coincidence window of ±20 ms has been shown to depolarize the $Cl^-$ equilibrium potential, effectively reducing the strength of inhibition (Woodin et al., 2003) (Figure 2). Interestingly, this coexists with a decrease

in conductance mediated by $GABA_A$ receptors that emerges when the temporal difference between pre- and postsynaptic firing exceeds ±50 ms. The effect on the $Cl^-$ driving force requires postsynaptic $Ca^{2+}$ influx via L-type channels, although NMDA receptors have also been implicated in slices from adult rodents (Ormond and Woodin, 2009). The nature of the signal contributed by presynaptic firing is however poorly understood. Indeed, a change in $Cl^-$ transport can be elicited by postsynaptic spiking alone or by activation of NMDA receptors or of the BDNF receptor TrkB, mediated by downregulation of the $Cl^-$ exporter KCC2 (Wardle and Poo, 2003; Rivera et al., 2004; Fiumelli et al., 2005; Kitamura et al., 2008). Protein kinase C has been shown to regulate both the trafficking and the activity of KCC2 (Lee et al., 2007). There is also evidence for activity-dependent regulation of the $Cl^-$ importer NKCC1 by spiking alone (Brumback and Staley, 2008) or coincident pre- and postsynaptic activity at GABAergic synapses (Balena and Woodin, 2008). These forms of activity-dependent plasticity coexist with the well-documented developmental shift of $Cl^-$ reversal potential from de- to hyperpolarizing (reviewed by Ben-Ari et al., 2007; Blaesse et al., 2009).

A further layer of activity-dependent modulation of $Cl^-$ homeostasis in immature neurons involves $GABA_B$ receptors (Xu et al., 2008). And a temporally asymmetric form of spike-timing-dependent plasticity of GABAergic signaling, superficially resembling that seen at glutamatergic synapses on principal cells, has also been reported (Haas et al., 2006). Again, the mechanism of the temporal coincidence detection remains obscure.

A role for astrocytes in potentiating GABAergic signaling has also been proposed: in one study, trains of action potentials in interneurons were followed by an enhancement in spontaneous GABA release from their terminals, and this required intact $GABA_B$ receptors in neighboring atrocytes (Kang et al., 1998). Finally, evidence exists for activity-dependent plasticity of inhibition among hippocampal interneurons, but the induction and expression mechanisms remain to be determined (Patenaude et al., 2005; Evstratova et al., 2011).

## Plasticity of Excitatory Synapses on Interneurons

Early reports of LTP at glutamatergic synapses on interneurons in vivo (Buzsáki and Eidelberg, 1982; Tomasulo and Steward, 1996) were hampered by indirect methods used to attribute extracellularly recorded action potentials to unidentified interneurons. Both increases in interneuron excitability and decreases in GABAergic transmission accompany LTP of glutamatergic transmission in the hippocampus (Stelzer et al., 1994; Lu et al., 2000). However, it is not always straightforward to identify the locus of plasticity if principal cells innervating interneurons are themselves recruited synaptically (Maccaferri and McBain, 1996). It has even been argued that interneurons are ill equipped to express conventional forms of synaptic plasticity seen in pyramidal neurons (McBain et al., 1999). Their dendrites are generally devoid of spines, widely assumed to provide biochemical compartmentalization to dendritic signaling (Chen and Sabatini, 2012), and they lack $Ca^{2+}$/calmodulin-dependent kinase type IIα (CaMKIIα) (Liu and Jones, 1996; Sík et al., 1998), which is a key kinase downstream of NMDA receptor-mediated $Ca^{2+}$ influx in pyramidal neurons. However, the evidence that spines are essential for LTP is purely circumstantial, and the dendrites of many interneurons are not completely smooth. As for the essential role of CaMKIIα, this does not rule out closely related kinases or alternative biochemical cascades, which sustain LTP induction in pyramidal neurons in early postnatal hippocampus (Yasuda et al., 2003) and in dentate granule cells of mice in which CaMKIIα autophosphorylation is prevented (Cooke et al., 2006).

