Inhibitory circuits in the brain rely on GABA-releasing interneurons. For long, inhibitory circuits were considered weakly plastic in the face of patterns of neuronal activity that trigger long-term changes in the synapses between excitatory principal cells. Recent studies however have shown that GABAergic circuits undergo various forms of long-term plasticity. For the purpose of this review, we identify three major long-term plasticity expression sites. The first locus is the glutamatergic synapses that excite GABAergic inhibitory cells and drive their activity. Such synapses, on many but not all inhibitory interneurons, exhibit long-term potentiation (LTP) and depression (LTD). Second, GABAergic synapses themselves can undergo changes in GABA release probability or postsynaptic GABA receptors. The third site of plasticity is in the postsynaptic anion gradient of GABAergic synapses; coincident firing of GABAergic axons and postsynaptic neurons can cause a long-lasting change in the reversal potential of GABA_A receptors mediating fast inhibitory postsynaptic potentials. We review the recent literature on these forms of plasticity by asking how they may be triggered by specific patterns of pre- and postsynaptic action potentials, although very few studies have directly examined spike-timing dependent plasticity (STDP) protocols in inhibitory circuits. Plasticity of interneuron recruitment and of GABAergic signaling provides for a rich flexibility in inhibition that may be central to many aspects of brain function. We do not consider plasticity at glutamatergic synapses on Purkinje cells and other GABAergic principal cells.

**Keywords:** interneuron, GABA, fast-spiking, oscillation, chloride, NKCC1, KCC2

**PLASTICITY IN EXCITATORY AFFERENTS OF INHIBITORY CIRCUITS**

Long-term potentiation (LTP) and depression (LTD) of glutamatergic synapses onto GABAergic interneurons has been discovered in several areas of the brain suggesting that plasticity in this locus is common in the CNS. Although these studies have concentrated heavily on the circuits of the hippocampal formation, there is evidence that similar plasticity takes place in the neocortex (Sah et al., 2008, Chen et al., 2009), as well as in striatum (Fino et al., 2008, 2009) and amygdala (Mahanty and Sah, 1998). In addition there are reports on analogous long-term plasticity in the spinal cord (Santos et al., 2009) and in sensory pathways (Tzounopoulos et al., 2004).

**PLASTICITY IS SPECIFIC TO GABAergic INTERNEURON TYPE**

One of the striking features of plasticity in this locus is that it can be highly specific to an interneuron type (Kullmann and Lambsa, 2007; Sah et al., 2008; Oren et al., 2009; Nissen et al., 2010). Subpopulations of unidentified interneurons may show LTP, LTD or no plasticity at all, for stimulation of the same afferent glutamatergic pathway (Buzsáki and Eidelberg, 1982; Lei and McBain, 2004; Lambsa et al., 2007a). Recent studies on identified interneurons in the hippocampus have revealed that these subpopulations are composed of anatomically distinct interneuron types. Plasticity has been shown to be consistent in individual anatomically identified GABAergic cell types (Alle et al., 2001; Oren et al., 2009; Nissen et al., 2010). More importantly, plastic properties can vary remarkably between two interneurons located in close proximity in the same hippocampal area, but showing different neurochemical marker expression or different axon distribution (Lambsa et al., 2007b; Nissen et al., 2010) (Figure 1). A specific pattern of pre- and postsynaptic activity that induces plasticity in one interneuron type can fail or elicit a different plastic change in another interneuron type located in the same layer (Lambsa et al., 2005, 2007b; Nissen et al., 2010).

These findings, that the interneuron plasticity is diverse and cell type-specific, have important impacts on the dynamics of the cortical networks. First, specific patterns of pre- and postsynaptic action potentials are capable of triggering plasticity in only a sub-population of inhibitory cells (Lambsa et al., 2005, 2007b). Second, plasticity is likely to be induced in different brain states in distinct interneuron types. It has been shown that the activity of interneurons and their glutamatergic afferents is highly specific to a cell type during neuronal oscillations related to different behavioral states (Klausberger and Somogyi, 2008). It is therefore tempting to speculate that the distinct forms of LTP and LTD discovered in interneurons in vitro might underlie the use-dependent dynamics reported in selective parts of the inhibitory networks in vivo (Buzsáki and Eidelberg, 1982; Csicsvari et al., 1998; Yazaki-Sugiyama et al., 2009). Several important questions remain to be answered on plasticity in interneurons and one of the most intriguing is related to the
physiological activity patterns that might generate cell type-specific plasticities in vivo. To answer this question it will be important to reveal spike-timing dependent plasticity (STDP) properties of common cortical interneuron types and their identified glutamatergic afferents (Klausberger and Somogyi, 2008).

