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Microcircuits and their interactions in epilepsy: Is the *focus* out of focus?

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Abstract

Epileptic seizures represent dysfunctional neural networks dominated by excessive and/or hypersynchronous activity. Recent progress in the field has outlined two concepts regarding mechanisms of seizure generation or ictogenesis. First, all seizures, even those associated with what have historically been thought of as “primary generalized” epilepsies appear to originate within local microcircuits and then propagate from that initial ictogenic zone. Second, seizures propagate through cerebral networks and engage microcircuits in distal nodes—a process that can be weakened or even interrupted by suppressing activity in such nodes. Here, we describe various microcircuit motifs, with a special emphasis on one broadly implicated in several epilepsies - feed-forward inhibition. Further, we discuss how, in the dynamic network in which seizures propagate, focusing on circuit “choke points” remote from the initiation site might be as important as that of the initial dysfunction—the seizure “focus.”

Introduction

Epilepsy research and neuroscience owe much to insights we have learned from operating on the human brain. In the first half of the last century, neurosurgeon Wilder Penfield and his colleague Herbert Jasper pioneered incredible advances, such as characterizing motor and sensory maps and describing the form of cerebral electrical activity during seizures[1]. Their findings have inspired a decades-long inquiry aimed at understanding and treating epilepsy. Since then, we have found many changes in structure and/or function in the epileptic brain of humans and animals, such as altered morphology and excitability of individual neurons, changes in expression of neurotransmitter receptors, astrocytic and blood-brain-barrier dysfunction, neuroinflammation, and gains or losses of individual circuit components, which would render a neural network hyperexcitable. These studies have documented molecular and/or anatomical changes associated with the epileptic brain, and have been comprehensively described elsewhere (e.g.[2]). Despite these insightful studies, there is still no cure for epilepsy. Existing treatments only aim at controlling seizures and have significant side effects, and more than one third of all epilepsies remain uncontrolled.

More recently, technological advances have begun to provide detailed descriptions of microcircuit function in both humans and animal models of epilepsy. The results of these state-of-the-art approaches—such as paired (or even higher order) intracellular recordings, high-density multi-site extracellular arrays, activity-dependent reporter dyes and proteins,

and optogenetics—are beginning to provide unique insight into how networks at the micro scale organize and contribute to generating, propagating, and modulating seizure activity. These findings challenge the established, yet somewhat simplistic, view that epilepsy simply results from imbalances between excitation and inhibition. These advances are starting to reveal critical circuit junctures or choke points, potentially outside of the ictogenic network, that likely represent targets for highly specific and effective anti-epileptic therapies. In this review, we discuss epileptic choke points in the context of several microcircuit motifs implicated in animal models of epilepsy, as well as those that have been confirmed in humans.

We will consider the following microcircuit motifs (Fig. 1): 1) feed-forward inhibition, in which excitatory inputs from extrinsic brain regions recruit local inhibitory networks that tune the strength and form of the efferent signal; 2) feed-back inhibition, in which locally-activated inhibitory neurons shape recurrent excitatory activity; 3) counter-inhibition, in which local connections between inhibitory neurons that, when active, can decrease output of inhibitory cells and induce disinhibition or alter oscillatory coupling; and 4) local recurrent excitatory circuits, a common motif in cortical networks in which ~80% of neurons and synapses are excitatory. We also briefly consider relevant circuits outside of the microcircuit. These considerations include longer-range excitatory, inhibitory, and neuromodulatory connections that link and influence local microcircuit activities. For each of these motifs, we will identify dysfunctions that have been described at the microcircuit level, illustrate the relevance of these defects to epileptic seizures, and highlight potential therapeutic approaches that might profitably improve treatment of persons with epilepsy. Notably, these motifs do not exist in isolation, but are embedded in larger networks; the fine balance between these motifs dictates the dynamics of large-scale networks. We focus on the concept that epileptic seizures emerge from dysfunction of specific microcircuits, which then progressively engage other microcircuits to activate the full seizure network—an overall process termed ictogenesis. In this context, ictogenic choke points are any microcircuits or bridges between microcircuits that are required for full expression of seizures.

Feed-forward Inhibition

Within the last decade, epilepsy research has provided compelling results regarding the particular importance of feed-forward inhibition (Fig. 2a, b), which will be a major focus of this review. Feed-forward inhibition commonly occurs in several regions of the nervous system, including neocortical, hippocampal, basal ganglia, and thalamic networks. We will discuss how changes in feed-forward inhibition within different circuits can cause abnormal circuit dynamics that underlie epileptic seizures.

Feed-forward inhibition in neocortex and hippocampus

Incoming sensory signals traveling from the periphery to the cortex arise from the thalamus in the form of glutamatergic excitation that is largely focused on the sensory receptive zone in the cortical layer 4[3]. In turn, intracortical circuits are composed largely of excitatory neurons that are recurrently connected[4,5]. These neurons amplify and process incoming signals by propagating through a canonical microcircuit to superficial and then deeper

cortical layers. While incoming sensory signals are excitatory, a prominent feature of neocortical microcircuits is feed-forward inhibition mediated predominantly by fast-spiking (FS) basket cells containing the calcium binding protein parvalbumin (parv). Thus, incoming sensory signals directly and potently excite parv cells in layer 4, causing them to fire and release the inhibitory neurotransmitter GABA onto excitatory neurons in this layer. This causes a powerful feed-forward inhibition that sets a brief window for temporal synaptic integration in which spikes can be generated[6], and an overall limit for overexcitation in the neocortex[5–8]. Similar circuitry exists in the other cortical regions, including, for example, hippocampal dentate gyrus[9]. Notably, individual parv cells have potent output, mainly onto cell bodies and proximal dendrites, through convergent input to individual pyramidal cells[10,11]. This feature positions parv cells to powerfully suppress output of pyramidal and other principal cells. Note that while feed-forward inhibition generally suppresses activity, under some conditions, feed-forward activation of inhibitory neurons, especially Chandelier cells, can enhance network output[12]. Recently, findings demonstrate connectivity rules that add a level of complexity to feedforward inhibitory circuits. Accordingly, parv basket cells in the CA1 region of hippocampus do not indiscriminately target all CA1 pyramidal neurons within the domain of their axonal arbor, but specifically target subsets of pyramidal neurons with their own specific output projections[13]. Thus, this represents another potential choke point, as targeted excitation of relevant parv cells that suppress output to a specific region could prevent propagation to that region.

