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Chapter 1
The Many Faces of Inhibitory Plasticity:
Adding Flexibility to Cortical Circuits Throughout Development

Lang Wang and Arianna Maffei

Abstract Neocortical circuits are highly interconnected networks of excitatory and inhibitory neurons. During postnatal development the connectivity and strength of excitatory and inhibitory synapses and the intrinsic properties of each neuron type sculpt the overall level of excitability of the circuit and support network function. Healthy neural circuits are characterized by a high sensitivity to changes in environmental stimuli and a finely tuned dynamic range. A balanced combination of excitatory and inhibitory inputs endows cortical circuits with the ability to maintain a dynamically stable level of excitability despite changes in sensory inputs. How this dynamically stable state is achieved during development is still matter of debate. In the past few decades, our knowledge of cortical neurogenesis, layer differentiation and circuit refinement has expanded dramatically. While most of the research has focused on the regulation of excitatory neocortical neurons, it is now accepted that inhibitory circuits contribute substantially to the achievement and maintenance of cortical circuit stability and function. Here we will focus on recent advancements in our understanding of the postnatal development of local inhibitory circuits and their role in the maintenance of cortical circuit excitability and stability.

Inhibitory Circuits

We will begin with a brief introduction about the many subtypes of inhibitory neurons in cortical circuits. Cortical inhibitory interneurons represent a morphologically, physiologically and chemically heterogeneous population of cells that perform different cortical functions (Burkhalter 2008). They have been classified in
multiple ways. In rat cerebral cortex, three distinct subtypes of GABAergic interneurons have been identified based on the expression of calcium binding proteins: parvalbumin (PV), calretinin (CR) and somatostatin (SOM) (Gao et al. 2000; Gonchar et al. 2007). Inhibitory neurons have also been classified according to their distinct firing properties (Kawaguchi and Kubota 1997; Beierlein et al. 2003; Contreras 2004). Fast-spiking (FS) are identified by their high-frequency firing and the lack of frequency adaptation during depolarization. They include a morphologically diverse population composed of basket cells, chandelier cells and neurogliariform cells, which are also known as late-spiking (LS) cells (Gupta et al. 2000). Another prominent population of interneurons is composed of regular-spiking non-pyramidal (RSNP) cells, which are subdivided into regularly adapting neurons and burst-spiking (BS) cells. BS cells are regular spiking inhibitory neurons that generate rebound burst spikes following hyperpolarization and are also known as low threshold spiking neurons (LTS; Beierlein et al. 2003). Interestingly, there are strong correlations between these classifications. For example, PV-expressing interneurons display FS properties (Xu et al. 2004; Butt et al. 2005), CR-expressing interneurons exhibit RS properties (Butt et al. 2005; Miyoshi et al. 2007), and SOM-expressing interneurons show BS properties (Butt et al. 2005; Miyoshi et al. 2007). Recent experiments suggest that the physiological subtype of cortical interneurons can be predicted by their temporal and spatial origins during neurogenesis (Butt et al. 2005).

Interneuron-Specific Synaptic Connections

Diverse subtypes of cortical interneurons form distinct synaptic contacts on pyramidal neurons and non-pyramidal neurons (Thomson and Lamy 2007). PV-expressing basket cells preferentially innervate somata and proximal dendrites of pyramidal neurons, while PV-expressing chandelier cells are thought to form connections with axon initial segments of pyramidal neurons (Kawaguchi and Kubota 1997; Gonchar and Burkhalter 1999b; Woodruff and Yuste 2008). Since the axon initial segment is the site where action potentials are generated, the synaptic contacts in this region are in a privileged position to control the output of pyramidal neurons. Chandelier cells were initially thought to be the only type of non-pyramidal cell to perform this fundamental function, but according to recent results the axon terminals of SOM-expressing cells also form symmetric synapses with the axon initial segments of pyramidal neurons in visual cortical supragranular layers (Gonchar et al. 2002). Unlike chandelier cells that innervate exclusively the axon initial segments of pyramidal neurons, SOM neurons also make synaptic contacts onto somata and dendrites of pyramidal neurons (Kawaguchi and Kubota 1997). This anatomical organization suggests that SOM neurons may modulate both the integration of inputs and the output of pyramidal neurons. All of these results imply a more complex regulation of pyramidal neuron output arising from the integration of different sources of inhibitory inputs.
Two distinct subtypes of interneurons, PV positive interneurons and those containing the neuropeptide cholecystokinin (CCK; Freund 2003) often form perisomatic nets consisting of multiple terminals with large boutons clustered around pyramidal soma and proximal dendrites (Wang et al. 2002; Chattopadhyaya et al. 2004). These large webs of perisomatic inhibitory synapses may be exceptionally suited for controlling the output of large groups of pyramidal neurons via synchronization of action potential firing. The formation and maintenance of terminal branches appears to be independent of neuronal activity and possibly relies on intrinsic developmental cues. Activity is necessary for the proliferation and extension of boutons on the perisomatic contacts (Chattopadhyaya et al. 2004). Thus the formation of perisomatic innervations likely depends on intrinsic developmental cues, whereas its maturation is modulated by driving inputs. CR-expressing neurons predominantly innervate other non-pyramidal interneurons (Gonchar and Burkhalter 1999a).

