Inhibitory regulation of dendritic activity in vivo

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Understanding a neural network requires knowledge of both the connectivity (anatomy) and the firing properties (physiology) of the embedded neurons (Figure 1A). To unravel neocortical microcircuits, the emphasis has historically been on mapping the architecture (Felleman and Van Essen, 1991; Binzegger et al., 2004; Helmstaedter et al., 2011; Kleinfeld et al., 2011; Figure 1B). Although network connectively determines potential neuronal interactions, the dynamic nature of the neocortex can only be revealed by also including details about the physiological firing properties of individual neurons (De Schutter et al., 2005; Markram, 2006; Izhikevich and Edelman, 2008). Three decades of research on dendritic properties have shown that the individual neurons are themselves astoundingly complex, with multiple sites of spike initiation, and complex interactions between these sites (Illán, 1988; Wong and Stewart, 1992; Magee, 2000; Heady et al., 2001; Schiller and Schiller, 2001; Häusser and Mel, 2003; Gulledge et al., 2005; London and Häusser, 2005; Spruston, 2008). In particular, the principal neuronal type of the neocortex, the pyramidal neuron (Nieuwenhuys, 1994), can sustain local sodium, calcium, and NMDA spikes which undergo complex spatiotemporal interactions (Figure 1C; Larkum et al., 2009). In this equation comes the attempt to understand the role of inhibitory neurons of the neocortex which are tremendously diverse (Petilla Interneuron Nomenclature Group et al., 2008). Although they are less numerous than pyramidal neurons (Meyer, 2011; Meyer et al., 2011) interneurons connect more densely to other neurons (Fino and Yuste, 2011) and can therefore match the influence of excitatory neurons in the cortical microcircuit (Wehr and Zador, 2003; Okun and Lampi, 2008; Renart et al., 2010). Particular inhibitory cell types have been shown to have dramatic effects on overall network activity (Cardin et al., 2009; Sohal et al., 2009) and recent developments in optogenetic approaches promise to accelerate our knowledge of the contribution to network function by cortical interneurons (Cardin et al., 2010; Cardin, 2011; Lovett-Barron et al., 2012). Neocortical inhibitory neurons tend to have simpler dendritic arbors than pyramidal neurons and direct dendritic recordings to date have failed to indicate the same level of ion channel diversity and subcellular spiking mechanisms that have been found in pyramidal neuron dendrites (Martina et al., 2000; Markram et al., 2004). On the other hand, the axonal arborizations of interneurons tend to be very complex and their output firing patterns differ tremendously (Petilla Interneuron Nomenclature Group et al., 2008). Of particular interest to the subject of this review, however, is the diversity and precision with which their axons target particular subregions of the pyramidal cell dendritic tree (Kawaguchi, 1995; Thomson and Lamy, 2007; Douglas and Martin, 2009; Druga, 2009).

Taken together, this means that the task of understanding the role of particular inhibitory neurons embedded within the neocortical microcircuit must therefore take into account a number of aspects simultaneously (Figure 1C). (1) Location of synaptic input and dendritic morphologies of cortical inhibitory neurons (Dantzker and Callaway, 2000; Markram et al., 2004; Cruikshank et al., 2007; Xu and Callaway, 2009; Lee et al., 2010; Kubota et al., 2011; Meyer, 2011; Meyer et al., 2011), (2) firing properties (Petilla Interneuron Nomenclature Group et al., 2008), and (3) axonal projections and their subcellular target regions (Kätzel et al., 2011; Meyer et al., 2011). In this review we highlight a fourth and generally under-appreciated aspect: (4) the specific local effects mediated within the dendritic tree due to the interaction of inhibition with active local dendritic properties.