The powerful nature of feed-forward inhibition in thalamocortical (and other) circuits results from several factors, including a larger convergence of single-afferent thalamocortical axons onto individual parv–inhibitory cells that reliably generate spikes[8,14–16]; divergence of output from such parv cells[17,18]; and the strength of unitary connections from individual parv cells[8,11]. These observations support the hypothesis that the nervous system operationally requires adequate feed-forward inhibition, and failure of this key microcircuit leads to over-excitation of cortical networks and seizures. This hypothesis is supported by evidence in several models of epilepsy, including those induced by neonatal cortical freeze lesions that result in focal cortical dysplasia[7], and in the stargazer[19], tottering[20] and *gria4*$^{-/-}$, [21] models of generalized-absence epilepsy.

Losing feed-forward inhibition is consistent with the “dormant basket-cell” hypothesis of epilepsy [22,23] – that inhibitory neurons would lose so much connectivity that they would begin to fail in their necessary role of providing timely feed-forward inhibition. While the dormant basket cell theory considers both feed-forward and feedback inhibition (discussed in the next section), the former has often been shown to play a major role in studies with *in vitro* slice or whole hippocampal models that acutely induce epileptiform activity with chemoconvulsants[24–26]. Indeed, Cammarota et al. found that parv cells are primarily involved in feed-forward inhibition, much greater than the second-largest population of interneurons, somatostatin-positive (SOM) interneurons, which appear to significantly effect feed-back inhibition. The dormant basket–cell hypothesis has been controversial in terms of the actual circuit changes that might cause dormancy; however, it remains critical, because loss of feed-forward inhibition, with its powerful effects on the function of local excitatory neurons, causes potent dysfunction of circuits. Importantly, feed-forward inhibition has been

shown to prevent seizures from developing. Indeed, selectively impairing Ca^{2+} channels in neocortical parv interneurons[27], which would cause a loss of feed-forward inhibition, produces generalized-absence seizures. Similarly, specific reduction of the intrinsic excitability or synaptic excitation of parv inhibitory interneurons, but not of excitatory cells, decreases feed-forward inhibition. In recent studies, reduced function of $Na_v1.1$ sodium channels in parv FS interneurons was implicated in epileptic seizures in a mouse model of severe Dravet syndrome[28–30]. Additionally, deficits in $Na_v1.1$ in parv neurons contribute to epileptiform hippocampal activity in mouse models of familial Alzheimer's disease. Moreover, overexpressing $Na_v1.1$ reduces epileptiform activity[31]. By considering how parv cells affect feed-forward inhibition, we propose that rescuing hypofunctional inhibition could prevent seizures by restoring feed-forward inhibition.

Can feed-forward inhibition regulate seizure propagation over long distances? According to studies with novel *in vitro* preparations that retain callosal or commissural connections, it can. For example, in a callosum-intact bilateral neocortical slice preparation[32], chemically-induced epileptiform activity leads mainly to feed-forward inhibition in the contralateral cortex. Similar effects occurred in bilateral-intact hippocampal preparations, especially in the early phase of seizure induction in which interictal spikes were most prominent[26]. Thus, prominent phasic inhibition from afar can signal an impending seizure.

Feed-forward inhibition also critically regulates the dynamics of the hippocampal network, as shown in models of temporal lobe epilepsy (TLE). In this network, the tri-synaptic loop is most often discussed with regards to activity propagation from entorhinal cortex to dentate gyrus to CA3 to CA1; however, this network contains other pathways that may play key roles in seizure genesis and/or propagation. For example, in addition to the entorhinal projection to dentate, there is also a projection directly to CA1 through the temporoammonic pathway. Losing feed-forward inhibition in this pathway occurs in the pilocarpine model of TLE as a result of several factors, including cell loss in superficial neurons in layer 3 of the entorhinal cortex[33], which project to hippocampal CA1 [34]; loss of stratum oriens-lacunosum moleculare (O-LM) interneurons[35] that in addition to their major role in feed-back inhibition also mediate feed-forward inhibition in the tempero-ammonic pathway[36]; and distal dendritic inhibitory denervation of hippocampal CA1 cells, a region preferentially regulated by O-LM interneurons[37,38]. Combining these processes would produce a loss of feed-forward inhibition from the entorhinal cortex to CA1. This hypothesis is consistent with results of a voltage-imaging study in which entorhinal stimulation massively activated the pathological network in CA1 hippocampus of post-pilocarpine epileptic animals[39]. Interestingly, surviving O-LM cells in CA1 send aberrant fibers into dentate gyrus, which may, at least partially, compensate for the loss of local dentate inhibitory cells[40].

Feed-forward inhibition can also be relevant to intra-areal cortical excitation. It is largely responsible for surround inhibition, which was documented decades ago in pioneering studies of acute neocortical or hippocampal seizures in felines[41,42]. Recently, both feed-forward and surround inhibition have been investigated with optical and electrophysiological methods to study the spread of seizures from a focal zone that initiates epileptic seizures—the "ictogenic" zone. These results, obtained largely in rodent models in which epileptic seizures were induced by chemoconvulsants, show that the earliest forms of

peri-ictal synaptic activity are multiphasic, repetitive, and create potent inhibitory signals. This early activity is associated with normal (non-ictal) background behavior in the network, but is followed by a sudden collapse of inhibition, such that strong excitatory signals dominate individual cellular responses. As a result, these signals produce precipitous step-like waves of local excitation at the network level, as observed with Ca^{2+} imaging[43]. This cycle then repeats to propagate seizure activity to the next microcircuit. Recently, analogous neural activities have been revealed from intra-operative intracranial electrical recordings obtained from the cerebral cortex of epilepsy patients being evaluated for neurosurgical resections[44]. These recordings suggest that during clinical seizures, feed-forward inhibition fails through mechanisms similar to those observed in experimental animals.

