believe that approaches like this could lead to the development of significantly better, more specifically targeted therapies to correct their hearing. Gene therapy-based approaches will probably become relevant to genetic forms of hearing loss in which the underlying cells or proteins can be identified, especially in cases in which critical cells and tissues survive until the age at which gene transfer protocols can be used. It would be truly groundbreaking if similar phenotypic rescue could be developed to treat some of the more common forms of hereditary deafness, such as those caused by the most prevalent forms of Connexin gene mutations, which collectively account for more than half of all cases of human hereditary deafness (Cryns and Van Camp, 2004). It is also reasonable to predict that the successful treatment approach reported in the VGLUT3 deafness mouse model could establish a framework for assessing the potential for gene replacement therapies for other senses and other hereditary neurological disorders. Finally, the results of this study may also help pave the way for personalized, gene-informed, targeted therapies that improve health for individuals with other Mendelian disorders. In case you have not heard, the future is now.

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Dendritic Ventriloquism: Inhibitory Synapses Throw Their Voices

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http://dx.doi.org/10.1016/j.neuron.2012.07.001

In a theoretical study in this issue of *Neuron,* Gidon and Segev (2012) identify several new principles governing how inhibition interacts with excitation in active dendrites. They show that inhibitory synapses can interact with excitability at a distance, effectively "throwing their voices" in the dendritic tree, such that distributed inhibitory synapses can act synergistically to provide a global veto of dendritic excitability.

The interplay between inhibition and excitation has fascinated neurophysiologists at least since Sherrington (1932) proposed that it forms the basis of the operation of the nervous system. Over the last 80 years, numerous functional roles have been proposed for inhibition, including regulation of timing, gain control, sharpening of tuning, and stabilization of ongoing activity in recurrent neural circuits (Isaacson and Scanziani, 2011). In addition, anatomical evidence has accumulated showing that principal neurons receive thousands of inhibitory synaptic contacts, made by distinct subtypes of inhibitory interneurons which target specific domains on the dendritic tree and which may also have distinct functional roles. And yet, the traditional view of how inhibitory synapses influences the output of a neuron has been dominated by a "somatocentric" perspective, in which the effect of inhibitory inputs is measured by their ability to control somatic membrane potential and the frequency of action potentials initiated in the axon. This classical perspective is based on the passive cable properties of dendrites, which result in spatial attenuation of membrane potential changes and even steeper attenuation of the visibility of a synaptic conductance with distance from the synapse (Koch et al., 1990). It's all about location, location, location: the conductance change induced by a single inhibitory synapse remains highly local and reaches its maximum at the site of the synapse, while the best place for an inhibitory synapse to act as a gatekeeper and control the influence of an excitatory synapse on neuronal output is "on the direct path" from the excitatory synapse

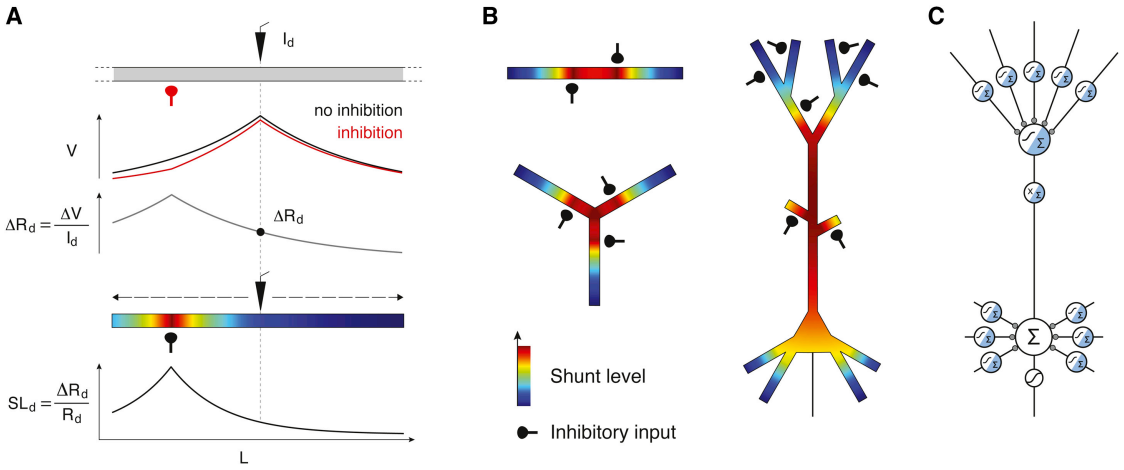

Figure 1. The Role of Inhibition from the Dendrocentric Point of View

(A) Definition of the shunt level in a simple dendritic cable (top). The membrane potential V (black) along a dendritic cable in response to a current injection I_d is changed by the presence of an inhibitory synapse (red). The change in input resistance ΔR_d caused by this synapse is given by the difference in membrane potential ΔV divided by the injected current I_d. At the site of injection, the local change ΔR_d (dot) is read out to calculate the shunt level $SL_d = \Delta R_d/R_d$, which measures the "visibility" of the synaptic conductance change at location *d*. To compute the shunt level along the entire dendrite, current is injected and the relative change in input resistance $\Delta R_d/R_d$ is measured at each dendritic location (bottom).