## LTP at Synapses on Hippocampal Interneurons in the Feedback Circuit

More direct evidence that excitatory synapses on interneurons could be persistently altered in a use-dependent manner came from targeted recordings in acute brain slices (Ouardouz and Lacaille, 1995; McMahon and Kauer, 1997; Cowan et al., 1998; Mahanty and Sah, 1998; Alle et al., 2001). Restricting attention to subsets of interneurons, consistent patterns of plasticity are beginning to emerge. Thus, LTP can be elicited in a subset of interneurons in stratum oriens (Ouardouz and Lacaille, 1995; Perez et al., 2001; Lamsa et al., 2007b; Jia et al., 2010), which can be recruited by axon collaterals of local pyramidal neurons and contribute to feedback inhibition. They include bistratified, basket, and axo-axonic cells, as well as oriens-lacunosum/moleculare (O-LM) cells. Although LTP in many of these cells can be induced by pairing presynaptic theta-burst stimulation with postsynaptic depolarization (Perez et al., 2001; Lapointe et al., 2004), it can also be triggered when the postsynaptic neuron is kept at resting membrane potential or even hyperpolarized (Lamsa et al., 2007b; Oren et al., 2009). Both induction protocols probably converge on a common cascade that depends on postsynaptic $Ca^{2+}$ signaling and mGluR1 receptors but not NMDA receptors. Roles have also been proposed for TRP channels, Src/ERK, and intracellular $Ca^{2+}$ release (Topolnik et al., 2006). LTP can also be induced by applying a group I mGluR agonist paired with hyperpolarization (Le Duigou and Kullmann, 2011). The preferential induction at relatively negative potentials is consistent with a role for inward rectifying, $Ca^{2+}$-permeable AMPA receptors (Oren et al., 2009). In keeping with an induction role for such receptors, excitatory postsynaptic currents recorded in cells exhibiting this form of plasticity show strong inward rectification and express low levels of GluA2 (Lamsa et al., 2007b; Szabo et al., 2012). Because a requirement for postsynaptic hyperpolarization is diametrically opposite to the conventional view of NMDA receptor-dependent LTP as a substrate for Hebb's postulate (Brown et al., 1988), this phenomenon has been described as ''anti-Hebbian'' LTP (Kullmann and Lamsa, 2007) (Figure 3A).

NMDA receptor-independent LTP in stratum oriens interneurons is associated with changes in trial-to-trial variability, paired-pulse ratios, failure rates (Alle et al., 2001; Perez et al., 2001; Lapointe et al., 2004), and susceptibility to a use-dependent blocker of postsynaptic rectifying AMPA receptors (Lamsa et al., 2007b), suggestive of a persistent increase in release probability. The putative retrograde messenger has not, however, been identified.

NMDA receptor-independent LTP occurs at synapses on O-LM, parvalbumin-positive basket, axo-axonic, and ivy cells, but not on CCK-positive CB1 receptor-expressing basket cells,