The spatiotemporal control of neuronal excitability is fundamental to the inhibitory process. We now have a wealth of information about the active dendritic properties of cortical neurons including axonally generated sodium action potentials as well as local sodium spikelets generated in the dendrites, calcium plateau spikes, and NMDA spikes. All of these events have been shown to be highly modified by the spatiotemporal pattern of nearby inhibitory input which can drastically change the output firing mode of the neuron. This means that particular populations of interneurons embedded in the neocortical microcircuitry can more precisely control pyramidal cell output than has previously been thought. Furthermore, the output of any given neuron tends to feed back onto inhibitory circuits making the resultant network activity further dependent on inhibition. Network activity is therefore ultimately governed by the subcellular microcircuitry of the cortex and it is impossible to ignore the subcompartmentalization of inhibitory influence at the neuronal level in order to understand its effects at the network level. In this article, we summarize the inhibitory circuits that have been shown so far to act on specific dendritic compartments in vivo.

Keywords: inhibition, interneuron, dendrite, cortex
As the explosion of molecular and imaging techniques occurred over the past 20 years, so too has our understanding of different sources of inhibition in the cortex. However, our understanding of which cortical inhibitory neurons provide dendritic inhibition and exactly where they synapse on to the dendritic tree is far from complete (DeFelipe, 2002; Markram et al., 2004; Petilla Interneuron Nomenclature Group et al., 2008). In particular, the functional connectivity (i.e., the influence of dendritic inhibition) has not yet been established in its entirety. In fact, it is not even clear whether the main effect is always inhibitory (Gulledge and Stuart, 2003; Glickfeld et al., 2009). Part of the problem is one of nomenclature and designating features that should be considered categorical (Petilla Interneuron Nomenclature Group et al., 2008). In this respect, while still formidable, the study of inhibitory microcircuits is more tractable in the hippocampus because of the simpler overall structure (Klausberger, 2009). Nonetheless, it is quite likely that most or all of the dendrite-targeting inhibitory neurons of the hippocampus have their counterparts in the neocortex (Thomson and Lamy, 2007).

It is not the purpose of this review to provide a systematic overview of all dendrite-targeting neurons complete with defining characteristics such as their anatomy, immunocytochemistry, and firing properties, but rather to explore the role of dendritic inhibition in cortical circuits and in particular the specific effect on pyramidal neuron firing within the cortical circuit. With regard to this second point, it is worth remarking that their diversity and precision of targeting suggests that each interneuronal type serves a particular function in the neocortical circuitry. This specificity also appears to be matched at the molecular level where specific receptors aggregate. Dendritic shafts and spines have both GABA_A and GABA_B receptors (Figure 2A). GABA_B receptors are also found on the presynaptic terminal but are composed of different subunits to the postsynaptic dendritic GABA_B receptors (Vigot et al., 2006). The GABA_B,-containing receptors found in the apical dendrites of layer 5 (L5) pyramidal neurons (Pérez-Garcí et al., 2006), open G-protein coupled inward rectifying K+ channels (GIRKs) and block both Ca^{2+} channels (Scholz and Miller, 1991; Campbell et al., 1993; Mintz and Bean, 1993; Pérez-Garcí et al., 2006; Chalifoux and Carter, 2011; Palmer et al., 2012) and NMDA channels (Chalifoux and Carter, 2010). This means that GABA_B receptor-activation can be segregated and act specifically either on synaptic transmission or on dendritic electrogensis. In the larger context, this implies that the cortical inhibitory circuitry is matched closely to subcellular molecular machinery.

