Short-term ionic plasticity at GABAergic synapses

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INTRODUCTION

Synaptic plasticity refers to structural and functional changes that occur at synapses in response to particular stimuli or patterns of activity. These processes can operate over a range of timescales, from short-term modification of synaptic transmission occurring over tens of milliseconds, to long-lasting changes that persist for hours and more. The changes that result are thought to contribute to phenomena as important and diverse as synaptic integration, the flow of information through neuronal circuits, learning and memory, neural circuit development and disease states such as epilepsy. In conjunction with the extensive research on plasticity at excitatory glutamatergic synapses, plastic processes at inhibitory synapses have received increasing attention over the past two decades. This reflects a growing appreciation of the importance of GABAergic transmission in brain function and disease. GABAergic transmission is thought to contribute to phenomena as important and diverse as learning and memory, neural circuit development and disease states such as epilepsy.

Fast synaptic inhibition in the brain is mediated by the pre-synaptic release of the neurotransmitter γ-Aminobutyric acid (GABA) and the post-synaptic activation of GABA-sensitive ionotropic receptors. As with excitatory synapses, it is being increasingly appreciated that a variety of plastic processes occur at inhibitory synapses, which operate over a range of timescales. Here we examine a form of activity-dependent plasticity that is somewhat unique to GABAergic transmission. This involves short-lasting changes to the ionic driving force for post-synaptic receptors, a process referred to as short-term ionic plasticity. These changes are directly related to the history of activity at inhibitory synapses and are influenced by a variety of factors including the location of the synapse and the post-synaptic cell’s ion regulation mechanisms. We explore the processes underlying this form of plasticity, when and where it can occur, and how it is likely to impact network activity.

Keywords: short-term ionic plasticity, GABA, chloride, GABAA receptors, synaptic transmission, EGABA, reversal potential, pH

GABA<sub>AA</sub> RECEPTOR MEDIATED SYNAPTIC TRANSMISSION AND PLASTICITY

Two principle variables determine the effect of GABA<sub>AA</sub>R mediated synaptic transmission on the post-synaptic membrane potential. The first is \( E_{GABA} \) and the second is the GABA<sub>AA</sub>R conductance (\( g_{GABA} \)). Open GABA<sub>AA</sub>Rs are approximately four times more permeable to chloride (\( Cl^- \)) than to bicarbonate (\( HCO_3^- \)) ions (Kaila and Voipio, 1987; Kaila et al., 1989). Therefore at rest, \( E_{GABA} \) (typically \(-75\) mV) is much closer to the very negative Cl⁻ reversal (\( E_{Cl^-} \); typically \(-85\) mV) than the considerably more positive HCO₃⁻ reversal (\( E_{HCO_3^-} \); typically \(-20\) mV) (Kaila et al., 1993; Lambert and Grover, 1995). When GABA binds to GABA<sub>AA</sub>Rs, the bulk of anion flux through the channel is Cl⁻ flowing down its electrochemical gradient from outside to inside the cell. This causes the membrane potential hyperpolarization typical of classic GABA<sub>AA</sub>R mediated inhibition. However, if \( E_{Cl^-} \) is positive of the resting membrane potential, GABA<sub>AA</sub>R activation will result in Cl⁻ efflux and depolarization. This can still have an inhibitory influence due to the shunting effect upon the membrane, and particularly if \( E_{Cl^-} \) and \( E_{GABA} \) remain more negative than the action potential threshold (Kaila, 1994; Farrant and Kaila, 2007). If \( E_{Cl^-} \) exceeds the action potential threshold, GABA<sub>AA</sub>R mediated transmission is likely to increase the probability of action potential generation and will therefore exert an excitatory effect. In this manner the intracellular Cl⁻ concentration \([Cl^-]\), by setting \( E_{Cl^-} \) and \( E_{GABA} \), determines the “mode” of GABA<sub>AA</sub>R operation. The extent to which GABAergic inputs can move a neuron’s membrane potential toward \( E_{GABA} \) is a function of gGABA. gGABA in turn...
is determined by a host of synaptic parameters including the amount of transmitter released, the number of GABAARs present, the GABAAR subunit composition, channel kinetics, phosphorylation state and presence of channel modulators. Whereas $E_{GABA}$ sets the “mode,” $g_{GABA}$ can be thought of as determining the “strength” of the GABAergic synapse.