Given that GABAergic interneuron diversity is rich in many areas of the brain and full identification of cells is often challenging, it is understandable that STDP has not yet been extensively studied among GABAergic interneuron types. Instead, most of these studies relatively robust extracellular stimulation protocols have been used. However, the major purpose of these pioneering studies has been to investigate a capacity for synaptic plasticity in inhibitory interneurons in distinct areas (Buzsaki and Eidelberg, 1982; Perez et al., 2001; Lei and McBain, 2004; Lamsa et al., 2005, 2007b; Galvan et al., 2008; Sarihi et al., 2008). Hebbian plasticity may even occur in the human motor cortex (Russmann et al., 2009). However, different studies have applied distinct patterns of presynaptic stimulation (high-frequency tetanization, ‘theta-burst’ or low-frequency stimulation), and have either allowed the postsynaptic neurons to be depolarized by the activated synapses, or have imposed action potentials via the recording pipette. It is therefore difficult to compare among studies. Nevertheless, some striking differences are emerging, both between LTD in interneurons and in principal cells, and among different interneurons.

**NMBA receptor-dependent LTD**

‘Hebbian’ LTD in pyramidal neurons is generally explained by the involvement of NMDA receptors, which require both presynaptic glutamate release and postsynaptic depolarization for their activation, and which trigger postsynaptic 
Ca$^{2+}$ influx and downstream activation of calcium/calmodulin-dependent kinase II$\alpha$ (CaMKII$\alpha$). NMDA receptor-dependent LTD with very similar properties can be elicited at synapses made by Schaffer collaterals on a subset of interneurons in stratum radiatum of the rodent hippocampus (Lamsa et al., 2005). This phenomenon can be elicited by delivering postsynaptic depolarizing steps synchronously with low-frequency presynaptic stimulation, or by delivering a continuous postsynaptic depolarization to allow the presynaptic stimuli to evoke postsynaptic spiking. However, a pre- before post-protocol has not been explicitly tested. Although this shares many features with LTD in pyramidal neurons, including sensitivity to pharmacological blockers of CaMKII$\alpha$ (Lamsa et al., 2007a), it exhibits one striking difference: LTD is intact in mice harboring a mutation that prevents autophosphorylation of CaMKII$\alpha$, which has a profound deficit in NMDA receptor-dependent LTD in pyramidal neurons (Giese et al., 1998). This is perhaps unsurprising, because CaMKII$\alpha$ has not been detected in interneurons, so the result of the pharmacological intervention suggests the involvement of another member of the calcium/calmodulin-dependent kinase family.
Non-NMDA receptor-dependent LTP

At many other synapses on interneurons, pharmacological blockade of NMDA receptors fails to prevent LTP induction. Postsynaptic chelation of Ca\(^{2+}\) is however effective (Alle et al., 2001; Perez et al., 2001), implying a critical role for Ca\(^{2+}\) which must enter the neuron from another source or be released from intracellular stores. Several studies have demonstrated an essential role for Ca\(^{2+}\)-permeable AMPA receptors (Mahanty and Sah, 1998; Lamsa et al., 2007b; Oren et al., 2009). A striking feature of such receptors, which are devoid of edited GluA2 subunits, is that they exhibit inward rectification, preferentially allowing Ca\(^{2+}\) influx at relatively negative potentials. Remarkably, LTP at synapses exhibiting strong inward rectification can be induced by pairing presynaptic action potentials with postsynaptic hyperpolarization. This phenomenon has been termed 'anti-Hebbian LTP' (Lamsa et al., 2007b; Oren et al., 2009; Nissen et al., 2010). It is most readily observed at synapses formed by axon collaterals of pyramidal neurons on interneurons in the feedback circuit in stratum oriens of the hippocampus, in particular (although not exclusively) in oriens lacunosum-moleculare (O-LM) cells, which have dendrites extending parallel to stratum pyramidale and an axon extending to stratum lacunosum-moleculare (McBain et al., 1994). Although STDP protocols have not been explored in detail, this form of LTP can be elicited by delivering presynaptic stimuli at the trough, but not at the peak, of a 5-Hz sinusoidal membrane potential oscillation delivered via the postsynaptic pipette.