Feed-forward inhibition in thalamus

Circuit motifs differ between brain regions, especially between cortical and subcortical microcircuits. The thalamus—as a sensory relay station—shapes incoming peripheral information through three inhibitory pathways: 1) feed-forward dendro-dendritic inhibition mediated by local circuit interneurons that sculpt packets of primary afferent signals to delay firing[45]; 2) direct feed-back inhibition driven by triggering thalamocortical (TC) drive of inhibitory thalamic reticular (RT) neurons; and 3) inhibition via the RT nucleus triggered by cortical feedback. The latter form can be confusing, because recurring excitatory signals from cortex to thalamus would normally be considered *feed-back*. Yet, from a microcircuit perspective, output from cortex triggers *feed-forward* inhibition, because the major effect of cortical output is preferred recruitment of inhibitory cells in the RT nucleus[21,46]. Thus, RT cells provide powerful inhibitory output onto excitatory TC relay cells.

Recent studies have suggested that loss of feed-forward inhibition in the cortico-thalamic pathway can be epileptogenic. For example, studies revealed that inhibitory RT neurons lose AMPA-mediated excitation in two genetic models of generalized-absence epilepsy: stargazer and *gria4*$^{-/-}$ mice[21,47,48]. In the latter model, the synaptic defects within the cortico-thalamic microcircuit were deconstructed with optogenetics—a promising new approach to studying epileptogenetic pathways. This approach revealed how loss of a specific microcircuit component—synaptic excitatory drive from neocortex onto inhibitory RT cells—can cause a deficit in feed-forward, but not feed-back, inhibition[21] (Fig. 2b). These findings suggest that even though cortical efferents are largely, if not exclusively excitatory, their primary effects on thalamic activity can be inhibitory (for discussion of the potential physiological roles for such feed-forward inhibition, see[49]). These results further suggest that specifically restoring excitatory inputs from the cortex onto RT cells would rescue feed-forward inhibition and suppress absence seizures that would otherwise develop in the thalamocortical network.

Feed-forward inhibition: a potential target of anti-epileptic drugs?

Feed-forward inhibition is critical for normal circuit function yet is also paradoxically fragile because of several factors, including intracellular Cl^- accumulation, GABA depletion, and presynaptic inhibition[50–53]. Altering these factors with drugs may create restorative treatments against epilepsy. Further, if a loss of feed-forward inhibition is a cause of epilepsy, then anti-epileptic drugs (AEDs) should in principle re-establish it, and in no

case should they suppress it. However, several AEDs, including phenytoin, carbamazepine[54,55], and lamotrigine[56], may work through a mechanism that blocks Na^+ channels, especially in the context of action potentials that fire at high-frequency. Parv cells, which largely mediate feed-forward inhibition and fire at high frequencies, may be susceptible to reduced firing by AEDs. Thus, AEDs could potentially worsen seizures. To resolve this paradox, a study recently addressed the effects of Na^+ channel blockers (e.g., the anti-convulsant drugs carbamazepine, phenytoin, and lamotrigine) on different cell types. These compounds specifically reduced repetitive firing in pyramidal neurons, but not in FS or other interneurons[57]. The AEDs also did not affect recruitment of inhibition during repetitive activity. Thus, AEDs reduce action potential firing primarily in excitatory neurons and spare interneurons to maintain feed-forward and other forms of inhibition.

To conclude, the anatomical connectivity and functional features of parv basket cells in cortex and hippocampus and parv RT cells in the thalamus enable them to serve as central players in feed-forward inhibition. Furthermore, this inhibition is well-positioned to prevent epileptic activity from bridging between microcircuits, and its failure could readily propagate seizures. Thus, mediators of feed-forward inhibition—mainly parv cells—could serve as potential seizure choke points.

Feed-back Inhibition

In contrast with feed-forward inhibition, which is a microcircuit motif engaged by *extrinsic* sources, feed-back inhibition generally results from excitation within *local* circuit elements (Fig. 3a, b). Like feed-forward, feed-back inhibition is a common theme in cerebral circuits. While different classes of inhibitory cells can mediate both forms of inhibition, their relative roles differ. Indeed, the parv cells described above appear to play a major role in feed-forward inhibition, while a second major class of inhibitory cells, SOM-containing interneurons, appear to play a more important role in feed-back inhibition.

Although diverse subclasses of SOM cells can be involved in epilepsy, we will focus our discussion mainly on one subclass of SOM cells—Martinotti neurons—which target distal dendrites of pyramidal neurons[10,58,59]. Compared with parv-mediated inhibition, Martinotti-mediated inhibition is weaker at baseline because post-synaptic cells have fewer synapses[11]. However, Martinotti-dependent inhibition is progressively recruited by simultaneous repetitive activity in multiple pre-synaptic pyramidal cells, as would happen, for example, during intense activation of local microcircuits in seizures. Such recruitment results from facilitating short-term synapses of both the excitatory inputs onto and the inhibitory outputs from neocortical Martinotti cells and related neurons of the hippocampus[60–62]. In contrast, inhibition from parv basket cells is initially robust because of convergent input coupled with high-probability sites of release onto pyramidal cells. However, due to short-term synaptic depression, the efficacy of parv-mediated inhibition rapidly drops during repetitive activation[61].

The progressive nature of Martinotti-cell recruitment could be important for dampening activity to locally suppress seizures in the microcircuit. Consistent with this, mice deficient in the transcription factor DLX1 show reduced SOM cells and a mild epilepsy phenotype[63].

Furthermore, in a murine model of Dravet syndrome, SOM-mediated inhibition is also reduced[28].