Changes to either $g_{GABA}$ or $E_{GABA}$ are known to underlie long-term plasticity at GABAergic synapses (Gaiarsa et al., 2002; Wright et al., 2011). These sustained changes to GABAergic transmission have been demonstrated in numerous brain regions, species type and experimental preparations, and can be generated by periods of either pathological or physiological activity (Cohen et al., 2002; Woodin et al., 2003; Fiumelli et al., 2005; Pathak et al., 2007). In addition to long-term changes in GABAergic synaptic function, it is known that post-synaptic responses can also vary on short time scales, as a function of recent pre-synaptic activity (Davies et al., 1990; Federvish and Gutnick, 1995; Gupta et al., 2000). Repeated activation at some synapses can result in enhanced transmission (facilitation), while at other synapses repeated use results in a transient decrease in transmission (depression). In reality, multiple short-term plasticity mechanisms are likely to co-occur at synapses and the resulting behavior will be a combination of facilitation and depression that depends on the timing of synaptic activation (Tsodyks and Markram, 1997; Varela et al., 1997). Indeed, GABAergic synapses are known to display an array of short-term plastic phenomena (Davies et al., 1990; Federvish and Gutnick, 1995; Jiang et al., 2000; Kirischuk et al., 2002; Mott et al., 1993), and in some cases have been related to the specific interneuron type that is the pre-synaptic source (Gupta et al., 2000; Pouille and Scanziani, 2004). Short-term plasticity phenomena such as these are generally understood to relate predominantly to pre-synaptic processes. For instance, synaptic facilitation is typically attributed to residual elevations of pre-synaptic calcium ($Ca^{2+}$), whilst synaptic depression is linked either to depletion of readily releasable synaptic vesicles (Zucker and Regehr, 2002) or the activation of pre-synaptic GABA receptors (Davies et al., 1990; Lambert and Wilson, 1994). However, post-synaptic mechanisms can also contribute to short-term synaptic plasticity at GABAergic synapses and these include desensitization of the post-synaptic receptors (McCarren and Alger, 1985; Overstreet et al., 2000) or changes in the ionic driving force for the post-synaptic receptors. This latter process—transient shifts in the ionic driving force of the post-synaptic GABAARs—will form the focus of the remainder of this review.

THE BASIC MECHANISM UNDERLYING SHORT-TERM IONIC PLASTICITY AT GABAergic SYNAPSES

Short-term changes to receptor reversal potentials via breakdown of ionic concentration gradients are not thought to occur at glutamatergic synapses. This is because the major ionotropic receptors for glutamate, AMPA, NMDA, and Kainate receptors, are equally permeable to $Na^+$ and $K^+$. The concentration gradients across the neuronal membrane for these two ions are diametrically opposed, resulting in a reversal potential for glutamate receptors of approximately 0 mV. During periods of intense glutamatergic synaptic activity, sodium influx and potassium eflux may reduce their respective local concentration gradients, but as both ion concentrations are perturbed to a similar extent, this will have a minimal effect on the combined reversal potential for glutamate receptors.