An essential role for group I metabotropic glutamate receptors (mGluRs) has also been demonstrated in LTP (and LTD) induction in interneurons (Perez et al., 2001; Lapointe et al., 2004; Galvan et al., 2008; Gibson et al., 2008). Although many studies are difficult to compare because they have examined different brain regions, group I mGluR-dependent LTP has also been most extensively examined in O-LM cells. Indeed, these interneurons have abundant mGluR1\(\alpha\), but also exhibit marked rectification of their synaptic AMPA receptors (Ferraguti et al., 2004; Oren et al., 2009). LTP at synapses made on O-LM cells by axon collaterals of local pyramidal neurons can be induced either with Hebbian or with anti-Hebbian protocols, and is sensitive to pharmacological blockade of either Ca\(^{2+}\)-permeable AMPA receptors or group I mGluRs (Perez et al., 2001; Oren et al., 2009). Although both group I mGluR subtypes (mGluR1 and mGluR5) are linked to Ca\(^{2+}\), albeit via different cascades (Topolnik et al., 2005), how they interact with Ca\(^{2+}\) signaling triggered by AMPA receptor activation remains to be determined. LTP in stratum oriens interneurons can, furthermore, be facilitated by co-activation of nicotinic acetylcholine receptors (Jia et al., 2010).

An additional role for L-type Ca\(^{2+}\) channels in induction of NMDA receptor-independent LTP has been reported in interneurons in stratum lacunosum-moleculare, at synapses made by mossy fibers (Galvan et al., 2008). This phenomenon was elicited by high-frequency stimulation of presynaptic axons while allowing the postsynaptic neurons to fire. Here too, pharmacological dissection has revealed an essential role for mGluR1, blockade of which converted LTP into LTD. LTP however occurred at synapses with Ca\(^{2+}\)-impermeable AMPA receptors, and was blocked by postsynaptic Ca\(^{2+}\) chelation or interference with intracellular Ca\(^{2+}\) stores.

In subtle contrast to LTP at mossy fiber synapses on interneurons in stratum lacunosum-moleculare of the hippocampus, Sarihi et al. (2008) found that LTP in fast-spiking in layer II/III interneurons of the visual cortex, elicited by theta-burst stimulation, depended on mGluR5, but not mGluR1, and that L-type Ca\(^{2+}\) channels were not involved. Nevertheless, this form of LTP was again independent of NMDA receptors, but was prevented by chelating postsynaptic Ca\(^{2+}\).

Unraveling how the different glutamate receptors and other sources of Ca\(^{2+}\) interact in LTP induction will require further work. Among possible factors influencing the outcome of different induction protocols is the method used to record from neurons: some studies resorted to perforated patch recordings to minimize disruption of the cytoplasm, but this approach renders voltage-clamping difficult, and prevents the routine introduction of markers for histological characterization (Kullmann and Lamsa, 2007). Furthermore, grouping together interneurons on the basis of their location or firing characteristics probably hides considerable diversity of subtypes (Klausberger and Somogyi, 2008).

Relatively little attention has thus far been given to the LTP expression mechanisms that maintain potentiation of synaptic transmission. NMDA receptor-dependent LTP in some interneurons appears not to be accompanied by changes in short-term plasticity (paired-pulse ratio), providing no evidence for an increase in presynaptic glutamate release probability (Lamsa et al., 2005). This phenomenon is therefore most simply explained by a postsynaptic insertion of AMPA receptors, much as has been reported for NMDA receptor-dependent LTP in pyramidal neurons. LTP dependent on group I mGluRs and Ca\(^{2+}\)-permeable AMPA receptors, on the other hand, has been shown at several synapses to be accompanied by changes in paired-pulse ratio, failure rates, trial-to-trial fluctuations, or sensitivity to use-dependent blockers of Ca\(^{2+}\)-permeable receptors (Perez et al., 2001; Oren et al., 2009). All of these observations point instead to an increase in presynaptic glutamate release (see also Alle et al., 2001; Galvan et al., 2008), implying the existence of a retrograde factor, the identity of which remains to be determined.