In addition to SOM/Martinotti cells, other neurons may contribute to feed-back inhibition in epileptic microcircuits. For example, neocortical chandelier cells, which target the initial axon segments of pyramidal neurons, may prevent hyperexcitation related to epilepsy. In an *in vivo* study that examined the spontaneous and whisker-evoked activity of a variety of neuronal types in the barrel cortex, chandelier cells only responded weakly to whisker stimulation; only small synaptic potentials were observed and they rarely evoked action potentials[64]. However, disinhibition induced by local cortical application of the GABA-receptor antagonist bicuculline caused a 20-fold increase in the spontaneous firing rate of chandelier cells, which exceeded that of any other cells recorded. This finding suggests that chandelier cells may be specifically recruited by epileptic activity, and that by vetoing spike output via shut-down of pyramidal cell axons, may serve as a microcircuit emergency brake. Although the specific excitatory versus inhibitory effects of activating chandelier cells remain controversial[12,65–67], their activation potentially represents another seizure choke point.

Another example of the role of feed-back inhibition in epilepsy comes from studies of thalamocortical circuits primarily implicated in generalized-absence epilepsy. Here, feedback inhibition has a powerful seizure-*promoting* role, especially within the thalamus. The thalamic network is composed of topographically related, reciprocally connected inhibitory neurons in RT and excitatory TC cells located in specific relay nuclei within dorsal thalamus[68] (Fig. 3b). Activity of the excitatory TC cells activates synapses of RT neurons to cause recurrent feed-back inhibition in the same TC cells. Such inhibition promotes activity of the oscillatory network within the thalamus, because TC cells exhibit a form of paradoxical activation—they fire post-inhibitory rebound bursts of action potentials when strongly inhibited by synchronized output of RT neurons. At the microcircuit level, enhancing feed-back inhibition with pharmacological interventions, such as those that block uptake of the inhibitory neurotransmitter GABA, or pharmacological treatments that specifically target RT-TC synapses, exacerbate epileptiform activity *in vitro*[69,70] (see also Fig. 3b) and worsen generalized-absence seizures in epilepsy patients[71].

In the thalamus, TC-RT-TC feed-back inhibition can promote seizure responses, whereas in the cortex, feed-back inhibition largely suppresses seizure activities. Thus, caution is required when interpreting results from global gene knock–out models that generally affect microcircuits, such as those that enhance feed-back inhibition. Similarly, treatments that non-specifically target feed-back inhibition through the brain might not only be ineffective, but might also exacerbate seizures.

To conclude, feed-back inhibition can engage specific microcircuits to either stimulate or inhibit seizure activity. Accordingly, we need to dissect relevant microcircuits involved in ictogenesis to identify specific seizure choke points in different types of epilepsies.

Counter-Inhibition

The nervous system makes its own, sometimes inscrutable, rules about the type and strength of connections made by any individual cell type. In some cases, the synaptic output of a particular neuronal class is quite promiscuous, as it couples indiscriminately to any nearby neurons that fall within its range of efferent axonal output[72]; however, in other cases, it exclusively targets either neurons of its own or other subclasses[73]. Inhibitory neurons have unique connectivity rules that seem to take this idea to the extreme. In addition to their potent inhibitory output to pyramidal neurons, parv basket cells form powerful autaptic connections (i.e., they synapse onto themselves)[74,75]—a relatively rare form of connectivity in the nervous system.

Along these lines, many classes of inhibitory interneurons make chemical and/or electrical synaptic connections with other interneurons within or outside their own class[72,76,77], and some inhibitory cell classes (in cortical layer I and/or expressing the peptide vasoactive intestinal peptide, VIP) have been shown to specifically mediate disinhibitory effects through inhibition of SOM and parv cells [78–80]. Thus, stimulation of a given set of inhibitory neurons could cause a specific disinhibitory effect, perhaps promoting overexcitation, while inhibition of Layer I/VIP cells might produce an increase in SOM/parv output and result in a seizure choke point. Given the diversity of inhibitory motifs in microcircuits described so far, blocking one of these motifs could have disparate and, perhaps, opposite consequences on the overall function of microcircuits. Thus, counter-inhibition—inhibition of inhibition—(Fig. 4a, b) is a key concept in epileptic microcircuits. For example, counter-inhibition of parv basket cells may largely suppress feed-forward inhibition (motif 1) and promote seizure propagation between regions, while counter-inhibition of Martinotti cells may promote local ictogenesis through loss of the progressively activated feed-back circuit[60,62]. Here, we will focus on one type of counter-inhibition: between cells of the same inhibitory class.

Counter-inhibition in neocortex and hippocampus

Counter-inhibition can promote activity through several mechanisms. First, among inhibitory cells, counter-inhibition can disinhibit downstream excitatory cells, leading to a general increase in firing. Alternatively, it can promote oscillatory activity in reciprocally connected networks. For example, synaptic inhibition between parv FS cells can promote oscillatory output from microcircuits to produce gamma-frequency oscillations[81]. Such gamma- and related higher-frequency oscillations have been implicated in ictogenesis in limbic epilepsy[82] (Fig. 4a).

Counter-inhibition in thalamus

Counter-inhibition affects thalamic function and has been implicated in ictogenesis in absence epilepsy. In thalamic microcircuits, RT neurons mediate feed-forward and feedback inhibition (as described above). Additionally, RT neurons are locally interconnected by both chemical-inhibitory[83] and electrical synapses[83,84]. Chemical inhibition between RT cells is potent and characterized by long-lasting synaptic responses[85], and also can limit the synchronous activation of RT cells during epileptiform oscillatory responses in the network[86]. Hence, specific loss of RT-RT counter-inhibition by deleting a critical, nucleus-

specific, $GABA_A$-receptor β3-subunit, is associated with enhanced emergent hypersynchrony and the development of epilepsy[87] (Fig. 4b). Accordingly, targeting hypersynchrony and epilepsy in thalamic networks with pharmacotherapies will need to cause a greater net effect on RT-RT inhibition (anti-oscillatory) versus TC-RT-TC feedback inhibition (pro-oscillatory)[69]. Indeed, the anti-epileptic drug clonazapam decreases output of RT neurons by specifically enhancing RT-RT counter-inhibition[88].

Thus, in contrast to the generally suppressive effects on target excitatory cells described above for feed-back and feed-forward inhibition, counter-inhibition can promote or reorganize the excitatory activity of microcircuits, respectively. These effects can occur either through disinhibition or entrainment of recurrent inhibitory networks that produce periodic-phased synaptic inhibition to control the timing of excitatory cells.