The situation within the GABAergic system is quite different. As described above, the major ionotropic receptor for GABA, the GABAAR, is permeable primarily to $Cl^-$ and to a lesser extent $HCO_3^-$ (Kaila and Voipio, 1987; Kaila et al., 1989). Therefore at rest, $E_{GABA}$ (typically ~75 mV) is considerably closer to the very negative $Cl^-$ reversal ($E_{Cl^-}$ typically ~85 mV) than the more positive $HCO_3^-$ reversal ($E_{HCO_3^-}$ typically ~20 mV) (Kaila et al., 1993; Lambert and Grover, 1995). During intense activation of GABAARs however, rapid $Cl^-$ influx can exceed $Cl^-$ extrusion mechanisms and a reduction in the transmembrane $Cl^-$ gradient occurs (Kaila and Voipio, 1987; Kaila et al., 1989; Staley et al., 1995; Staley and Proctor, 1999). It is thought that a corresponding collapse of the $HCO_3^-$ gradient is prevented by the activity of intra- and extra-cellular carbonic anhydrases, which use CO$_2$ as a substrate to rapidly regenerate intracellular $HCO_3^-$ (Kaila et al., 1990; Rivera et al., 2005). As a result, the intracellular $Cl^-$ accumulation that occurs during repeated activation of GABAARs means that $E_{Cl^-}$ and hence $E_{GABA}$ shift toward the more positive $E_{HCO_3^-}$ (Figure 1). Such a process is thought to contribute to short-term synaptic depression of GABAergic potentials (McCarron and Alger, 1985; Huguenard and Alger, 1986).

This process does not only reduce the size of inhibitory post-synaptic potentials (IPSPs), but strong GABAAR activation may cause IPSPs to change from being hyperpolarizing to depolarizing, as $E_{GABA}$ shifts in a positive direction (Figure 1). Such biphasic responses have been widely documented (Alger and Nicoll, 1979; Andersen et al., 1980; Thompson and Gahwiler, 1989a,b). As described above, the most accepted explanation for this phenomenon is the differential collapse of the opposing concentration gradients of $Cl^-$ and $HCO_3^-$ (Kaila et al., 1989; Staley et al., 1995; Staley and Proctor, 1999), although some contradictory observations remain unexplained (Perkins and Wong, 1997; Perkins, 1999). The magnitude of the late phase of the biphasic response is accentuated by extracellular potassium accumulation which further serves to depolarize the cell membrane (Kaila et al., 1997; Smirnov et al., 1999; Voipio and Kaila, 2000). This is thought to occur via the activity of the electroneutral $K^+-Cl^-$ co-transporter KCC2, which leads to the accelerated extrusion of both $Cl^-$ and $K^+$ in response to the GABAAR-mediated accumulation of intracellular $Cl^-$ (Viitanen et al., 2010). It should be remembered that such shifts in $E_{GABA}$ are expected to be temporary, which is why this phenomenon can be thought of as a short-term plastic change. Once GABAAR activity subsides, transporter proteins will return $[Cl^-]$, to resting levels on a timescale of seconds or minutes, depending upon the size of the $E_{GABA}$ shift (Staley and Proctor, 1999; Raimondo et al., 2012a).

FACTORS THAT INFLUENCE IONIC PLASTICITY AT GABAergic SYNAPSES

Any factor that affects the rate of $Cl^-$ accumulation during GABAAR activation will influence how rapidly and by how much
FiguRe 1 | Biphasic responses to intense GABAAR activation are caused by a rapid shift from hyperpolarizing to depolarizing $E_{GABA}$. (Left) a schematic of a patched pyramidal neuron receiving strong GABAAR input either via stimulation of GABAergic afferents or application of GABA. (Right) traces showing the putative changes in ionic and synaptic parameters as a result of the GABAAR activation. Separate traces show the cell’s membrane potential ($V_m$, black); the GABAAR conductance ($g_{GABA}$, red), the reversal potentials for the GABAAR ($E_{GABA}$, gray dashed), HCO$_3^-$ ($E_{HCO_3}$, green) and chloride ($E_{Cl}$, blue); plus the extracellular K$^+$ concentration ($[K^+]_{out}$, black). Insets (within dashed boxes) show transmembrane ion fluxes and gradients at two points during the response to GABAAR activation. At the start of GABAAR activation (left inset) $[Cl^-]$ is typically much higher outside neurons (e.g., 135 mM) as opposed to inside neurons (e.g., 6 mM). In contrast, $[HCO_3^-]$ is only moderately higher outside (23 mM) as compared to inside (12 mM). Therefore at a typical resting membrane potential of $-60$ mV, when GABA (red wedge) binds to ionotropic GABAARs, Cl$^-$ flows into the cell (blue arrow) while HCO$_3^-$ flows out (green arrow). As GABAARs are approximately four times more permeable to Cl$^-$ than to HCO$_3^-$ ions (Kaila and Voipio, 1987), the bulk of anion flux through the receptors is Cl$^-$ . This causes the membrane potential hyperpolarization typical of classic GABAAR mediated inhibition. With continued GABAAR activation (right inset), Cl$^-$ influx ultimately exceeds Cl$^-$ extrusion mechanisms and a reduction in the transmembrane Cl$^-$ gradient occurs (Staley and Proctor, 1999). A corresponding depletion of intracellular HCO$_3^-$ is prevented by the activity of carbonic anhydrase, which uses CO$_2$ as a substrate to rapidly regenerate HCO$_3^-$ (Rivera et al., 2005). As a result, $E_{Cl}$ (blue trace) and hence $E_{GABA}$ shift toward the more positive $E_{HCO_3}$ (green trace) causing the membrane depolarization typical of the biphasic GABAergic response. Intracellular Cl$^-$ accumulation also results in the delayed extrusion of K$^+$ into the extracellular space via the Cl$^-$/K$^+$ cotransporter KCC2. This further contributes to the late-stage depolarization of the biphasic response (Kaila et al., 1997; Viitanen et al., 2010).