(B) The combined effect of inhibitory synapses in dendritic cables. The interaction of inhibitory synapses on more than two different branches creates a larger effect at the junction than locally. For two dendrites with two inputs, the SL is highest locally (dark red at the synaptic sites), whereas for three branches or more, the SL can be maximal at the junction while exhibiting a local (but smaller) maximum at each synapse. For a pyramidal cell morphology, a distribution of inhibitory inputs on apical oblique and tuft branches (resembling the distribution of inhibitory input from Martinotti cells) generates a maximum SL in the main apical dendrite.

(C) Multiple roles of inhibition in a simplified three-layer network model of a pyramidal cell. Inhibitory synapses exert three types of control (blue): they can veto both local and global dendritic regenerative events (NMDA spikes, Ca^{2+} spikes) and switch the gain between dendritic and axosomatic spike initiation sites from multiplicative to additive operations.

to the soma (Rall, 1964; Jack et al., 1975; Koch et al., 1983). This "on-the-path theorem" has been, and continues to be, a key rule for the integration of excitatory and inhibitory inputs, and has been very influential conceptually, so much so that results apparently contradicting it (e.g., Miles et al., 1996; Archie and Mel, 2000) seemed counterintuitive.

However, it has also been known for some time that the dendrites of most neurons are not passive but contain voltage-dependent conductances which can support nonlinear amplification of synaptic inputs as well as the initiation of local and not-so-local dendritic spikes (Magee, 2000; Gulledge et al., 2005). These dendritic mechanisms can be used to implement computations, such as improved discrimination of synaptic input patterns, and their effect on the input-output relation of a single neuron can be represented by simplified models with two or three layers of nonlinear subunits (Häusser and Mel, 2003). In these models, the ultimate decision whether to generate neuronal output by initiating an action potential in the axon is preceded and prepared by multiple decisions in the dendrites whether to nonlinearly boost different synaptic inputs, or generate dendritic spikes, or whether to nonlinearly couple somatic and dendritic spikes.

What is the function of different types of inhibitory synaptic inputs in controlling the action potential output of a neuron if its dendrites are active? In this issue of *Neuron*, Gidon and Segev (2012) lay the essential groundwork for answering this question. To do this, they adopt a firmly "dendrocentric" viewpoint, which is necessary because inhibitory synapses already influence those decisions taken locally in the dendrite, which in turn determine the final decision about action potential output in the axon. They first develop a new index, the shunt level (Figure 1A), to quantify the influence of local or remote inhibitory (and excitatory) synapses on the local dendritic input resistance. The shunt level is a relative measure, describing the percent change (due to activation of the synapse) in the local input resistance normalized by the local input resistance before activation of the synapse, and reflects for instance the relative influence of a synaptic conductance on the threshold for evoking a local dendritic spike (assuming that the voltage threshold for spiking is approximately constant). The shunt level can be calculated analytically for multiple conductance perturbations in passive dendritic trees, but also allows conclusions about changes in the threshold of active dendritic events due to activation of local or remote synaptic conductances.

Based on this new measure, the authors are able to explain some "counterintuitive" experimental results and reveal new principles governing the effect of inhibition in dendrites. First, they demonstrate analytically that off-path inhibition is—surprisingly—more effective than on-path inhibition at dampening nonlinearities in dendrites. In a simple passive dendrite model containing an "NMDA hotspot," they compare the impact of a proximal versus a distal inhibitory synapse and show that the asymmetry of dendrites conveys an advantage to distal inhibitory inputs. The electrotonic structure of most dendritic trees is known to be strongly

asymmetrical, as on the proximal side they are connected to the soma, which creates a large sink, and on the distal side, dendritic diameters tend to become smaller and terminate in a "sealed end," increasing local input resistance. This property favors the "off path" inhibition in two ways: first, the local shunt level caused by a synaptic conductance is larger due to the proximity of the end of the dendrite, and second, its spatial attenuation is shallower than for a proximal input as it lies further from the somatic sink. Gidon and Segev (2012) demonstrate that this result is robust with respect to the exact synapse location, dendrite geometry, and type of inhibition. The effect is indeed even larger when the inhibitory synapse is hyperpolarizing, rather than just providing "silent inhibition" by shunting. Recently, the stronger effect of "off path" inhibition on the threshold for evoking a local dendritic spike was also demonstrated experimentally in layer 5 pyramidal neurons by Jadi et al. (2012).