**TWO KNOWN MICROCIRCUITS INVOLVING DENDRITIC INHIBITION (FIGURE 2)**

The advent of optogenetic approaches is transforming our understanding of the contribution of specific subtypes of inhibitory neurons to cortical network behavior because, for the first time, it is now possible to activate or inactivate a particular cell type (Cardin, 2011; Atallah et al., 2012; Lovett-Barron et al., 2012). Nonetheless, assessing the inhibitory influence at the dendritic level requires a range of approaches. Because of the complexity of cortical network dynamics, it can be easier to empirically measure the effects of activating parts of the network (regions, cell types or physiological stimuli) in _vivo_ rather than predicting their activation from targeted recordings _in vitro_. So far, two cortical microcircuits involving dendritic inhibition have been uncovered using the _in vivo_ approach. One circuit involves deep-layer Martinotti neurons and the other layer 1 neurogliaform cells. While both cell types act on the apical dendrites of pyramidal neurons, they are recruited under different circumstances and act via different mechanisms. Both these inhibitory microcircuits were uncovered during the investigation of pyramidal cell dendritic properties _in vivo_ highlighting the importance of inhibitory control in cortical networks.
GABA<sub>A</sub>-MEDIATED DENDRITIC INHIBITION VIA MARTINOTTI NEURONS

The Martinotti neuron was first described over a century ago (Martinotti, 1890) and is distinguished by its axon which extends vertically through the cortical layers ramifying extensively only in layer 1 (Kawaguchi and Kubota, 1996; Figure 2B). Since it receives facilitatory synaptic input from nearby pyramidal neurons (Wang et al., 2004; Kapfer et al., 2007; Silberberg and Markram, 2007), pyramidal neurons. Their apical dendrite targets the dendritic initiation zones of nearby pyramidal neurons (Silberberg and Markram, 2007). (C) Top, repetitive activation of Martinotti neurons causes brief and small hyperpolarizing potentials in the dendrites of pyramidal neurons but Ca<sup>2+</sup> spikes generated by local dendritic depolarization (middle) are still powerfully blocked by GABA<sub>A</sub>-mediated dendritic inhibition (bottom) because of the profound block of the underlying mechanisms for Ca<sup>2+</sup> spikes (Murayama et al., 2009). (D) Late-spiking neurogliaform neurons of layer 1 also target the dendrites of cortical pyramidal neurons (Chu et al., 2003). (E) Neurogliaform cells mediate a large fraction of their inhibitory action on the dendrites through GABA<sub>B</sub> receptors (Olah et al., 2007).
it is maximally recruited by burst firing in these neurons (Berger et al., 2010). Network activity leading to bursts in pyramidal neurons therefore disynaptically inhibits the calcium spike initiation zone in the same or neighboring pyramidal cells (Murayama et al., 2009; Figure 2C). Various suggestions have been made as to the function of this circuitry, from synchronizing pyramidal cell activity (Berger et al., 2010) to controlling their sensitivity and dynamic range (Kapfer et al., 2007; Murayama et al., 2009; see also Figure 3).

Since the dendritic Ca$^{2+}$ spike itself leads to bursting in pyramidal neurons (Schwindt and Crill, 1999; Williams and Stuart, 1999), this circuitry may also be a “winner-take-all” mechanism in which the first pyramidal neurons to be recruited above a threshold frequency prevent neighboring pyramidal neurons from joining in. Interestingly, the effects of Martinotti neurons on dendritic Ca$^{2+}$ activity were found to be mediated almost entirely via GABA$A$ receptors in vivo (Murayama et al., 2009).