$E_{GABA}$ shifts. For example, one would expect that the greater the Cl$^-$ extruding capability of a neuron, the more resistant it would be to activity induced Cl$^-$ accumulation. Several mechanisms have been identified to play a role in Cl$^-$ efflux. These include Cl$^-$ co-transporters such as KCC2 (Gamba, 2005), the Cl$^-$/HCO$_3^-$ exchanger (Sterling and Casey, 1999) and voltage-sensitive Cl$^-$ channels (Rinke et al., 2010). Despite these multiple potential Cl$^-$ extruding pathways, electrophysiological experiments have shown that following a Cl$^-$ load, it is possible to fit the recovery of $[Cl^-]$ with a single exponent (Staley and Proctor, 1999; Raimondo et al., 2012a). This suggests that a single transporter, described by a single exponential process, is likely to play a dominant role in the recovery from Cl$^-$ accumulation. In most adult neurons, KCC2 has been identified as the major player in this process (Blaesse et al., 2009). As one would expect, reducing KCC2 activity within the context of a computational model (Doyon,
et al., 2011), or experimentally by genetic knockdown or pharmacological inhibition (Thompson and Gahwiler, 1989; Jarolimek et al., 1999; Rivera et al., 2005; Zhu et al., 2005; Doyon et al., 2011), causes a depolarizing shift in resting \( E_{GABA} \). In addition, evidence suggests that reduced KCC2 activity hampers a neuron’s ability to deal with an accumulation of intracellular \( Cl^{-} \) and therefore slows the time to recover normal synaptic inhibition (Jin et al., 2005; Doyon et al., 2011). What may be underappreciated is that KCC2 has a limited \( Cl^{-} \) affinity and transport capacity (Payne, 1997; Staley and Proctor, 1999; Song et al., 2002; Blaesse et al., 2009). This means that at a local level, and during the short time periods accompanying intense GABAAR activation, the volume of the compartment into which \( Cl^{-} \) flows and the rate of diffusion into other areas are also important parameters in governing the extent to which the \( Cl^{-} \) concentration increases intracellularly (Staley and Proctor, 1999; Doyon et al., 2011).