Maturation of Inhibitory Circuits

Neurotrophic factors including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3/4 (NT-3/4) are implicated in the regulation of neuronal differentiation (Ghosh and Greenberg 1995), axonal and dendritic growth (Horch and Katz 2002; Spatkowski and Schilling 2003), and synapse formation (Genoud et al. 2004; Gomes et al. 2006). In 1997, Marty and collaborators proposed that neurotrophins may play a role in cortical development and plasticity by regulating GABAergic inhibitory interneurons (Marty et al. 1997). Subsequent experiments confirmed this hypothesis. In cortical cell culture, BDNF promotes interneuron axon growth, stimulates the expression of GABA and of several calcium-binding proteins, and regulates the strength of synaptic inhibition (Cellerino 1996; Rutherford 1998). In transgenic mice in which the postnatal increase in BDNF in the forebrain was accelerated, the maturation of the GABAergic inhibitory circuit was completed earlier than in wild types, suggesting a causal relationship between the levels of BDNF and the maturation of inhibition (Huang et al. 1999). Another factor crucial to the maturation of cortical inhibition is polysialic acid (PSA), a long, linear homopolymer of a-2,8-linked sialic acid attached almost exclusively to the neural cell adhesion molecule (NCAM) in vertebrates (Di Cristo et al. 2007). During postnatal development, premature decline of PSA levels in visual cortex results in enhanced inhibitory synaptic transmission and accelerated maturation of perisomatic innervations by basket interneurons (Di Cristo et al. 2007). Recently a new factor was identified as fundamental for the postnatal maturation of inhibitory synaptic transmission: the homeodomain protein Otx2. Otx2 is normally required for embryonic head formation (Acampora et al. 2001), and is also restricted to relay centers along the primary visual pathway at birth, including retina, lateral geniculate nucleus (LGN) and visual cortex (Nothias et al. 1998). The expression of Otx2 in regions of the dorsal forebrain in rats was
expected to be lost by postnatal days 13 (P13) until very recently, when Hensch and collaborators found non-cell-autonomous Otx2 coordinates the maturation of PV-expressing interneurons even after the third postnatal week and that visual experience promotes the accumulation of Otx2 in PV-cells (Sugiyama et al. 2008). The implications of these results are quite important: the experience–dependent transfer of a homeoprotein may regulate the maturation of inhibitory circuits during the first few weeks of postnatal life.