GABA$B$-MEDIATED INTERHEMISPHERIC INHIBITION

About 30–40% of layer 1 (L1) interneurons are neurogliaform cells (Hestrin and Armstrong, 1996; Chu et al., 2003) with a dense axonal arbor mostly confined to L1 (Kubota et al., 2011; Figure 2D). Because of this arrangement, they can only provide inhibition to other interneurons within L1 (Oláh et al., 2007, 2009) or to the distal dendrites of pyramidal neurons (Oláh et al., 2007; Wozny and Williams, 2011). They are notable for responding with a long delay to threshold current injection (Chu et al., 2003; Tamás et al., 2003) and for their disproportionately large influence on pyramidal neuron dendrites via GABA$B$ receptors.
Palmer et al. Inhibitory regulation of dendritic activity in vivo (Tamás et al., 2003; Oláh et al., 2009; Wozny and Williams, 2011), although they also mediate inhibition via GABA<sub>A</sub> receptors (Oláh et al., 2007; Figure 2E). A recent study in vivo points to their likely activation via callosal fibers (Palmer et al., 2012) arising from ipsilateral sensory stimulation (see also Figure 4) which probably recruits this specific subpopulation but not other L1 interneurons. The influence of neurogliaform GABA<sub>B</sub>-mediated inhibition on pyramidal cell firing is remarkable given the negligible affect on membrane potential (Palmer et al., 2012). Whereas the subthreshold effect is hardly detectable at the cell body, this form of interhemispheric inhibition reduces the average firing frequency of L5 pyramidal neurons by 25%. In fact, reductions of up to 75% were achieved with complete activation of local dendritic GABA<sub>B</sub> receptors via application of a GABA<sub>B</sub> receptor agonist. This study not only highlighted the importance of GABA<sub>B</sub>-mediated inhibition but also demonstrated that dendritic conductances play a large role in determining the output of cortical pyramidal neurons.

**TIMING AND DENDRITIC INHIBITION**

With respect to neuronal computation, timing is everything. Neurons must receive input within a given temporal window in order to achieve maximal integration and summation (for a review, see Dan and Poo, 2004). Because of the filtering of electrical signals in...
the dendrite, the temporal and spatial effects of inhibition inter-
mingle with the precise timing of action potentials in the network
(Pouille and Scanziani, 2001; Glickfeld and Scanziani, 2006) and
the precise location of synapses on the dendritic tree (Sjöström
and Häusser, 2006; Letzkus et al., 2011). This has been powerfully
demonstrated in CA1 pyramidal neurons of the hippocampus
where inhibitory input shifts from the soma to the dendrite
depending on the timing and firing rate of the pyramidal neu-
ron (Pouille and Scanziani, 2004). In addition, the kinetics of the
different GABA_A receptors differ greatly, which also strongly
determines their network influence. The effects of GABA_A-
mediated inhibition last tens of milliseconds (Galarreta and Hestrin,
1997) whereas metabotropic GABA_B receptor activation can last for hun-
dreds of milliseconds (Newberry and Nicoll, 1984; Gähwiler and
Brown, 1985; Benardo, 1994; Shao and Burkharter, 1999; Tamás
et al., 2003). Therefore the timing of GABA_A-mediated inhibition
needs to be more exact than GABA_B mediated inhibition to effect
the specific input patterns and processing of input onto dendrites.
GABA_B receptor activation can also occur on a much longer time
scale by the activation of extrasynaptic receptors (Oláh et al., 2009;
Agnati et al., 2010; Wang et al., 2010).

Inhibitory and excitatory interactions are also best captured in vivo
and can now be triggered by activation of subclasses or areas of cortex (Adesnik and Scanziani, 2010; Olsen et al., 2012). For example, specific optogenetic excitation of layer 2/3 (L2/3)
pyramidal neurons causes oscillatory activity in these neurons
which is dependent on their interaction with local inhibitory
neurons. These kinds of interactions clearly also have a spatial
dimension because, when combined with cell firing, this specific
form of activation led to suppression of activity in L2/3 pyrami-
dal neurons and facilitation of activity in L5 pyramidal neurons
(Adesnik and Scanziani, 2010). While this complex behavior is
dependent on interactions between excitatory and inhibitory neu-
rons and presumably also involves different target sites (since only
the dendrites of L5 pyramidal neurons are present in L2/3), it is
not yet clear which inhibitory neurons were recruited. However,
this example illustrates that the possible combinations of excitatory and inhibitory interactions in the neocortex are formi-
dable and a priori predictions are extremely difficult. Moreover,
since anesthetics used in many in vivo experiments (including
the one described above) have a profound effect both on inhibi-
tion (Franks and Lieb, 1994) and dendritic properties (Potez and
Larkum, 2008), it is likely that dendritic inhibition and network
activity are also extremely dependent on the state of consciousness
of the animal.