Computational models (Qian and Sejnowski, 1990; Staley and Proctor, 1999; Doyon et al., 2011; Jedlicka et al., 2011) predict that for a given amount of synaptic GABAAR activation and its accompanying \( Cl^{-} \) influx, smaller postsynaptic volumes will result in relatively larger increases in \( [Cl^{-}] \); and hence greater depolarizing shifts in \( E_{GABA} \). This explains the experimental finding that depolarizing responses to GABAAR activation are more easily elicited over dendritic as opposed to somatic compartments (Figure 2 and Staley and Proctor, 1999). In a theoretical paper, Qian and Sejnowski (1990) employed this reasoning to suggest that GABAAR-mediated inhibition is likely to be ineffective on dendritic spines. Due to their minute volume, even small amounts of \( Cl^{-} \) influx into a spine would be predicted to cause a local increase in \( [Cl^{-}] \) that would rapidly depolarize \( E_{GABA} \). Consistent with this idea, it has since been confirmed that most GABAergic synapses are localized to dendritic shafts as opposed to spines (Freund and Buzsáki, 1996; Megías et al., 2001). In a similar vein, distal dendrites, apical tufts and the axon are also predicted to be prone to \( Cl^{-} \) accumulation effects (Doyon et al., 2011). In addition to their small volume, the narrow diameter of these processes means that longitudinal diffusion of \( Cl^{-} \) to other parts of the cell is severely restricted. This implies that multiple dendrite-targeting GABAergic inputs originating from a single pre-synaptic cell would have a larger inhibitory effect if the synapses are distributed throughout the dendritic tree, as opposed to being clustered along a single branch. Once again, such a morphological arrangement appears to be evident in different systems (Doyon et al., 2011; Jedlicka et al., 2011).

As well as the volume and rate of diffusion out of the intracellular compartment, another important factor that affects \( Cl^{-} \) accumulation during GABAAR activity is the presence, affinity and capacity of carbonic anhydrase. For example, Staley et al. (1995) have shown that blocking carbonic anhydrase, the enzyme that maintains intracellular levels of HCO\(_3\)^−, prevents a depolarizing response to strong GABAAR activation. In addition, Ruusuvuori et al. (2004) demonstrated that it is the developmental up-regulation of carbonic anhydrase VII by the end of the second postnatal week that permits the emergence of biphasic GABAergic potentials in response to high frequency stimulation in rat hippocampus. HCO\(_3\)^− ions therefore provide a pivotal link between neuronal regulation of \( Cl^{-} \) and pH (Kaila et al., 1989, 1993; Doyon et al., 2011). For instance, although carbonic anhydrase activity is largely able to regenerate HCO\(_3\)^− intracellularly in the face of GABAAR induced HCO\(_3\)^− efflux, the additional generation of intracellular hydrogen that accompanies intense activity (Schwiening et al., 1993; Wang et al., 1994; Xiong et al., 2000; Raimondo et al., 2012b) will shift the equilibrium set point of the carbonic anhydrase catalyzed reaction of H\(_2\)O and CO\(_2\), to HCO\(_3\)^− and H\(^+\). Therefore activity induced acidification is predicted to cause a reduction in the available intracellular HCO\(_3\)^− and hence a hyperpolarization of \( E_{HCO_3^-} \). This would ultimately reduce the depolarization achievable by intense GABAAR activation in the face of progressive intracellular acidification. For instance, an acidic shift of 0.2 pH units would be predicted to generate a hyperpolarization of \( E_{GABA} \) on the order of 5 mV, although this remains to be verified experimentally (Kaila et al., 1990, 1993; Doyon et al., 2011). Finally, the membrane potential at which GABAAR activation occurs will determine the driving force for \( Cl^{-} \) influx. If GABAergic inputs occur synchronously with post-synaptic spiking or depolarizing glutamatergic EPSPs, this will increase the relative driving force for co-active GABAARs and greatly facilitate \( Cl^{-} \) accumulation.
and a positive shift in $E_{\text{GABA}}$. Given the influence of the above mentioned parameters, it is perhaps not surprising that different cell types might differ in their susceptibility to $\text{Cl}^-$ accumulation. For example, Lamsa and Taira (2003) found that high frequency trains of stimulation generate depolarizing shifts in the $E_{\text{GABA}}$ of hippocampal interneurons. However, corresponding stimulation did not elicit similar changes in $E_{\text{GABA}}$ within CA3 pyramidal neurons.