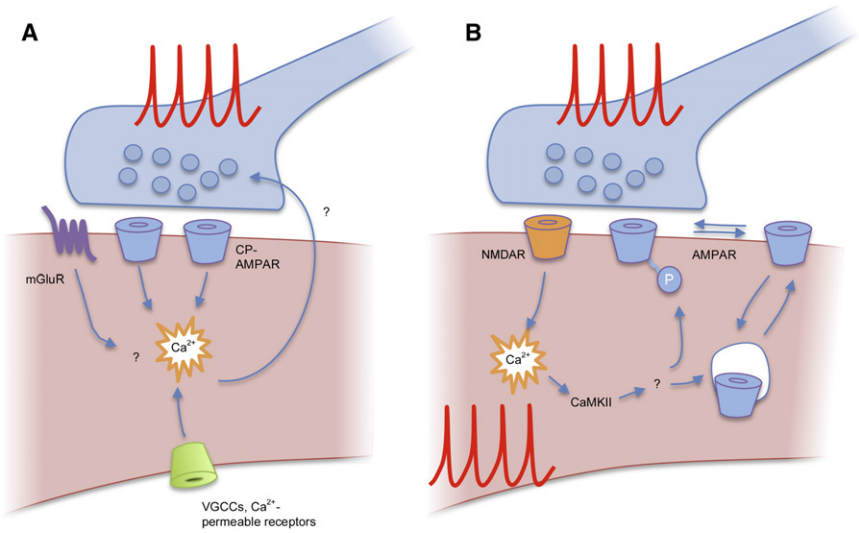


**Figure 3. LTP and LTD at Glutamatergic Synapses on Interneurons**

Both NMDAR-independent (A) and NMDAR-dependent (B) forms of plasticity occur at many glutamatergic synapses on interneurons.

(A) NMDAR-independent plasticity requires postsynaptic group I mGluRs and $Ca^{2+}$-permeable rectifying AMPARs and, at some synapses, is preferentially induced when the postsynaptic neuron is at a relatively negative potential (anti-Hebbian LTP). Other ion channels (L-type VGCCs, nicotinic receptors) can influence the balance of LTP and LTD. Although most studies have reported that expression is presynaptic, the retrograde messengers have not been conclusively identified.

(B) The conjunction of pre- and postsynaptic depolarization or activity leads to NMDAR-dependent "Hebbian" LTP at some synapses, the expression of which is likely to be postsynaptic. The relative roles of AMPAR trafficking and phosphorylation are not known. Although CaMKII$\alpha$ is absent, a related kinase is likely to play a role in NMDAR-dependent LTP.

while synapses on bistratified neurons are persistently depressed by similar induction stimuli (Lamsa et al., 2007b; Nissen et al., 2010; Szabo et al., 2012). Strikingly, LTP is restricted to the pathway that was stimulated during the induction protocol, suggesting a role for micron-scale $Ca^{2+}$ compartmentalization in relatively aspiny dendrites (Goldberg and Yuste, 2005; Castillo and Khodakhah, 2006; Topolnik et al., 2009).

## Plasticity in Hippocampal Interneurons in the Feedforward Pathway

Both NMDA receptor-dependent LTP (Figure 3B) and NMDA receptor-independent LTD occur at synapses made by Schaffer collaterals on interneurons in stratum radiatum or stratum pyramidale (McMahon and Kauer, 1997; Cowan et al., 1998; Wang and Kelly, 2001; Lamsa et al., 2005). These cells have not, in general, been classified systematically and probably include several different types.

The induction and expression properties of LTP at Schaffer collateral synapses are similar in most respects to those of LTP in principal cells (Wang and Kelly, 2001; Lamsa et al., 2005), although CaMKII$\beta$ may play the role of the $\alpha$ isoform (Lamsa et al., 2007a). As for LTD induction, this is insensitive to the postsynaptic membrane potential and independent of NMDA receptors but requires intact group I mGluR and postsynaptic $Ca^{2+}$ signaling and is accompanied by changes in trial-to-trial variability suggestive of presynaptic expression (McMahon and Kauer, 1997; Gibson et al., 2008). It has also been reported to spread to nonstimulated synapses. Presynaptic TRPV1 channels have been implicated as receptors for a retrograde factor, mimicked by the endogenous eicosanoid 12-(S)-HPETE (Gibson et al., 2008). However, TRPV1 is not abundant in intrinsic hippocampal neurons (Cavanaugh et al., 2011). Another signaling cascade coexists, leading from postsynaptic mGluR5s to long-lasting depression of glutamate release from Schaffer collaterals independently of either TRPV1 or CB1 receptors (Le Duigou et al., 2011; Edwards et al., 2012).