Another form of tetanic LTP at synapses on somatostatin-positive interneurons in the neocortex appears to be exclusively presynaptic, in that it does not depend on postsynaptic Ca\(^{2+}\) signaling (Chen et al., 2009). Instead, it depends on protein kinase A and therefore shares mechanisms in common with tetanus-induced mossy fiber LTP.

LTD

At several other synapses, LTD has been reported more robustly than LTP (Maccabber et al., 1998; Laezza et al., 1999; Laezza and Dingledine, 2004). However, at least two forms of LTD have emerged. At synapses made by hippocampal mossy fibers equipped with calcium-impermeable AMPARs and NMDA receptors, high-frequency presynaptic stimulation leads to depression, which appears to share mechanisms with NMDA receptor-dependent LTD at glutamatergic synapses on pyramidal neurons (Lei and McBain, 2004). At other synapses equipped with rectifying AMPA receptors, similar stimuli trigger a form of LTD that is sensitive to postsynaptic Ca\(^{2+}\) chelation or blockade of group III mGluRs, and which appears to be expressed presynaptically. Synapses made
by hippocampal mossy fibers can express both forms of plasticity although it remains to be determined to what extent the identity of the postsynaptic neurons determine the outcome of the pairing protocol. Importantly, the somata of the mossy fiber-LTD expressing interneurons are located in a different layer (mainly strata lucidum and radiatum) than the mossy fiber-LTP interneurons reported by Galvan et al. (2008) (stratum lacunosum-moleculare) and described earlier in this review. Interestingly, synapses where mGluR-dependent LTD has been elicited can be rendered capable of subsequent potentiation with repeated rounds of high-frequency stimulation (Pelkey et al., 2005). This phenomenon has been related to internalization of mGluR7, which plays a key role in triggering the initial depression.

High-frequency stimulation of Schaffer collaterals has also been shown to induce a form of NMDA receptor-independent LTD at interneurons in stratum radiatum (McMahon and Kauer, 1997). This too appears to be expressed presynaptically, and depends on mGluR1 receptors (Gibson et al., 2008). Interestingly, the phenomenon is also sensitive to manipulation of TRPV1 receptors, suggesting that these channels may act as presynaptic receptors for a retrograde messenger.

**STDP at excitatory synapses on interneurons**

STDP protocols have not been tested systematically at all the synapses where LTD or LTP can be elicited. However, the patterns that are beginning to emerge from published studies of STDP suggest that multiple mechanisms interact to determine the outcome of the pairing, and that the relative importance of these mechanisms differs extensively among synapses. In a study of layer 2/3 interneurons of the somatosensory cortex, low-frequency pairing delivered with various pre-post intervals exclusively yielded LTD in fast-spiking cells, which could be prevented by postsynaptic Ca2+ chelation or broad-spectrum blockade of mGluRs (Lu et al., 2007). However, in the dorsal cochlear nucleus, presynaptic spikes delivered 8 ms before postsynaptic depolarization led to NMDA receptor-dependent LTD in low-threshold-spiking interneurons (Tzounopoulos et al., 2004). This work has shown that the outcome of pairing presynaptic action potentials with postsynaptic depolarization depends both on the repetition rate and on the spike-EPSP interval. A protocol that generally yields LTD in principal cells (pre before post) appears to engage both postsynaptic cannabinoid-dependent LTD and postsynaptic CaMKII-dependent LTD in ‘cartwheel’ interneurons. STDP in striatal NOS-positive interneurons is equally puzzling, with pairing leading to LTD for most intervals between the presynaptic spike and the postsynaptic depolarization, and LTD only elicited when the postsynaptic depolarization is delivered approximately 40 ms after the spike (Fino et al., 2009).

**Glutamatergic afferent plasticity in network function**

A key feature of the plasticity in this locus is that it allows afferent-specific modulation of the inhibitory circuit. This means that a potentiated excitatory pathway has an increased contribution to firing of the inhibitory cell and consequently to the disynaptic inhibition of the GABAergic neurons’ target cells (Nissen et al., 2010). This is important because during cortical network oscillations, which provide spatiotemporal framework for information processing, synchronized cell assembly formation must be dynamic. Accordingly, the synaptic strengths between pyramidal cells and inhibitory interneurons must change in behaviorally relevant time scales (Csicsvari et al., 1998). Plasticity at glutamatergic afferents onto interneurons is a good candidate mechanism for maintaining the necessary flexibility in these connections during the formation or dissolution of cell assemblies.