In addition to cell type differences, the maturational state of a neuron is also likely to impact GABAergic ionic plasticity as $\text{Cl}^-$ homeostasis mechanisms are known to change during development. Compared to the $\text{Cl}^-$ extruder KCC2, immature neurons tend to express relatively high levels of the $\text{Na}^+\text{-K}^+\text{-Cl}^-$ co-transporter, NKCC1, which imports $\text{Cl}^-$ into the cells. This means that $[\text{Cl}^-]_i$ is often significantly higher than in adult neurons (Ben-Ari, 2002). As a consequence, $E_{\text{GABA}}$ is often depolarized relative to the resting membrane potential. Under these conditions it is predicted that repeated activation of GABAARs would actually lead to a cumulative depletion of $[\text{Cl}^-]_i$, which would hyperpolarize $E_{\text{GABA}}$ and reduce excitability in young tissue (Marchetti et al., 2005). Consistent with this, activity-dependent depletion of $[\text{Cl}^-]_i$ has been demonstrated within the chick spinal cord and is implicated in the termination of spontaneous network events (Chub et al., 2006). In addition, repetitive intense GABAAR activation via exogenous application of GABA or muscimol in young rodent cortex and hippocampus has been shown to deplete $[\text{Cl}^-]_i$; and hyperpolarize $E_{\text{GABA}}$ (Brumback and Staley, 2008; Kolbbaev et al., 2011). At a more general level, this work confirms that a cell’s $\text{Cl}^-$ handling mechanisms have fundamental effects on the nature of ionic plasticity at GABAergic inputs.

Given the multiple factors that can influence short-term ionic plasticity at GABAergic synapses, it is important to consider how they might interact under different scenarios. For example, the axon initial segment (AIS) of pyramidal neurons is known to receive input almost exclusively from GABAergic axo-axonic cells. This subcellular compartment therefore offers an intriguing example of how the parameters described above might combine to generate $[\text{Cl}^-]_i$ accumulation or depletion effects. Firstly, the small volume of the AIS is predicted to amplify the effects of any $\text{Cl}^-$ flux on transmembrane concentration gradients. Secondly, the AIS has been shown to express the $\text{Cl}^-$ importer NKCC1, instead of the $\text{Cl}^-$ extruder KCC2, which results in a relatively positive $E_{\text{GABA}}$ at rest (Szabadics et al., 2006; Khirug et al., 2008; Woodruff et al., 2010). This compartment is therefore predicted to experience $[\text{Cl}^-]_i$; depletion in response to repeated GABAergic inputs at hyperpolarized membrane potentials. However, if GABAergic inputs were to arrive coincident with membrane potential depolarization, such as during action potential firing, rapid $[\text{Cl}^-]_i$; accumulation could still occur. As the AIS is the site of spike generation, dynamic, local changes to $E_{\text{GABA}}$ could have a significant effect upon neuronal output. Future research is necessary to determine the existence and possible relevance of activity-dependent $\text{Cl}^-$ fluxes within the AIS.

To date, activity-dependent shifts in $E_{\text{GABA}}$, have been demonstrated in response to intense GABAAR activation, typically elicted either by exogenous application of GABAAR agonists or high frequency stimulation of GABAergic afferents. Evidence that activity driven, short-term changes in $E_{\text{GABA}}$ could occur in vivo have come from studies of hyper-active network activity states, such as those generated in experimental models of epilepsy. It is thought that the intense activation of GABAARs in combination with the concurrent membrane depolarization that occurs during epileptiform activity can cause rapid $\text{Cl}^-$ accumulation (Lamsa and Kaila, 1997; Isomura et al., 2003; Fujiiwara-Tsuchamoto et al., 2010; Ilie et al., 2012). Indeed, the resultant erosion of GABAAR mediated inhibition serves to initiate or exacerbate the hyperexcitability that is characteristic of epileptiform events (Lopantsev and Avoli, 1998; Lasztoczi et al., 2011; Ilie et al., 2012; Lillis et al., 2012). Beyond heightened network activity, it is currently an open question as to what sort of physiologically relevant activity patterns could lead to short-term changes to $E_{\text{GABA}}$. Nonetheless, it is important to note that levels of $[\text{Cl}^-]_i$; accumulation appear to increase linearly with the intensity of GABAAR activation. Even relatively weak stimulation can produce small changes in $[\text{Cl}^-]_i$ (Isomura et al., 2003; Berglund et al., 2006).