Both LTP and LTD also occur at synapses made by mossy fibers (the axons of dentate granule cells) on dentate basket cells or interneurons in CA3 (Laezza et al., 1999; Alle et al., 2001; Lei et al., 2003; Laezza and Dingledine, 2004; Lei and McBain, 2004; Galván et al., 2008; Sambandan et al., 2010). Here too, either $Ca^{2+}$-permeable AMPA receptors or NMDA receptors are required at different synapses, and multiple forms of plasticity coexist: stimuli that normally induce NMDA receptor-independent LTP result in LTD when mGluR1 receptors are blocked (Galván et al., 2008) or when postsynaptic spiking is prevented during tetanic stimulation (Alle et al., 2001). Conversely, activity-dependent internalization of presynaptic mGluR7 receptors has been suggested to underlie a metaplastic switch from LTD to LTP (Pelkey et al., 2005). Pre- and postsynaptic intracellular signaling cascades at many glutamatergic synapses innervating interneurons are thus finely balanced and can be tipped toward one form of plasticity or the other depending on the state of the neuron and, presumably, the precise conjunction of pre- and postsynaptic activity.

## LTP and LTD in Interneurons of the Amygdala, Striatum, Neocortex, and Brainstem

Although much of what we know of plasticity of inhibition has emerged from studies in the hippocampus, related forms of plasticity have been reported in several other regions of the mammalian brain.

LTP in interneurons dependent on $Ca^{2+}$-permeable AMPA receptors was first described in the amygdala (Mahanty and Sah, 1998), where it is restricted to interneurons that express NMDA receptors lacking NR2B subunits, although $Ca^{2+}$ influx via these receptors appears not to contribute to plasticity (Polepalli et al., 2010). In contrast to NMDA receptor-independent plasticity in the hippocampus, the locus of expression of LTP in these cells appears to be postsynaptic.

In the striatum, several interneurons have been shown to express STDP at synapses made by cortical glutamatergic afferents (summarized in Fino and Venance, 2011). In FS interneurons, for example, NMDA receptor-dependent LTP was elicited when the presynaptic action potential preceded the postsynaptic spike and LTD when the order was reversed (Fino et al.,

2008). This STDP rule is thus broadly similar to that seen in neocortical pyramidal cells.

In FS interneurons of the somatosensory cortex, in contrast, one study reported mGluR-dependent LTD whether the presynaptic spike preceded or followed the postsynaptic spike (Lu et al., 2007). A similar pattern was observed at intracortical glutamatergic synapses on regular-spiking interneurons in barrel cortex (Sun and Zhang, 2011). mGluR5 receptors also play a central role in NMDA-independent LTP of excitatory postsynaptic potentials in FS interneurons of the visual cortex (Sarihi et al., 2008). In contrast, low-threshold spiking cells in the same cortical area exhibit both NMDA receptor-dependent LTP with a "pre before post" protocol and mGluR-dependent LTD when the spike order is reversed. A further form of LTP induced by theta-burst stimulation has been reported in somatostatin-positive neocortical interneurons, which is insensitive to manipulation of postsynaptic $Ca^{2+}$ channels or NMDA receptors and may therefore not involve postsynaptic signaling at all (Chen et al., 2009). At synapses made by layer 2/3 pyramidal neurons on bitufted interneurons in rat neocortex, postsynaptic action potentials have been reported to lead to a $GABA_B$ receptor-dependent persistent depression of glutamate release (Zilberter et al., 1999). This finding raises the possibility that GABA released from dendrites could act as a retrograde messenger.

Another layer of complexity was revealed in the somatosensory cortex where homo- or heterotypic pairs of synaptically coupled FS and somatostatin-positive interneurons exhibit distinct short-term plasticity properties (Ma et al., 2012). Further supporting the principle of circuit-wide plasticity in interneuron assemblies, LTD has been observed at electrical synapses in pairs of burst firing interneurons in the thalamic reticular nucleus (Haas et al., 2011).

Finally, eCB-dependent LTD of EPSCs in GABAergic cells has been reported in the brainstem, where it coexists with NMDA receptor-dependent plasticity (Tzounopoulos et al., 2007).