In a recent study Yazaki-Sugiyama et al. (2009) demonstrated that inhibitory circuits of fast-spiking interneurons express robust use-dependent plasticity in the visual cortex by visual experience. By modeling a cortical circuit the authors conclude that the plasticity either locates in excitatory afferents onto PV+ inhibitory cells or in the GABAergic synapses made by these cells onto pyramidal cells. Interestingly, PV+ fast-spiking interneurons have recently been demonstrated to express robust LTP in the visual cortex and in the hippocampus (Lamsa et al., 2007b; Sarihi et al., 2008; Nissen et al., 2010).

**LASTING PLASTICITY OF GABAergic SYNAPSES IS ROBUST AT EARLY DEVELOPMENTAL STAGES**

Long-lasting potentiation or depression of inhibitory synapses has also been reported in many areas of the brain. However, unlike plasticity at glutamatergic synapses reviewed above, LTP in hippocampal GABAergic synapses is almost exclusively restricted to early developmental stages (Gaiarsa et al., 2002). Yet, GABAergic LTP can be induced also in mature hippocampal circuits by certain extracellular stimulation patterns (such as theta-burst high-frequency stimulation) but even in these cases LTP is smaller than in neonatal synapses (Paternaude et al., 2003, 2005). In neonatal hippocampus and in some areas of juvenile neocortex both LTP and LTD of GABAergic synapses are triggered by processes that depend on postsynaptic Ca2+ and involve either activation of NMDARs or voltage-gated calcium channels (VGCCs) (Holmghen and Zilberter, 2001; Haas et al., 2006). Interestingly, GABAergic LTP and LTD in neonatal hippocampus are expressed presynaptically (Caillard et al., 1999a,b; Guléllini et al., 2005) whereas LTD (and LTP) in mature hippocampus is postsynaptic (Stelzer et al., 1994; Lu et al., 2000; Patenaude et al., 2003; Maffei et al., 2006). In the visual cortex expression of LTP and LTD is also developmentally regulated (Maffei et al., 2006) and similar to hippocampus GABAergic LTP is less likely in mature animals (Komatsu, 1994). However, the expression site for the plasticity in the visual cortex is always postsynaptic, which suggests that the LTP is probably different from that described in the neonatal hippocampus. Induction of plasticity in GABAergic synapses with STDP protocols has been tested in a small number of studies only. In GABAergic synapses of juvenile rat entorhinal cortex, a pre-post-spiking sequence triggers LTP and a post-pre sequence elicits LTD. STDP plasticity of GABAergic synapses has also been demonstrated in GABAergic synapses in the Xenopus retino-tectal system during early development, where coincident pre- and post-activity leads to LTD (Lien et al., 2006). Interestingly in mature hippocampus STDP protocol induces mainly ionic shift plasticity, and changes in GABA release probability or postsynaptic receptor activity are negligible (Woodin et al., 2003).

In some GABAergic synapses a short or long-term suppression of GABA release can be triggered by postsynaptic activity without a specific requirement for presynaptic firing. Because many
of these plasticity forms such as cannabinoid receptor-mediated LTP characteristically affect transmission in a large number of local GABAergic synapses without recognizing presynaptic terminal activity history, they are not reviewed any further here. This type of GABAergic synapse modulation has been reviewed recently elsewhere (Nugent and Kauer, 2008; Heifets and Castillo, 2009; McBain and Kauer, 2009).

Altogether, plasticity at the site of GABAergic synapses provides a powerful modulation mechanism of neuronal networks in particular during the development of cortical circuits. However, more knowledge on the plasticity in this locus especially concerning STDP and GABAergic cell type-specificity would be needed to understand its role widely in the hippocampal and neocortical networks.