Cortical Inputs to Inhibitory Interneuron

The function of an individual neuron is largely determined by the synaptic input onto that neuron. Differently from inhibitory innervations in areas without “laminar patterns”, cortical interneurons receive distinct laminar inputs that are subtype-specific (Thomson and Lamy 2007). In layer 2/3 of rat visual cortex, FS basket cells receive strong excitatory inputs from middle cortical layers (Dantzker and Callaway 2000). In contrast, adapting inhibitory interneurons receive their strongest excitatory inputs either vertically from deep layers or laterally from within layer 2/3 (Dantzker and Callaway 2000). In layer 5 of rat frontal cortex, it was found that the probability of reciprocal connectivity between pyramidal neurons and FS cells within the same layer was much higher than that between pyramidal neurons and non-FS cells, whereas non-FS cells in layer 5 received a more substantial set of inputs from pyramidal neurons in layer 2/3 (Cruikshank et al. 2007; Otsuka and Kawaguchi 2009). Such layer- and subtype-specific inputs contribute to the functional diversity of cortical inhibitory circuits and might depend on the fact that cortical circuit maturation is driven simultaneously by the cooperation of activity-independent cues within the local environment and by sensory inputs. Distinct subtypes of interneurons in layer 4 have specific laminar input (Hajós et al. 1997; Beierlein et al. 2003) but little is known about how their intracortical input integrates with that carried by thalamocortical afferents. Both FS and RSNP inhibitory neurons are thought to take part in a feedforward inhibitory circuit that receives thalamic input as well as in the widespread feedback recurrent inhibitory network (Beierlein et al. 2003; Cruikshank et al. 2007; Thomson and Lamy 2007; Tan et al. 2008; Hull et al. 2009).

Cortical Circuit Refinement

As early as in 1963, Sperry, Hubel and Wiesel had noted that the high degree of anatomical and functional precision in the visual pathway is present even before vision begins (Sperry 1963; Wiesel and Hubel 1963a). According to these findings, it was hypothesized that the wiring of cortical circuits relies on “innate cues” (Sperry 1963; Wiesel and Hubel 1963b). After eye opening, however, the
Inhibitory Plasticity and Cortical Circuit Refinement

Inhibitory Plasticity and Cortical Circuit Refinement postnatal development of cortical circuits occurs through a sequence of adjustments in connectivity and synaptic strength that promote the stabilization of active synaptic pathways and the elimination of synapses that are not stimulated by the appropriate input (Katz and Shatz 1996). This fine scale refinement occurs during periods of heightened sensitivity to changes in the driving input known as “critical” periods (Hensch 2004). About 50 years ago, Hubel and Wiesel discovered that the reduction or the elimination of visual input to one eye during the first few weeks of postnatal development induces a dramatic anatomic reorganization of the primary visual cortex (Wiesel and Hubel 1965, 1974). Similar reorganizations were subsequently observed in somatosensory (Inan 2007), auditory (Yu 2007), in motor cortex (Harms 2008), olfactory bulb (Tyler 2007; Marks 2006) and in the superior colliculus (Chandrasekaran 2007). Critical periods usually last only a few weeks; if sensory inputs are manipulated after the expected closing of these windows of opportunity, the rearrangements observed are not as dramatic or do not occur at all (Fagiolini et al. 1994; Hensch 2004). The opening and duration of the windows for plasticity vary depending on the area of cortex and in some brain areas more than one critical period has been identified (Feller and Scanziani 2005; Tagawa et al. 2005; Hensch 2004). The study of critical periods is especially important to understand basic mechanisms controlling neural circuit stability and flexibility in the face of the constant changes in environmental inputs. In the following paragraphs we will discuss the potential roles for inhibitory circuits and their plasticity in acquiring and maintaining circuit stability during critical periods for visual cortical development.

Plasticity of Inhibitory Synapses onto Cortical Pyramidal Neurons

Inhibitory circuits show complex, broadly defined plasticity: the relative proportion of specific populations of neurons can be regulated differentially in areas of the cortex processing different functions and/or in response to exposure to environmental factors (Harvey 2001; Fountain 2000); the axonal arborization and complexity can change both during development and in the adult in an activity-dependent manner (Dantzker and Callaway 1998; Chattopadhyaya et al. 2004); the subunit composition of GABA receptors is developmentally regulated (Dunning et al. 1999; Heinen et al. 2004). Finally, the strength of their functional synapses and their intrinsic properties are modulated by activity (Maffei 2006; Sun 2009). The diversity of interneurons populations and the complexity of their plasticity allows for an extraordinary flexibility in the way inhibitory neurons regulate cortical circuit excitability. During development, a subset of inhibitory synapses onto pyramidal neurons mediated by specific interneuron types may change the subunit composition of GABA receptors on the postsynaptic terminal (Dunning et al. 1999; Heinen et al. 2004). GABA receptors from most basket neurons contain alpha 3 and alpha 5 early in development and switch to alpha 1 around the third postnatal week. This switch is considered a hallmark of the maturation of GABAergic synapses
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(Dunning 1999; Heinen 2004; Bosman et al. 2002). Differently, inhibitory synapses postsynaptic to chandelier cells express alpha 2 containing GABA_A receptors throughout development and those postsynaptic to bipolar neurons contain mostly alpha 5 subunits (Ali and Thomson 2008). The difference in subunit composition underlies specific pharmacological and functional properties. In visual cortex, lack of alpha 1 alters the opening and duration of the classical critical period for ocular dominance plasticity (Hensch et al. 1998). Differently, lack of alpha 2 subunits during development strongly affects pyramidal neuron input/output function, but does not change neuronal responsiveness to visual stimulation (Fagiolini and Hensch 2000). Alpha 5 containing synapses mediated by bipolar neurons are thought to control the dendritic integration of inputs onto excitatory neurons (Ali and Thomson 2008).