**FUNCTIONAL EFFECTS OF SHORT-TERM IONIC PLASTICITY AT GABAergic SYNAPSES**

What functional effects do short-term alterations in $E_{\text{GABA}}$ have in the context of evolving pathological and physiological network activity? As described above, large depolarizing shifts in $E_{\text{GABA}}$ have been shown to play a role in exacerbating and sustaining epileptic seizures. In addition, it has been observed that high frequency stimulation, of the sort used to induce classic long-term potentiation (LTP) at glutamatergic synapses, is sufficient to induce GABAAR mediated depolarization (Thompson and Galwiler, 1989a). This has led to the suggestion that one function of a short-term activity-dependent depolarizing shift in $E_{\text{GABA}}$ is to modulate the $\text{Mg}^{2+}$ block on NMDA receptors. This would suggest that the short-term GABAergic plasticity described above may play an important role in regulating NMDA-dependent mechanisms of synaptic plasticity (Staley et al., 1995).

By artificially setting the $E_{\text{GABA}}$ of a neuron, one may investigate how physiologically plausible shifts in the ionic driving force for GABAARs may impact activity. This has been performed experimentally by dialyzing neurons during whole-cell recordings with internal solutions of set $[\text{Cl}^-]_i$; using dynamic clamp to simulate GABAergic inputs with different $E_{\text{GABA}}$ values, or more recently using a light-activated $\text{Cl}^-$ pump to load neurons with different amounts of $\text{Cl}^-$ (Raimondo et al., 2012a). Studies performed in this manner have demonstrated that shifting $E_{\text{GABA}}$ to moderately depolarizing values can result in enhanced spiking probability and reduced spike latencies in response to GABAergic inputs (Wang et al., 2001; Akerman and Cline, 2006; Saraga et al., 2008; Valeeva et al., 2010; Wright et al., 2011; Raimondo et al., 2012a). Computational models have also been used to study the impact that modest changes in $E_{\text{GABA}}$ might have upon neuronal signaling. For instance, shifting the $E_{\text{GABA}}$ in a model of a mature CA1 pyramidal neuron from $-75\text{ mV}$ to $-70\text{ mV}$ results in an increase in action potential firing frequency by approximately 40% (Saraga et al., 2008). Similarly, depolarizing shifts
in inhibitory reversal potentials by as little as 10 mV can considerably shorten the duration of inhibitory inputs at the soma (Jean-Xavier et al., 2007). Small changes to $E_{\text{GABA}}$ are more likely to be functionally significant when a fine balance exists between GABAergic inhibition and facilitation. For instance, in neocortical layer 5 neurons and dentate granule cells, $E_{\text{GABA}}$ has been reported to lie at values more depolarized than the resting membrane potential, but below the action potential threshold (Kaila et al., 1993; Gulledge and Stuart, 2003; Chiang et al., 2012). This means that small changes in $E_{\text{GABA}}$ could bidirectionally modulate neuronal firing rates and spike times (Morita et al., 2006; Chiang et al., 2012).