**'IONIC SHIFT PLASTICITY' PROVIDES MODULATION OF GABAergic INHIBITION**

GABAergic synapses are susceptible to a form of plasticity dependent upon alterations in ion gradients (Fiumelli and Woodin, 2007). Low-frequency STDP induction protocols cause long-term changes in the postsynaptic chloride (Cl−) gradient. The Cl− gradient predominantly determines the reversal potential for GABA receptor-mediated transmission (E\textsubscript{GABA}), which in turn is largely responsible for determining the strength of inhibition. At early developmental stages STDP induction at GABAergic synapses hyperpolarizes the reversal potential, which effectively strengthens inhibition (Balena and Woodin, 2008; Xu et al., 2008). In contrast, the same STDP induction protocol weakens inhibition in the mature CNS by depolarizing the reversal potential (Woodin et al., 2003; Fiumelli and Woodin, 2007; Ormond and Woodin, 2009). These bi-directional forms of GABAergic STDP are often referred to as ‘ionic shift plasticity’ (Figure 2).

**MECHANISMS REGULATING THE GABA\textsubscript{A} REVERSAL POTENTIAL**

Fast inhibitory GABAergic transmission in the mature CNS is largely mediated by GABA\textsubscript{A}Rs. These are ionotropic receptors permeable to Cl− and HCO\textsubscript{3}−, but due to differences in the permeabilities and reversal potentials of these two ions it is Cl− that plays the most important role in determining the strength of GABAergic transmission under normal physiological conditions (Farrant and Kaila, 2007). The regulation of this gradient depends on the balance and function of the prominent neuronal Cl− transporters: KCC2 and NKCC1. They are both members of the cation–chloride cotransporter gene family SLC12a1-9 (Payne et al., 2003; Mercado et al., 2004; Gamba, 2005). They are also both secondary active transporters that depend on ionic gradients established by the primary active transporter Na\textsuperscript{+}−K\textsuperscript{+}-ATPase; KCC2 derives energy from the K\textsuperscript{+} gradient to transport Cl− out of the cell, while NKCC1 derives energy for the Na\textsuperscript{+} gradient to transport Cl− inward.

During embryonic development and early postnatal life, NKCC1 is the dominantly expressed Cl−-cotransporter (Xu et al., 1994; Plotkin et al., 1997; Russell, 2000; Dzhala et al., 2005), and as a result neuronal Cl− is high and GABAergic transmission causes postsynaptic depolarization that is sometimes excitatory (although E\textsubscript{GABA} may also be affected by recording conditions, see Rheims et al., 2009). However during early postnatal development there is a significant increase in KCC2 expression that results in a hyperpolarizing shift in E\textsubscript{GABA} below the resting membrane potential that produces synaptic inhibition (Rivera et al., 1999; Blaesse et al., 2009). This dynamic regulation of the sign of GABAergic transmission (excitatory vs. inhibitory) is also observed during neuronal injury, epilepsy, and neuropathic pain (van den Pol et al., 1996; Cohen et al., 2002; Rivera et al., 2002; Coull et al., 2005; Blaesse et al., 2009). In these pathophysiological cases KCC2 expression dramatically decreases, rendering

![Figure 2](image-url)
GABAergic transmission excitatory – in what has been proposed to be a recapitulation of developmental programs (Payne et al., 2003; Blaesse et al., 2009).

**DEVELOPMENTALLY REGULATED IONIC SHIFT PLASTICITY**

It is not just developmental and pathophysiological events that alter the electrochemical gradient for Cl⁻. Physiologically normal patterns of neuronal activity such as those used during the induction of STDP can also shift the Cl⁻ gradient, resulting in changes in the strength of GABAergic transmission. Coincident pre- and postsynaptic activity within ±20 ms (at 5 Hz for 30 s) depolarizes E_{GABA_A} (with no corresponding change in conductance) (Woodin et al., 2003). Beyond ±50 ms GABAergic inhibition is weakened by a decrease in conductance (but no change in E_{GABA_A}). The result is a symmetrical spike timing window which leads to two initial observations: (1) GABAergic synapses are also sensitive to spike timing; and (2) the shape of the spike timing window differs from the asymmetrical window for glutamatergic synapses. This last point also implies that the pre-post order is not essential during GABAergic STDP induction, as it is during glutamatergic STDP. Rather during GABAergic STDP the essential requirement is correlated timing.