Morphologically, the structures of the axonal arbors of inhibitory neurons are regulated in an activity dependent manner (Chattopadhyaya et al. 2004). The reorganization of inhibitory synaptic connectivity depends on the maturation and plasticity of functional synapses. An interesting finding is that somatic inhibitory synapses have the ability to respond to changes in driving input with opposite direction plasticity during two stages of development: the pre-critical period (from eye opening to the end of the third postnatal week) and the critical period for visual cortical plasticity (Maffei et al. 2004, 2006; Maffei and Turrigiano 2008b). While the specific mechanisms of these forms of plasticity are yet to be elucidated, the timing of the change in the direction of inhibitory plasticity raises the possibility that cellular mechanisms underlying the maturation of inhibitory synapses might also promote the switch in direction of their plasticity. A variety of patterns of activity producing depression and potentiation have been reported for fast inhibitory synapses (Komatsu and Iwakiri 1993; Holmgren and Zilberter 2001; Nugent et al. 2007). Potentiation of inhibitory inputs onto cortical pyramidal neurons transmission was induced with extracellular high frequency stimulation (Komatsu and Iwakiri 1993).

This groundbreaking work demonstrated for the first time that inhibitory synapses are plastic and suggested this plasticity as a potential new mechanism for the formation of memory. High frequency potentiation of IPSPs depends on the heterosynaptic activation of NMDA receptors (Komatsu and Iwakiri 1993; Kurotani et al. 2008). In layer 5 of rodent visual cortex high frequency stimulation also induced a form GABA_B receptor dependent inhibitory LTP (Komatsu 1996). Both GABA_B and NMDA dependent forms of inhibitory plasticity relied on postsynaptic dendritic exocytosis, possibly promoting the insertion of new GABA_A receptors in the postsynaptic membrane (Komatsu and Iwakiri 1993; Komatsu 1996). Extracellular stimulation does not allow the subtype of inhibitory interneuron mediating plasticity to be identified, and simultaneously activates quite strongly all of the axons (excitatory and inhibitory) travelling in the region of stimulation, suggesting that the NMDA dependence of inhibitory synaptic plasticity might be specific to this particular mode of induction. Inhibitory circuits mediated by different interneuron subtypes are not all affected by experience in the same way (Maffei et al. 2004; Bartley et al. 2008). The diversity in experience dependent plasticity is also supported by growing experimental evidence in favor of a rich set of plastic and experience-dependent changes in inhibitory circuits with potentially important
implications for circuit stability and function (Komatsu 1996; Holmgren and Zilberter 2001; Fritschy and Brüning 2003; Haas et al. 2006; Bartley et al. 2008; Maffei and Fontanini 2009).