Although the above catalog of synaptic plasticity in interneurons reveals extensive diversity, two important methodological issues must be borne in mind. First, a consistent classification of interneuron types has yet to be agreed, and so the data sets reported in different studies are not necessarily comparable. And second, there is a wide variability in species and strains, recording temperatures, stimulation protocols, and electrophysiological methods used by different laboratories. Indeed, LTP is difficult to elicit in some interneurons when recording in whole-cell mode but can be elicited reliably when recording with the perforated-patch method that minimizes disruption of the cytoplasm (see, for instance, Lamsa et al., 2005).

## Other Forms of Plasticity of Inhibition

This Review focuses mainly on activity-dependent changes in synaptic strength. Much less well understood is plasticity of intrinsic excitability of interneurons. An example of this phenomenon has been reported in fast-spiking interneurons of the somatosensory cortex, whose excitability decreases after whisker trimming, a model of chronic sensory deprivation (Sun, 2009). Structural changes in inhibitory pathways have also been reported. Thus, both fear conditioning and spatial learning are accompanied by extensive changes in the density of filopodial synapses made by hippocampal mossy fibers on dentate hilar interneurons, suggesting a role for feedforward inhibition in some aspects of memory (Ruediger et al., 2011).

## Adaptive Roles of Plasticity of Inhibition

Given the diversity of plasticity of inhibition summarized above, it is difficult to propose a unifying theoretical framework to explain its adaptive significance. Nevertheless, several roles can be suggested on teleological grounds.

During development, strengthening of GABAergic synapses in response to postsynaptic activity (McLean et al., 1996; Caillard et al., 1999; Xu et al., 2008) may represent a tuning of inhibition to counteract overexcitation of target neurons. In keeping with this expectation, experimental suppression of activity in neuronal culture results in loss of $GABA_A$ receptors (Kilman et al., 2002). In the developing auditory brainstem, use-dependent plasticity of inhibition occurs in parallel with a switch from GABAergic to glycinergic signaling at several synapses (reviewed by Sanes and Kotak, 2011). In the visual cortex, reinforcement of GABAergic synapses increases lateral inhibition, which contributes to the formation of ocular dominance columns (reviewed by Hensch, 2005).

A closer look at the spatiotemporal profile of excitation and inhibition in the mature neocortex reveals that feedforward inhibition and direct excitation of principal neurons in target structures are closely matched (Wehr and Zador, 2003; Priebe and Ferster, 2005; Okun and Lampl, 2008). This calls for a mechanism for fine adjustment of inhibition to achieve "detailed balance" (Vogels and Abbott, 2009) (Figure 4). A recent computational model (Vogels et al., 2011) illustrates how this might be established and even store memories when embedded in a recurrent network. This relies on a symmetrical STDP rule that leads to LTP of inhibition when a feedforward interneuron fires within ±25 ms of the postsynaptic cell but LTD at larger intervals, which comes close to, but does not coincide with, some experimentally determined forms of plasticity (e.g., Woodin et al., 2003; Maffei et al., 2006).

Pairing-dependent LTP at GABAergic synapses between fast-spiking interneurons and star pyramidal cells in the visual cortex is occluded by monocular visual deprivation (Maffei et al., 2006). Because these interneurons participate in feedback inhibition, this may reflect a mechanism to limit local amplification of activity or to sharpen opponent or lateral inhibition (Maffei and Turrigiano, 2008; Yazaki-Sugiyama et al., 2009). Indeed, the modifiability of GABAergic neurons to monocular deprivation has even been shown to exceed that of excitatory cells in certain conditions (Kameyama et al., 2010). Excitatory inputs to GABAergic neurons also undergo rapid structural plasticity after focal retinal lesions, as does the density of GABAergic boutons (Keck et al., 2011).