Recurrent Excitation

This recurrent excitation microcircuit motif (Fig. 5a, b) falls well within the context of the excitation/inhibition discussions of epileptogenic mechanisms—and for good reason. Recurrent excitation is enhanced in most experimental epilepsies. Yet, modern approaches are now promoting identification of specific, and sometimes *de novo*, changes in excitatory circuits. One powerful approach is photostimulation, often with photo-labile ligands such as caged-glutamate[89]. With this approach, originally reported over a decade ago, light can be focally delivered to specific locations in a brain circuit, most commonly in an acute brain slice. This light activates neurons in that region and generates synaptic excitatory signals in neurons post-synaptic to the stimulated cells. This approach showed that recurrent excitation within the dentate gyrus commonly occurred in a limbic epilepsy model[90]. More recently, this approach revealed intricate changes in dentate connectivity, with notable increases in inputs to dentate gyrus granule cells from not only other granule cells, but also hilar excitatory neurons and CA3 pyramidal neurons[91] (Fig. 5b). Such changes can create a strong basis for a hyperconnected, epileptic network, if the reorganization follows the principles of hub-cell connectivity, in which a small number of well-connected neurons help develop complex network activity such as seizures[92].

In neocortex, recurrent excitatory connections are enhanced following cortical injury and are notably precise. For example, in the isolated cortical slab, which produces epileptogenic insult (Fig. 5a), enhanced connectivity was restricted to infragranular layers, especially layer 5[93]; however, in a model of focal cortical dysplasia, enhanced connectivity to layer 5 cells was seen from both infra and supra-granular regions[94]. These findings suggest that lesion-specific reorganization occurs in different injury models.

Interventions that counteract or reverse such enhanced reorganization of excitatory microcircuits may yield novel therapeutic approaches. Note that these approaches would be most effective if they specifically targeted maladaptive reorganizations in excitatory networks and maintained normal function of recurrent excitatory networks.

Microcircuit interactions

So far, we have reviewed the properties of isolated microcircuits relevant to ictogenesis, including the important features of connection sign (inhibitory/excitatory), spatial pattern (convergence/divergence), and target region (soma/dendrite/axon). These features are all relatively static in microcircuits, yet many synaptic and cellular components of the circuits can be dynamically modulated to create a stable microcircuit that could, under the right (or wrong!) conditions, progressively shift to an ictogenic form. Further, as indicated at the outset of this review, individual microcircuits do not exist in isolation, and epilepsy results from propagation of ictal activity through the distributed microcircuits. Furthermore, we suggested the novel concept that an imbalance between diverse microcircuit motifs—such as between feed-back and feed-forward inhibition—can be ictogenic. As mentioned above with regards to *gria4*$^{-/-}$ mice, absence epilepsy results from lack of feed-forward, but unaffected feed-back, inhibition. In this case, a specific defect at the cortico-RT synapse results in lack of cortico-RT-TC feed-forward inhibition, which causes abnormal recruitment of TC cells by afferent excitatory inputs (i.e., multiple TC cells are concurrently activated by cortical output), while the intact TC-RT pathway results in powerful TC-RT-TC synchronized feed-back inhibition. Thus, an imbalance between feed-forward and feed-back inhibition enables normal excitatory inputs to recruit seizures[21].

To conclude, this case, in particular, supports the emerging concept that the field needs to expand beyond the historical view that epilepsy simply results from an imbalance between excitation and inhibition and consider that epilepsy can also result from an imbalance between different microcircuit motifs.

In this next and last section, we briefly discuss two issues relevant to seizure choke-points: internal dynamics and external influences on microcircuits.

Dynamics in microcircuits

As indicated above, synaptic connections are considerably heterogeneous, not only in targets and connection strength, but also in short-term dynamics. For example, basket-cell output synapses show short-term depression and lose efficacy over time, and SOM/Martinotti cells show the opposite by augmenting synapses that increase in efficacy over time. Such dynamic changes will inevitably alter the balance between different forms of inhibition. Thus, the normally high ratio of inhibitory output of basket cells (mainly parv to somatic targets) to Martinotti and related cells (SOM to dendritic targets) observed during physiological activity will be replaced by an inverted ratio in which Martinotti-cell output predominates[61]. This effect may suppress abnormal activity within an ictogenic microcircuit, but leave that same microcircuit vulnerable to additional extrinsic ictogenic signals caused by a loss of feed-forward inhibition.

External influences on microcircuits

Activity can be propagated between microcircuits through efferent projections to circuit elements outside of the microcircuit. Indeed, long-range excitatory projections connect distal cerebral areas. For example, the corpus callosum is composed largely of axons of excitatory

cortical neurons[95], and this major commissural tract is responsible, in large part, for propagation of seizures[96]. In recent work, certain classes of inhibitory neurons also made long-range connections that would influence local and global epileptic networks. These findings have recently been reviewed elsewhere[97] and will not be further discussed here, except to highlight that this theme is emerging with potential relevance to the motifs described above and their ictal choke points.

As with intra-hemispheric cerebrocortical networks, corticothalamocortical networks are connected through long-range, reciprocal excitatory projections. Sensory regions of dorsal thalamic nuclei are composed largely of excitatory feed-forward TC excitatory neurons that transfer peripheral sensory information to the cortex via projections primarily to cortical layer 4. There, activity reverberates and propagates between cortical layers[4] to, ultimately, end up in deep cortical layers, including layer 6. Layer 6 neurons then emit axons back to thalamus to re-excite the TC neurons. In sensory thalamus and cortex, this synaptic relationship is topographic in both directions, leading to a highly localized, but long-loop, excitatory recurrent network. Interposed on this, and indeed embedded within it, is the intrathalamic loop between TC neurons and inhibitory RT neurons. As we described above, this embedded reciprocal relationship between circuits is kept in check by powerful feed-forward inhibition from the cortex that prevents significant excitation of relay neurons that might lead to runaway excitation and seizures.