Specific Inhibitory Circuits and Their Long Term Plasticity

The use of paired recording electrophysiological techniques and of transgenic mouse lines in which the different interneuron subtypes can be identified offered new possibilities to investigate the specificity of inhibitory plasticity. The first fundamental finding of this novel approach was that plasticity is induced at specific connections of inhibitory onto excitatory neurons with different patterns of activity depending on the subtype of inhibitory neuron, the brain circuit under analysis, and development (Jiao et al. 2006; Maffei and Turrigiano 2008b). In layer 2/3 of neocortex, pyramidal neuron bursting followed by delayed FS neuron spiking potentiates or depresses inhibitory synapses depending on the duration of the delay (Holmgren and Zilberter 2001). Both potentiation and depression of FS to pyramidal neuron inhibitory plasticity depends on calcium influx into the postsynaptic terminal and is independent of GABA$_B$ receptor activation (Komatsu 1996; Holmgren and Zilberter 2001). The requirements for the induction of FS mediated plasticity in layer 4 are different than those observed in layer 2/3. Successful potentiation of these synapses depends on a timed activation of pre (FS) and postsynaptic (Pyramidal) neurons but FS interneuron bursting needs to be paired with pyramidal neuron subthreshold depolarization (Maffei et al. 2006). Despite these differences in induction, the LTP of inhibition in layer 2/3 and 4 present some interesting similarities: both appear to have a postsynaptic site of expression and no detectable changes at the presynaptic site (Holmgren and Zilberter 2001; Maffei et al. 2006). Several intracellular pathways are involved in regulating the number of GABA$_A$ receptors at inhibitory synapses (Heuschneider and Schwartz 1989; Brandon et al. 2000; Kumar et al. 2005; Bogdanov et al. 2006) but whether they are also involved in the fast transport required for plasticity is not known. Much less is known about the patterns of activity inducing plasticity at inhibitory synapses mediated by non-FS interneurons. Experiments measuring the experience-dependent changes at low threshold spiking interneurons (LTS) in the barrel cortex and at regular spiking non-pyramidal neurons (RSNP) in visual cortex prove that these inhibitory connections onto pyramidal neurons are plastic and sensitive to changes in the environment (Maffei et al. 2004; Bartley et al. 2008). These connections present some interesting differences between cortical areas. In visual cortex, reduction of visual drive right at eye opening strengthens their synapses onto pyramidal neurons, decreases their connection probability, and leaves their short term dynamics unaffected (Maffei et al. 2004). In barrel cortex, LTS neurons – also classified as SOM neurons – change their short term dynamic in response to activity blockade (Bartley et al. 2008). In slice culture from the somatosensory cortex, 5 days incubation with tetrodotoxin, a treatment that completely silences neurons in the circuit, specifically affected the
short term dynamics of synapses mediated by LTS neurons onto pyramidal neurons, leaving FS driven inhibition unaffected (Bartley et al. 2008). These changes may shift the relative influence of the two most prevalent inhibitory circuits, differently in different cortical areas, and may be specific to the function of RSNP and LTS neurons perform in their specific circuits. Combinations of different forms of inhibitory plasticity contribute to sculpting the level of excitability of the circuit and the integration of sensory inputs (Bartley et al. 2008; Maffei and Fontaninini 2009).