Since dendritic inhibition exhibits such a powerful block of Ca^{2+}-
electrogenesis (Larkum et al., 1999; Pérez-Garcí et al., 2006),
it might be suggested that such local events should be perpetually
blocked in vivo where one would expect a constant background
firing of inhibitory neurons. However, the fact that dendritic Ca^{2+}-
activity does occur in vivo (Hirsch et al., 1995; Helmcen et al.,
1998, 1999; Tank et al., 1998; Svoboda et al., 1999; Larkum et al.,
2002; Murayama et al., 2009; Chen et al., 2011; Kitamura and
Häusser, 2011; Rochefort et al., 2011; Varga et al., 2011) makes
it likely that special disinhibitory systems exist to release pyra-
midal neurons from inhibition acting on the dendritic Ca^{2+}-
region.

DENDRITIC INHIBITION AND GAIN CONTROL

Despite the complexity of inhibition in the neocortical network,
there are some generalizations that appear to be emerging. For
instance, it has been shown in several systems that dendritically
located inhibition can change the slope (gain) of the firing fre-
cuency versus synaptic input in pyramidal neurons (Figure 3).
In a classic study, Holt and Koch (1997) showed counter intuitively that
shunting inhibition should not change the gain of a neuron. This
was predicated on the assumption that the inhibition occurred in a
passive system with no active conductances (Figure 3A). However,
inhibiting the active dendrites of pyramidal neurons in electric fish
(Mehaffey et al., 2005; Figure 3B), and CA1 (Lovett-Barron et al.,
2012; Figure 3C) and neocortical pyramidal neurons (Murayama
et al., 2009; Figure 3D) in rodents can very effectively alter the
gain of the neuron. In all these systems, the distal dendrites receive
top-down excitatory input that also controls the gain of the neu-
ron (Bernander et al., 1994; Larkum et al., 2004) suggesting that
dendritic inhibition may be a mechanism for regulating the influ-
ence of feedback or “predictive” information to the neuron (Rao
and Ballard, 1999).

The above examples show the importance of considering the role
of inhibition within the context of the network architecture in
combination with the active properties of the neuron. Other
aspects of network function are also important. For instance, in
a network with balanced inhibition and excitation, the synaptic
noise can start to influence the input-output relation of the neu-
ron such that even somatic and perisomatic inhibition control
the gain of the neuron (Chance et al., 2002). Furthermore, when
considering the recruitment of neurons throughout the network
related to the threshold synaptic activity for firing), feed-forward
perisomatic input can control the dynamic range of the network
as a whole (Pouille et al., 2009).

SILENT INHIBITION

A fundamental feature of neocortical networks is the tuning
of individual neurons, for instance orientation in the primary
visual cortex (Hubel and Wiesel, 1962) and frequency in the
auditory cortex (Merzenich et al., 1975). The fact that each neu-
ron has a receptive field within which it can extract features
was originally hypothesized to be dependent on the pattern of
inputs it receives. However, in different systems across the cor-
tex, researchers consistently observe that subthreshold input to
neurons does not match the suprathreshold output which is
typically more differentiated (Figure 4; Bringuier et al., 1999;
Candiani and Ferster, 2000; Brecht and Sakmann, 2002; Jia et al.,
2010). If the output of the neuron is not entirely determined
by its input it follows that the integrative properties of neurons
are also crucial to understanding this basic property of corti-
cal networks. One possibility is that fluctuations around thresh-
old account for the tuning properties of neurons, the so-called
“iceberg effect” (Rose and Blakemore, 1974; Priebe and Ferster,
2008). Here, considerations of the mechanisms for gain control
are important because the iceberg hypothesis appears incom-
patible with the invariance of tuning to signal strength (Sclar
and Freeman, 1982; Sadagopan and Wang, 2008; see Figure 3).
For this reason, several researchers have reasoned that inhibition
must play an important role in the tuning properties of neurons.
(Frégnac et al., 2003; Shapley et al., 2003; Priebe and Ferster, 2008).