An additional consideration regarding extrinsic influences on microcircuits is the effect of neuromodulatory pathways, which can selectively and specifically act on individual microcircuit components. For example, cholinergic modulation disparately inhibits basket cells and activates presumed SOM cells[10]. Of note, recent studies have shown that a subset of narrow spiking neurons, presumed basket cells, is negatively modulated by attendance to a visual task. This finding suggests that attentional states can lead to disinhibition through specific changes in inhibitory microcircuits[98].

Circuit therapy: where are the choke points?

While the process of developing epilepsy—*epileptogenesis*—likely entails multiple adaptive and maladaptive circuit changes, here we have addressed several simple microcircuit motifs in which dysfunction in one element (e.g., a synapse or neuron) either through gain- or loss-of-function (e.g., change in synaptic strength or intrinsic excitability), can effectively entrain local network activity. The build-up of such local activity to the point of initiating a seizure is an ictogenesis. Thus, in each of the four different cases of maladaptive circuit motifs, restorative treatments that would reverse or counteract the specific dysfunction (or perhaps prevent the dynamic recruitment of that dysfunctional element during ictogenesis) could create an effective anti-seizure therapy. By extending this approach, some regions other than the point of maximal dysfunction might be targeted (Fig. 6a–d). Distal targeting might be more efficient because the distal sites are either critical in global ictogenesis and/or are more spatially restricted and thus easier to maximally target. If the cells in distal sites are only modestly involved in global ictogenesis, then reducing the activity of only some of them will not be effective. However, if they are concentrated in a region such that the bulk of relevant cells in the distal subnetwork can be effectively targeted, then great efficacy would be

gained. For example, a rat model of cortical photothrombotic stroke developed epilepsy over time (Fig. 6a). Here, specifically inhibiting the portion of thalamus projecting to the surviving peri-infarct cortex was sufficient to abort, in real-time, automatically detected seizures[99]. Because of extensive long recurrent excitatory connections with cortex, these results suggest that thalamus could be an important target in epilepsies resulting from cortical lesions other than stroke.

Several additional examples of localized, off-site seizure control are evident and further support that remotely regulating seizures might create a generally useful concept regarding ictogenic choke points. For example, in a model of limbic epilepsy caused by unilateral intrahippocampal injection of the excitotoxin kainic acid, optogenetic excitation of inhibitory cells of either the primary ipsilateral epileptogenic zone or in the contralateral hippocampus reduced seizures[100] (Fig. 6c). In another example of off-site control this same group has shown that optogenetic activation of cerebellar Purkinje neurons suppresses seizures in this animal model of epilepsy [101]. Additionally, experimental seizures induced by either electrical or chemical stimulants are strongly suppressed by locally inhibiting the substantia nigra [102]. Thus, targeting such subcortical structures, such as the thalamus or substantia nigra, remote from the initial cortical dysfunction, might have major advantages. For instance, targeting the thalamus in real time would be less deleterious than targeting the eloquent cortex. We propose that the thalamus could be a choke point in epileptic circuits in the same way that the subthalamus (STN) is a choke point for abnormal circuit dynamics in Parkinson's disease. Indeed, the concept of circuit motif choke points can be broadly applied to nervous system disorders. In the case of Parkinson's disease, the initial dysfunction results from the degeneration of neurons in the substantia nigra pars compacta and, therefore, is remote from the STN. However, targeting the STN is the major therapy used in Parkinsonian patients. Indeed, the STN is a choke point of abnormal circuits in Parkinson's disease because of its key location within the circuit, even though the initial dysfunction is remote (Fig. 6b) [103]. Of note, high-frequency stimulation of STN or inhibition of substantia nigra pars reticulata[104,105] also strongly suppresses seizures in GAERS[106]—a model of generalized-absence epilepsy—further supporting the concept of distal epileptic choke points.

Conclusions

While we need to identify the "focus" of the initial dysfunction, we also need to look for potential control or choke points that are remote and could be distant from the "focus" of the initial dysfunction. Thus, by scanning regions outside that of the initial insult, we may find "foci" far from what has historically been considered the focus, and, in so doing, may find unique opportunities for effective therapies that target these circuits.

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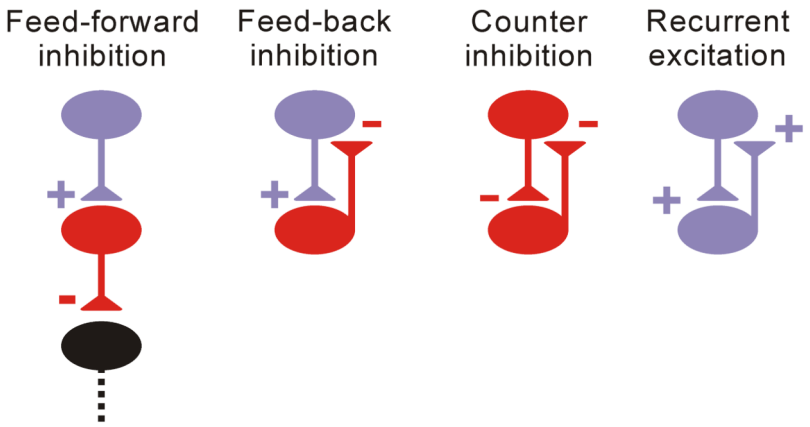

Figure 1. Microcircuit motifs whose dysfunctions have been identified in epilepsy

Feed-forward inhibition: excitatory inputs from remote brain regions recruit local inhibitory networks that control the strength of the efferent signal; **Feed-back inhibition**: local activation of inhibitory neurons creates local recurrent excitatory activity; **Counter-inhibition**: local connections between inhibitory neurons shape network-inhibitory output; **Recurrent excitation**: major mode of connectivity in cortical networks; Purple and red represent excitatory glutamatergic and inhibitory GABAergic neurons, respectively, in this and all following figures.