The full power of the new shunt level measure is revealed when the authors apply it to the question of multiple inputs and their nonlinear interactions in dendrites. Gidon and Segev (2012) show that multiple inhibitory inputs on different branches can cooperate to create a larger effect centrally than locally (Figure 1B). This cooperation is a direct consequence of passive cable properties and therefore applies in principle to all neurons receiving multiple inhibitory inputs. This result provides a potential explanation for the design of the synaptic connections observed between specific types of interneurons and principal cells. Typically, multiple synaptic contacts per connection are distributed across the dendritic tree of pyramidal cells. For the specific example of Martinotti cell (MC) to layer 5 pyramidal cell (PC) connections, they are targeting rather distal apical oblique and tuft branches, combining their effects to generate a maximal shunt level on the main apical dendrite. This suggests that multiple MC-to-PC connections can act as an inhibitory "council" for dendritic events in a pyramidal cell, taking the decision to either completely censor a Ca^{2+} spike in the apical dendrite, or alternatively veto coupling of the dendritic Ca^{2+} spike and somatic Na^{+} spikes.

By pioneering a new approach for analyzing inhibition in active dendrites, Gidon and Segev (2012) provide a solution to the longstanding puzzle of why so many interneuron subtypes target different parts of the dendritic tree (Klausberger and Somogyi, 2008). In particular, they highlight how biophysical principles can act as important design constraints for the detailed structure of neural circuits. For example, Gidon and Segev (2012) explain how a single interneuron can provide effective inhibitory coverage of a large dendritic region by distributing its synaptic contacts. Of course, there are other constraints on wiring architecture that must be considered, such as developmental or metabolic costs, and since the optimal architecture for inhibitory coverage also involves a significantly increased metabolic investment (more contacts and longer axons), it will be important to examine how the tradeoffs between the different constraints end up determining the actual structure of the circuit.

The results of Gidon and Segev (2012), together with those of Jadi et al. (2012), deliver a fresh emphasis on the functional importance of dendritic inhibition. In contrast to the traditional "somatocentric" viewpoint, they show that the "dendrocentric" viewpoint is essential for understanding the interplay between excitation and inhibition in controlling the integrative properties of neurons and outline multiple scenarios for how dendritic inhibition can be deployed. Not only can targeted inhibition veto nonlinearity in individual dendritic branches, but by strategic placement of multiple synapses, inhibition can also exert more global effects, such as changing the threshold of Ca^{2+} spikes in the main apical dendrite and switching the gain between dendritic Ca^{2+} spikes and somatic Na^{+} spikes from multiplicative to additive operations. This shift in perspective is encapsulated in the model of a pyramidal cell shown in Figure 1C, which illustrates how dendritic inhibition can modify a three-layer neural network representation of the pyramidal cell (Häusser and Mel, 2003; Spruston and Kath, 2004). This in turn implies that the location of inhibition is important (Mel and Schiller, 2004), but its spatial scale relevant for computation in dendrites may be variable, depending on the exact spatiotemporal pattern of inhibition and excitation. Of course, further refinements of this model are necessary. Gidon and Segev (2012) focused mostly on the spatial domain, but since the timing of inhibition is also known to be crucial, it will be important to examine how the timing of active inhibitory synapses interacts with and affects the temporal dynamics of neurons during network activity. The impact of inhibition on synaptic plasticity also needs to be considered, particularly because homeostasis of the excitation-inhibition balance is important for the stability of neural circuits. Ultimately, it will be necessary to develop a unifying theory in order to integrate the classical somatocentric and the new dendrocentric viewpoints and determine the effects of different spatiotemporal configurations of inhibitory inputs on both the threshold of nonlinear dendritic events and the gain with which they influence somatic spiking (see also Jadi et al., 2012).

What is particularly exciting is that we now may be in the position to address many of these questions experimentally. We are entering a golden era for the study of inhibition, because a range of new tools has recently become available for direct investigation of the structure and function of inhibitory circuits. High-throughput electron microscopy offers the prospect of anatomical reconstructions of all the elements in the circuit, allowing us to precisely identify the connectivity rules governing inhibitory axons and their relationship with excitatory synapses (Denk et al., 2012); two-color two-photon glutamate and GABA uncaging now permits us to independently control the temporal and spatial distribution of excitatory and inhibitory inputs onto dendrites and examine their interaction (Kantevari et al., 2010); two-photon in vivo imaging methods now allow us to record the activity of specific inhibitory populations (Sohya et al., 2007; Ma et al., 2010), ultimately during behavior; and optogenetics permits the specific activation or inactivation of different interneuron populations to probe their functional role independently (Atallah et al., 2012; Lovett-Barron et al., 2012). Together with the theoretical approaches introduced by the present study, these new tools should allow us to crack the problem

of how Sherrington's "admixture of inhibition and excitation" controls nervous system function.

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