Although equivalent data are not available in the somatosensory cortex, whisker trimming has been shown to facilitate LTD of glutamatergic synapses elicited by an STDP protocol in regular-spiking interneurons (Sun and Zhang, 2011). Recent in vivo imaging has also revealed extensive structural plasticity of GABAergic synapses affected by whisker trimming (Chen et al., 2012; van Versendaal et al., 2012).

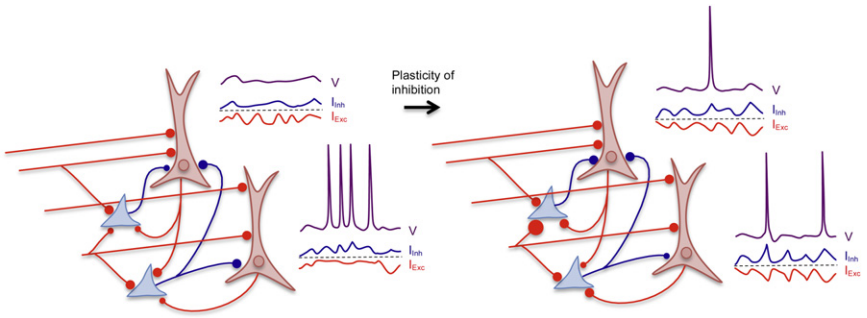


**Figure 4. A Possible Developmental Role of Plasticity of Inhibition**

Plasticity of inhibition is likely to contribute to the emergence of balanced excitation (blue) and inhibition (red) observed in many feedforward projections in the CNS. Maturation of such circuits is associated with a gradual shift away from burst firing of principal cells toward a sparse-firing regime in which excitatory and inhibitory currents are temporally correlated (indicated schematically as inward and outward currents, $I_{Exc}$ and $I_{Inh}$). Such a redistribution of inhibition of principal cells may be achieved by changes in both glutamatergic synapses on interneurons and GABAergic synapses on pyramidal neurons (indicated schematically as changes in bouton size). Several other computational roles have been proposed for plasticity of inhibition, including refinement of lateral inhibition or temporal discrimination, release from inhibition mediated by CCK-positive interneurons, and habituation to sensory inputs.

If LTP at glutamatergic synapses on principal cells were not accompanied by an enhancement of inhibition, interneuron-dependent functions such as the temporal precision of information processing should be degraded. A similar rule applies to the hippocampus, where the ability to detect temporal coincidences depends on feedforward inhibition and can be studied by measuring action potential generation in CA1 pyramidal neurons in response to asynchronous stimulation of converging Schaffer collaterals (Pouille and Scanziani, 2001). When LTP was restricted to Schaffer collateral synapses on pyramidal neurons, a degradation of this ability was confirmed (Lamsa et al., 2005). The fidelity of temporal coincidence detection was restored when NMDA receptor-dependent LTP was induced not only in the pyramidal neuron, but also at synapses on interneurons in the feedforward pathway. Carvalho and Buonomano (2009) examined the behavior of a similar feedforward circuit to argue that while plasticity of monosynaptic excitation of target cells can only alter gain, plasticity of inhibition could change both gain and offset, thus increasing computational flexibility.

The possible roles of NMDA receptor-independent plasticity at principal cell synapses on interneurons are open to wide speculation, not least because of discordant evidence on the need for postsynaptic depolarization or hyperpolarization for induction. Nevertheless, with some exceptions, LTP dominates in the feedback loop and LTD in the feedforward pathway. Taking into account the characteristic firing patterns of identified interneurons and pyramidal cells in different brain states, anti-Hebbian LTP in the feedback loop might play a role in dynamically reconfiguring cell assemblies participating in oscillations (Kullmann and Lamsa, 2007). Plasticity at mossy fiber synapses on fast-spiking interneurons in the dentate gyrus is facilitated by synchronous afferent input in the perforant path, and so this form of plasticity is associative, suggesting a role in maintaining sparse activity of granule cells (Sambandan et al., 2010).