During the induction of GABAergic STDP postsynaptic Ca²⁺ influx through VGCCs leads to a decrease in the function of KCC2 (Woodin et al., 2003). This results in less outward Cl⁻ transport and thus a depolarization of E_{GABA_A} that weakens inhibition. This plasticity occurs in cultured hippocampal neurons (Woodin et al., 2003), and hippocampal slices prepared from juveniles and mature rats (Woodin et al., 2003; Ormond and Woodin, 2009). The central requirement for the induction of ionic shift plasticity appears to be an appropriate level of Ca²⁺ influx, and not the Ca²⁺ source. In hippocampal cultures and slices from juveniles, Ca²⁺ influx via VGCCs is sufficient (Woodin et al., 2003). However in slices from adults, Ca²⁺ influx through both VGCCs and NMDARs is required (Ormond and Woodin, 2009). In these experiments STDP was induced by paired stimulation of the Schaeffer collaterals and pyramidal neurons with both glutamatergic and GABAergic transmission intact. Thus in the adult there is cooperation between glutamatergic and GABAergic transmission; glutamate facilitates the opening of NMDARs, which is required for GABAergic STDP. Regardless of the source of Ca²⁺ influx, the mechanism appears to be a posttranslational modification of KCC2 (Acton et al., 2009; Ormond and Woodin, 2009). Ionic shift plasticity can also be induced by repetitive prolonged stimulation of the postsynaptic neuron (Fiumelli et al., 2005; Brumback and Staley, 2008). However there is discrepancy regarding the mechanism of this plasticity. In one scenario, the required Ca²⁺ influx occurs via release from internal stores, and results in a PKC-dependent regulation of KCC2 (Fiumelli et al., 2005). In the other scenario, the spiking resets the thermodynamic equilibrium for NKCC1 transport which indirectly lead to changes in neuronal Cl⁻ (Brumback and Staley, 2008).

During early postnatal life when NKCC1 is the dominantly expressed Cl⁻-transporter, the same STDP induction protocol that induces ionic shift plasticity in the mature CNS also modifies immature synapses (Balena and Woodin, 2008; Xu et al., 2008). The difference is that at immature synapses we see the direction of the plasticity reverse. Coincident pre- and postsynaptic activity at 5 Hz hyperpolarizes E_{GABA_A} through a regulation of NKCC1 which strengthens inhibition. In the developing CNS ionic shift plasticity appears to be frequency dependent. Increasing the stimulation frequency above 20 Hz (while maintaining the spike timing interval) produces a GABA_R and CaMKII-dependent depolarization of E_{GABA_A} likely due to GABA spillover that occurs at higher frequencies (Xu et al., 2008).

**SYNAPSE-SPECIFICITY OF IONIC SHIFT PLASTICITY**

One of the most prominent differences between ionic shift plasticity and glutamatergic plasticity onto interneurons is that while the latter is mainly homosynaptic, ionic shift plasticity has the potential to be heterosynaptic. Ionic shift plasticity produces a change in the Cl⁻ gradient at the activated synapse; because Cl⁻ is a diffusible ion we can expect this gradient change to also affect neighboring synapses within the same neuronal compartment. Moreover, given that GABAergic synapses terminate on pyramidal cell dendritic shafts rather than spines, any postsynaptic change in the Cl⁻ concentration is unlikely to be restricted to the activated postsynaptic site. Because basket cell interneurons primarily target the principal cell perisomatic region, we would expect the shift in the Cl⁻ gradient to extend throughout the somatic compartment. However we would not necessarily expect the change in the Cl⁻ gradient to extend beyond the somatic compartment to dendrites or axon because it is known that pyramidal cells can maintain domain-specific intracellular Cl⁻ gradients (Szabadi et al., 2006; Khirug et al., 2008).

**REGULATION OF INHIBITORY STRENGTH IN NEURONAL NETWORKS**

What is the function of this ionic shift plasticity? Neuronal patterns of activity that induce glutamatergic STDP in the CA1 region of the hippocampus can also induce GABAergic STDP of interneurons onto pyramidal neurons (Ormond and Woodin, 2009). It has been demonstrated both computationally and experimentally that GABAergic STDP regulates pyramidal neuron spiking (Saraga et al., 2008) and produces a disinhibition-mediated LTP (Ormond and Woodin, 2009). This is perhaps not surprising given that GABAergic inhibition in the CA1 is known to regulate synaptic integration and spike timing (Pouille and Scanziani, 2001; Lamsa et al., 2005).

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