An intriguing possibility is that $Cl^-$ accumulation might adjust the processing capacity of a neuron’s dendritic tree, and in a manner that depends upon the amount of information flowing through a particular network (Viitanen, 2010). The mechanism would operate as follows. If $E_{\text{GABA}}$ is more negative than the resting membrane potential, then hyperpolarizing GABAergic inputs would spread further in time and space than their underlying conductances (Gulledge and Stuart, 2003). During periods of enhanced activity however, synaptic inputs to dendrites would be predicted to cause modest $Cl^-$ accumulation such that $E_{\text{GABA}}$ moves toward the resting membrane potential, where GABAergic inputs will generate an exclusively shunting effect (Doyon et al., 2011; Jedlicka et al., 2011). Such a transition would serve to increase the spatial and temporal precision for integrating synaptic inputs, changing the fidelity of spike generation and effectively increasing the processing capacity of the dendritic compartment (London and Häusser, 2005; Viitanen, 2010). As such, short-term GABAergic plasticity involving shifts in $E_{\text{GABA}}$ could allow a neuron to adjust the information processing capacity of its dendritic tree “on the fly,” to meet the varied computational demands of changing levels of neural activity. Given that interneurons are fundamental for the synchronization of neuronal networks (Whittington et al., 1995; Wang and Buzsáki, 1996), the activity dependent transition of inhibitory post-synaptic potentials from hyperpolarizing to shunting could also have important consequences for network oscillations. For instance, Vida et al. (2006), using a network model of interneurons, showed that shifting $E_{\text{GABA}}$ from hyperpolarizing ($-75 \text{mV}$) to shunting ($-55 \text{mV}$) resulted in oscillations of markedly increased coherence and higher band frequency. Even larger shifts in $E_{\text{GABA}}$ however, ultimately result in a loss of synchrony (Jedlicka and Backus, 2006). Considering the role of gamma oscillations in spike timing dependent plasticity and sensory processing (Paulsen and Sejnowski, 2000; Engel and Singer, 2001; Buzsáki and Draguhn, 2004), it is conceivable that the dynamic modulation of $E_{\text{GABA}}$ may have consequences for information coding and memory processes (Buzsáki, 2006; Mu and Poo, 2006; Richards et al., 2010).

An important question that can be asked about any plasticity phenomenon is one of synapse specificity. Does a plasticity process affect individual synapses between pre- and post-synaptic neurons, multiple surrounding synapses, or every connection to the post-synaptic cell in question? Considering that GABAergic interneurons are a highly heterogeneous cell population involved in a diverse array of functions, from setting network oscillations to providing dynamic gain control (Freund and Buzsáki, 1996; Gabernet et al., 2005), $E_{\text{GABA}}$ changes could be relevant over a range of spatial scales. At one extreme, one can consider whether $Cl^-$ accumulations could be sufficiently compartmentalized so as to remain specific to a single GABAergic synapse, akin to $Ca^{2+}$ compartmentalization within a single dendritic spine (Bloodgood and Sabatini, 2007; Yuste, 2011). Földy et al. (2010) provide suggestive evidence that $[Cl^-]$ may be regulated on an input specific level. They show selective expression of the voltage gated $Cl^-$ channel, CLC2, at post-synaptic sites receiving input from parvalbumin-expressing basket cells (PVBCs), but not at post-synaptic sites receiving input from cholecystokinin-expressing basket cells (CCKBCs). The presence of this inward-rectifying $Cl^-$ channel means that the synapses are able to extrude $Cl^-$ at a faster rate in the face of intense $GABA_A$ activation, whereas synapses without CLC2 show a greater propensity to exhibit shifts in $E_{\text{GABA}}$. As Földy et al. point out however, the somatodendritic distribution of PVBC and CCKBC synapses are somewhat different, which is likely to contribute to $E_{\text{GABA}}$ differences (Földy et al., 2010). Nonetheless, this work demonstrates that ionic plasticity could be regulated according to synapse type, although the effects are not necessarily restricted to a single synapse. Indeed, modeling and experimental studies suggest that $Cl^-$ diffuses rapidly between synapses, with accumulations often only remaining localized at the level of a dendritic branch (Doyon et al., 2011; Jedlicka et al., 2011). This would suggest that activity dependent $Cl^-$ accumulations are likely to extend to surrounding synapses and therefore affect levels of inhibition in a spatially diffuse manner. Taken together, these studies highlight that future work is required to systematically explore the cell and synapse specific rules that influence short-term $E_{\text{GABA}}$ changes.

**CONCLUSION**

Like the glutamatergic system, GABAergic synapses may undergo a wide array of both short- and long-term plasticity phenomena that rely on alterations in pre-synaptic release and/or post-synaptic receptor conductance. However, the GABAergic system is somewhat unique in that its function can also be relatively easily modified via changes to the ionic driving force for the $GABA_A$ receptor and in a way that relates to the history of synaptic activity. It seems clear that $E_{\text{GABA}}$ should not be assumed to be invariant across a neuron, it is a dynamic variable that evolves across both time and space as a function of varied patterns of neural activity. We anticipate that examining how this aspect of neuronal signaling contributes to network activity will provide fertile ground for future research.

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