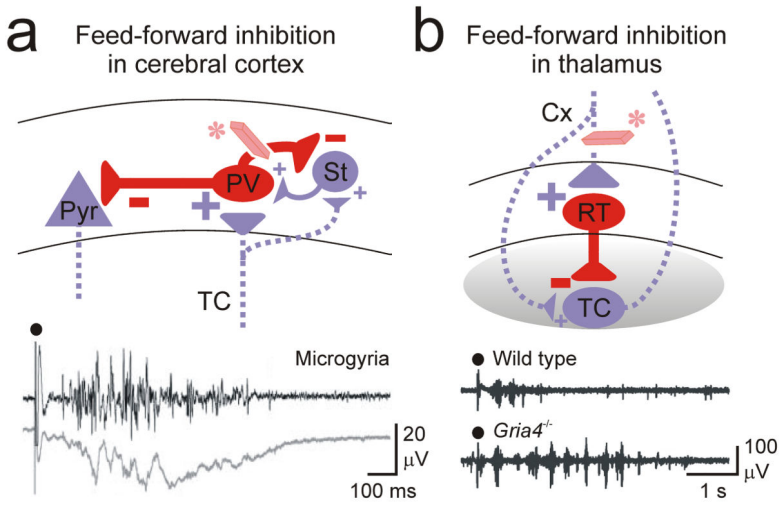

Figure 2. Feed-forward inhibition in cortical and thalamic microcircuits

(**a**) Extrinsic excitatory projections from regions outside of local cortical networks recruit feed-forward inhibition. Cortical inter-areal or thalamic inputs to the cortex result in stronger activation of FS parv cells than excitatory stellate and pyramidal cells, thus causing a robust feed-forward inhibition of excitatory cells. In case of a loss of this feed-forward inhibition (eraser*), thalamic inputs to the cortex recruit epileptiform activity in a neocortical microgyrus model of focal neocortical epilepsy (bottom multi-unit and local field recordings[7]). (**b**) Excitatory inputs from the cortex to the thalamus results in stronger activation of the inhibitory interneurons, which causes a strong feed-forward inhibition of relay excitatory neurons. Loss of feed-forward inhibition (eraser*) has been implicated in the *gria4*$^{-/-}$ mouse model of absence epilepsy (multi-unit recordings[21]) Black circle: electrical stimulation of excitatory afferents. Cx, cortex; parv, parvalbumin-positive interneuron; Pyr, pyramidal neuron; RT, reticular thalamic neuron; St, stellate; TC, thalamocortical neuron.

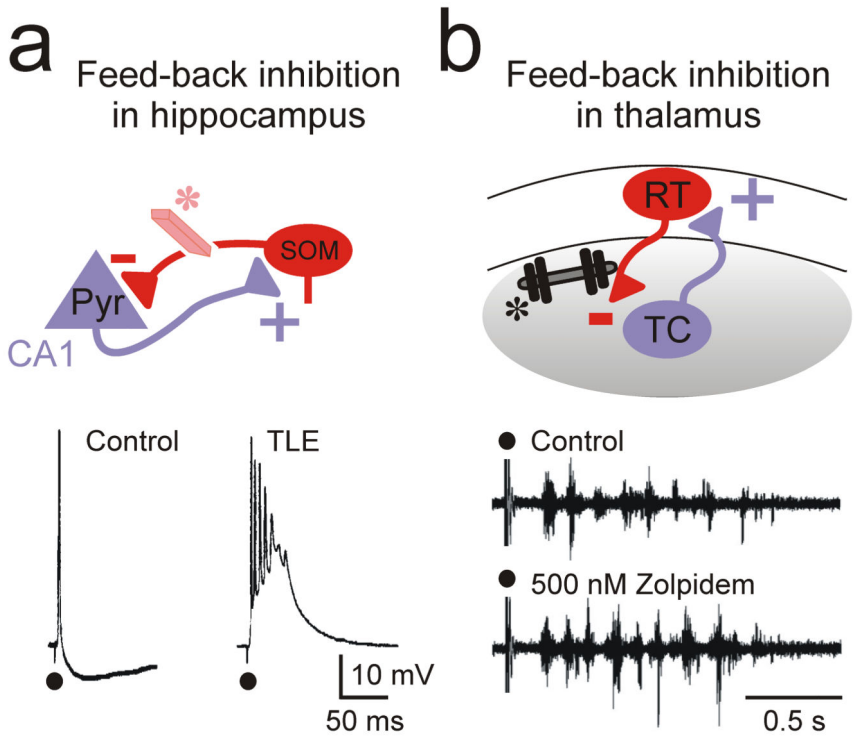

Figure 3. Feed-back inhibition in cortical and thalamic microcircuits

(**a**) In the cortex, inhibitory SOM interneurons provide a feed-back inhibition to pyramidal neurons that excite them. Loss of this inhibition (eraser*) has been implicated in temporal lobe epilepsy (TLE)[37]. (**b**) In the somatosensory thalamus, inhibitory interneurons provide a robust feed-back inhibition to TC neurons that excite them. Increasing this feed-back inhibition (dumbbell weight *) by Zolpidem, or by clonazepam in α3H126R mice (not shown[69]), which specifically affects RT-TC but not RT-RT connections, enhances epileptiform oscillations. Pyr, pyramidal; SOM, somatostatin-positive; RT, reticular thalamic neuron; TC, thalamocortical neuron.