As for DSI, this is most prominently expressed at perisomatic synapses made by CCK-positive basket cells. These cells are thought to complement fast-spiking parvalbumin-positive basket cells, which synchronize principal cells during gamma rhythms. They express several receptors for neuromodulators released by subcortical afferents (Freund and Katona, 2007). DSI may therefore represent a "release" from such modulatory influences after intense principal cell firing. iLTD has also been proposed to have a metaplastic role, facilitating the subsequent induction of LTP at glutamatergic synapses (Chevaleyre and Castillo, 2004).

In *Drosophila*, a role for plasticity of feedback inhibition has been proposed in the habituation to specific odors (Das et al., 2011; Sudhakaran et al., 2012). Local circuit interneurons in the antennal lobe regulate the excitation of projection neurons, and a persistent enhancement of GABA release at a subset of their terminals differentially modulates the behavioral response to different odors. NMDA receptors in the projection neurons are proposed to act as detectors of persistent activity in odorant-specific glomeruli, leading to the recruitment of synapsin at GABAergic interneuron synapses via the release of an as-yet-unknown diffusible factor.

Finally, plasticity of $GABA_A$ receptors may play a role in changes in excitability of layer 5 pyramidal neurons, depending on arousal state. Different membrane potential excursions as occur during slow-wave sleep and wakefulness alter the relative contributions of different $Ca^{2+}$ channels that bidirectionally modulate $GABA_A$ receptor trafficking (Kurotani et al., 2008).

## Possible Maladaptive Roles of Plasticity of Inhibition

Given the involvement of inhibition in all aspects of brain function, it is not surprising that changes in GABAergic signaling, and interneuron structure and function, have been reported in many pathological states, including schizophrenia (Lewis et al., 2012), autism (Chao et al., 2010; Pizzarelli and Cherubini, 2011), affective disorders (Brambilla et al., 2003; Möhler, 2012), and fragile X syndrome (Olmos-Serrano et al., 2010). Deficits in cognitive functions in Down syndrome have also been attributed in part to altered inhibition, and chronic partial blockade of $GABA_A$ receptors with picrotoxin at subconvulsant doses ameliorates some behavioral deficits in a mouse model (Fernandez et al., 2007).

$GABA_A$ receptor plasticity has an important and potentially maladaptive role in status epilepticus, in which desensitization and internalization are thought to contribute to a progressive loss of effect of benzodiazepine anticonvulsants (Kapur and Coulter, 1995; Kapur and Macdonald, 1997; Brooks-Kayal et al., 1998). In the longer term, several $GABA_A$ receptor subunits undergo changes in expression, and $\alpha 5$ subunits in particular undergo a robust downregulation (Houser and Esclapez, 2003). This subunit contributes to tonic inhibition at intermediate ambient GABA concentrations. Although a loss of tonic inhibition

might be expected (and to contribute to epileptogenesis after severe seizures), compensation by other subunits has been reported (Scimemi et al., 2005). Changes in subunits contributing to tonic inhibition, as well as in progesterone metabolites acting on these subunits, also occur during the estrus cycle, possibly contributing to catamenial dysphoric symptoms and changes in susceptibility to seizures (Maguire et al., 2005). Several other forms of plasticity of inhibition in epilepsy have been reviewed by Fritschy (2008). Altered inhibition has also been reported in other disorders including pain sensitization (Sivilotti and Woolf, 1994) and opiod addiction (Nugent et al., 2007). In many of these disorders, however, it is difficult to disentangle a pathogenic role of the primary alteration in inhibition from a compensatory effect.

## Conclusions

Despite the absence of an obvious local coincidence detector at GABAergic synapses, abundant forms of inhibitory plasticity have emerged. The computational roles of these phenomena are likely to go far beyond mere stabilization of brain excitability. Indeed, the psychotropic effects of recreational CB1 agonists hint that modifying GABAergic signaling has extensive consequences for many cognitive and vegetative functions. Whether and how the numerous forms of inhibitory plasticity can be harnessed for therapeutic purposes represents a challenge for further work.

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