**Functional Implications**

What is the role of inhibitory plasticity in cortical circuits? The ability to directly control pyramidal neuron input integration, excitability, and output suggest that inhibitory synaptic transmission is fundamental for cortical circuit function. Furthermore, the sensitivity of inhibitory synapses to changes in input and their ability to adjust their strength in response to specific patterns of activity allows fast regulation of cortical circuit activity and increases flexibility (Maffei and Fontanini 2009). During the first few weeks of postnatal development, the maturation of GABAergic transmission promotes the maturation of connectivity and excitability of local microcircuits (Komatsu 1994; Hensch and Fagiolini 2005; Kotak et al. 2008; Maffei and Turrigiano 2008a). Part of this process is activity dependent and driven by the incoming input (Jiao et al. 2006; Katagiri et al. 2007; Kotak et al. 2008; Maffei and Turrigiano 2008a). Inputs from the environment together with the state of excitability of the microcircuit, in turn, promote the refinement of cortical maps (Cang et al. 2005; Chandrasekaran et al. 2007; Cheetham et al. 2007). While the process of cortical map refinement has been ascribed for the most part to changes in synaptic weight and connectivity of glutamatergic synapses (Bender et al. 2006; Cheetham et al. 2008; Yoon et al. 2009), there is now growing evidence that inhibitory circuits and their plasticity are also prominently involved (Hensch et al. 1998; Maffei et al. 2004, 2006; Maffei and Turrigiano 2008a; Mainardi et al. 2009). A strong correlation between the refinement of cortical maps and inhibitory synaptic transmission and plasticity lies in the strong temporal correlation between maturation of inhibitory circuits and that of cortical connectivity (Fagiolini and Hensch 2000; Maffei et al. 2004, 2006; Katagiri et al. 2007). Specific inhibitory circuits may contribute differently to the refinement process, as suggested by the differential effects of sensory deprivation paradigms on the two major populations of inhibitory neurons (Maffei et al. 2004; Bartley et al. 2008; Sun 2009). In rodent neocortex, both the barrel field of somatosensory cortex and primary visual cortex show depression of FS synaptic inhibition onto pyramidal neurons in response to sensory deprivation during early postnatal development (Maffei et al. 2004; Jiao et al. 2006). The decrease in strength of somatic inhibition has been observed in layer 4, the main recipient of thalamocortical projections. In layer 4, a substantial
remodeling of FS perisomatic axonal arbors around pyramidal neurons was also reported (Chattopadhyaya et al. 2004). In layer 2/3, dark-rearing from birth, a paradigm that delays the development of visual cortex, reduces the number of somatic puncta from GAD65-positive inhibitory terminals onto pyramidal neurons (Kreczko et al. 2009), but whether this is also accompanied by a decrease in strength of functional synapses is currently unknown. Together these results suggest a strong experience-dependence of FS inhibitory synaptic strength and connectivity. In visual cortex, one of the possible interpretations of the reduced FS inhibition is that it preserves the overall state of excitability of the circuit in the face of a reduced driving input, thus promoting a homeostatic regulation of cortical excitability (Maffei and Fontanini 2009). In favor of this hypothesis, monocular deprivation does not shift ocular dominance between eye opening and the beginning of the classical critical period for amblyopia (Fagiolini et al. 1994). The lack of ocular dominance plasticity might depend on the increase in cortical excitability (Maffei et al. 2004). In the barrel cortex, the decrease in somatic inhibition might play a similar homeostatic role (Jiao et al. 2006; Bartley et al. 2008). After the third postnatal week, visual deprivation was reported to potentiate FS mediated inhibition onto pyramidal neurons (Maffei et al. 2006). The switch in sign of FS inhibitory plasticity correlates with the expected time of initiation of the critical period for ocular dominance plasticity (Fagiolini et al. 1994). An intriguing possibility is that the potentiation of inhibition contributes to the silencing of neurons driven by the deprived eye, thus promoting the shift in ocular dominance. So far, a switch in sign of inhibitory plasticity was reported only for visual cortex, but might be a general mechanism for cortical map refinement. Beyond cortical maps, inhibitory synaptic transmission located in very critical compartments of pyramidal neurons might contribute to shaping neuronal receptive fields. There is in fact evidence for a developmentally regulated sharpening of cortical receptive fields that is temporally correlated with the maturation of inhibitory synapses, and for the role of lateral inhibition in shaping the size and morphology of receptive fields (de la Rocha et al. 2008) (Fig. 1.1).

Conclusion

A growing body of evidence suggests that inhibitory synaptic plasticity is involved in regulating neuronal function, cortical circuit connectivity, and sensory input integration. The richness in plasticity and the specificity of inhibitory circuits might provide fast and efficient regulation of local circuit excitability, which, in turn, will affect the integration of pyramidal neurons input/output function, circuit stability and network computation. Beyond sensory cortices, GABAergic plasticity has been observed in areas involved in several learning and emotional functions, suggesting that inhibitory transmission and plasticity play complex roles in cortical circuit function.
Fig. 1.1 Developmental regulation of inhibitory plasticity and its functional implications. The cartoon represents a summary of the data describing developmental changes in inhibitory synaptic strength, their experience-dependent changes in response to alteration of sensory input, their effects on circuit excitability, and their possible functional implications. Pre-critical period is defined in rodents as the postnatal week between eye opening (postnatal day 14, P14) and the expected beginning of the critical period for visual cortical plasticity (P21). The critical period is expected to begin at P21 and to end by P35. Pyr: pyramidal neurons; FS: fast spiking inhibitory interneurons; RSNP: regular spiking inhibitory interneurons. The thickness of the lines indicates the strength of the connections (thicker: stronger; dotted: weaker).
Acknowledgments  This work was funded by the NIH/NEI R01 grant EY019885 (AM). We thank Martha Stone and Alfredo Fontanini for useful comments and discussions.

References


Inhibitory Plasticity and Cortical Circuit Refinement