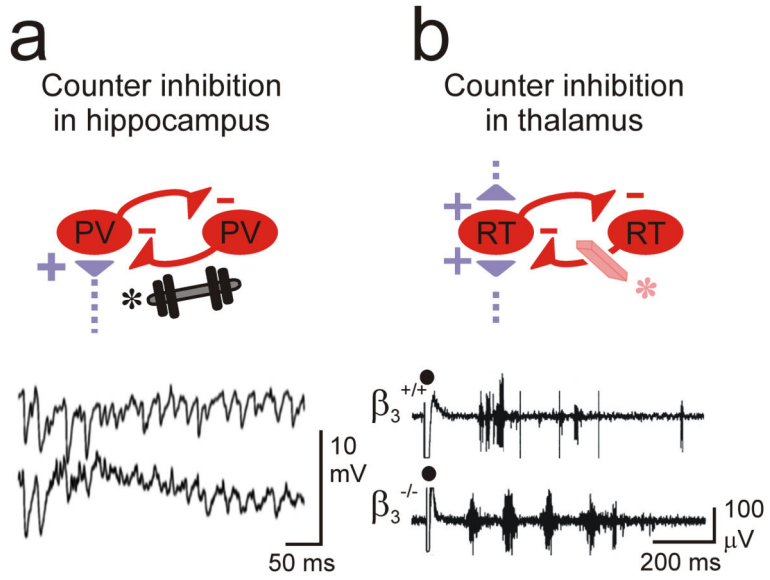

Figure 4. Counter-inhibition in hippocampal and thalamic microcircuits

(**a**) Inhibition between FS parv cells in the hippocampus can enhance gamma rhythmicity[81]. Increasing this inhibition (weight*) has been suggested to enhance network synchrony associated with epilepsy. (**b**) Inhibition between RT neurons in the thalamus desynchronizes the thalamic network oscillations between TC and RT cells. Loss of RT-RT counter-inhibition (eraser*) in a $\beta3^{-/-}$ mouse enhances intra-thalamic network synchrony and has been implicated in epilepsy[87]. RT, reticular thalamic neuron; TC, thalamocortical neuron.

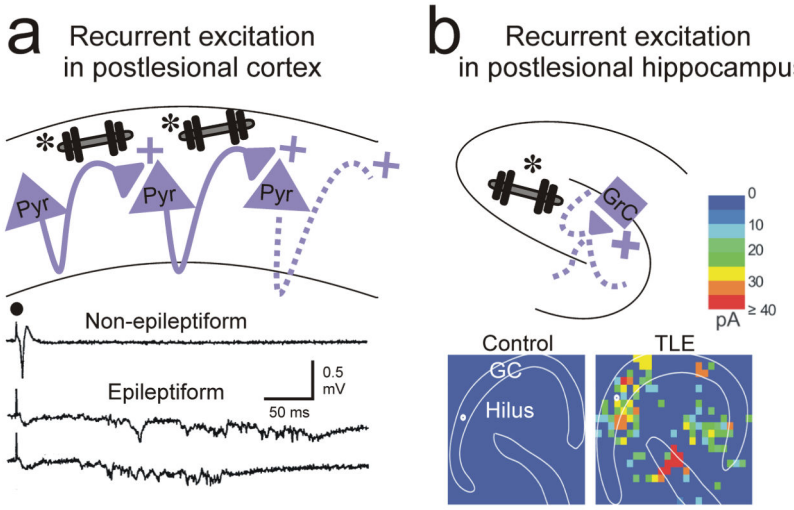

Figure 5. Recurrent excitation in cortex and hippocampus

(**a**) Recurrent excitation between pyramidal excitatory cells (weights*) develops after neocortical lesions and has been implicated in epileptiform activities in the undercut model of focal neocortical epilepsy [107]. Bottom traces: local recordings of epileptiform field potentials from the injured neocortex evoked by electrical stimulation (black circle). (**b**) Ectopic recurrent excitation (weight*) between presynaptic excitatory neurons in dentate, hilus, and CA3 and post-synaptic granule cells in the hippocampus develops in the pilocarpine model of temporal lobe epilepsy. Bottom: Connectivity maps based on glutamate photo-uncaging evoked excitatory postsynaptic currents in slices from control and epileptic (TLE) mice[91].

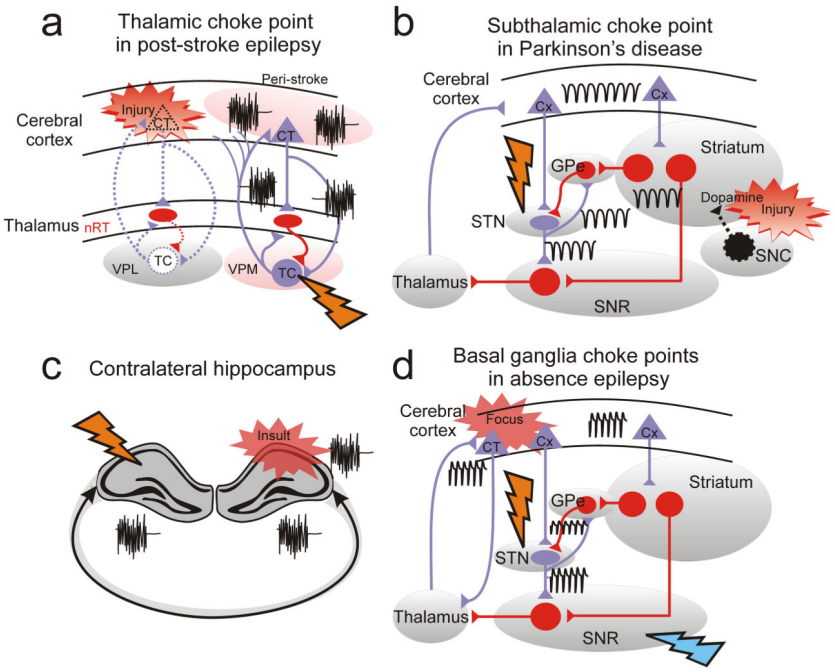

Figure 6. Circuit therapy: focus on choke points

(a) The thalamus is a choke point for epileptic seizures in post-stroke epilepsy[99]. Note that the choke point (flash: thalamus) is remote from the initial dysfunction (red flash), which is a stroke in the cerebral cortex. (**b**) The subthalamus (STN) is an efficient choke point for pathological circuit oscillations in Parkinson's disease. Note that the choke point (black flash: STN) is remote from the initial dysfunction (yellow flash), which results from degeneration of dopaminergic cells (Dopamine) projecting from the substantia nigra compacta (SNC) to striatum. (**c**) Contralateral hippocampus is a choke point for controlling ipsilateral hippocampal epileptic activity[100]. (**d**) STN and SNR are choke points for spike-and-wave discharges associated with absence epilepsy and generated in somatosensory cortex [108]. Black oscillations: pathological oscillations; Red flash: initial injury or insult; Orange flash: choke point for pathological network oscillation. Other abbreviations: GPe: External globus pallidus; SNR: substantia nigra pars reticulata. Purple cells/projections: excitatory glutamatergic; Red cells/projections: inhibitory GABAergic.