While there is ample evidence that inhibition is fundamental to cortical processing (Sillitio, 1975; Borg-Graham et al., 1998; Bruno and Simons, 2002; Wehr and Zador, 2003; Rudolph et al., 2007; Cardin et al., 2009; Douglas and Martin, 2009; Runyan et al., 2010; Isaacson and Scanziani, 2011; Letzkus et al., 2011), there is still much debate about the details and whether it actually contributes to processes such as orientation tuning (Nelson et al., 1994; Ferster et al., 1996; Hofer et al., 2011; ShuShruth et al., 2012). Taking into account that further computation can be carried out post-synaptically via active dendritic processes when combinations or clusters of synapses on particular dendritic branches (Mel, 1994; Archie and Mel, 2006; Larkum and Nevian, 2008; Takahashi et al., 2012) activate local dendritic conductances (Brando and Häusser, 2010), it would also be possible for inhibition to contribute in a complex way to these processes. In a recent study of sets, the group of Arthur Konnerth examined synaptic input on to the dendritic trees of L2 neurons with sensory stimuli and found no evidence for local clustering of inputs or dendritic electrogene-
sis (Jia et al., 2010; Varga et al., 2011; Grienberger et al., 2012; although it has been observed in other systems; Takahashi et al., 2012). Nonetheless, the Konnerth group showed that orientation selectivity as measured by the spiking output of the neurons was intact despite the nearly uniform subthreshold responses (Figure 4A).

What could account for the enormous specificity of output in the face of relatively uniform input? At first glance, inhibition seems to be a poor candidate. In the first place, perisomatic inhibition appears to affect the output firing rate of all neurons uniformly retaining the tuning of the excitatory neurons (Atallah et al., 2012; Olsen et al., 2012). Nevertheless, it has been suggested that the effects of inhibition might be ‘silent’ and therefore overlooked when measured by conventional methods (Frégnac et al., 2003). Such silent inhibition was recently shown both in vivo and in vitro in the somatosensory cortex of rats. Here, the effects of dendritic inhibition in vivo were undetectable at the cell body (Palmer et al., 2012; Figure 4B). In this instance, it was demonstrated that dendritic inhibition acts on channels that are opened only in the suprathreshold state by the invasion of action potentials from the cell body to the dendrites (Stuart and Sakmann, 1994; Mehaffey et al., 2008; Palmer et al., 2012; Figures 4C–E). This form of dendritic inhibition can shape the computational properties of the neuron and therefore network function while being invisible to standard recording approaches. In the case of orientation selectivity (Jia et al., 2010), for instance, silent inhibition could manifest by shifting the regions of the dendritic tree (and hence the particular synaptic inputs) that could interact with backpropagating APs. In that particular study, hyperpolarization of the cell body was used to prevent APs in order to detect calcium changes in the dendrites that were not contaminated by backpropagating APs. If a form of silent inhibition is involved in the orientation selectivity in these neurons, the suppression of APs could be interpreted as causing the broadening in tuning. However, by its nature, silent inhibition is hard to detect under most situations which makes it difficult to investigate its influence on sensory processing.

CONCLUSION

Historically, even though they have been shown to have active membranes (Llinás et al., 1968; Kuno and Llinás, 1970; Wong et al., 1979), dendrites were often treated as passive structures and the computational possibilities have tended to be ignored by researchers trying to understand networks and systems. This is nowhere more prevalent than when considering the effects of inhibition at the network level even though evidence for dendritic inhibition goes back several decades (Llinás, 1975; Wong and Prince, 1979; Buzsáki et al., 1996). The common techniques for recording from neurons in vivo, both electrical and optical, generally make statements about dendritic function difficult, however recent advances suggest that the situation is changing. In this review, we have shown the evidence for the importance of considering dendritic inhibition and shown a few examples of where their influence could be demonstrated definitively. We predict that more examples will emerge as more systems are investigated.

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