

THE MARCH OF EPILEPTIC ACTIVITY ACROSS CORTEX IS LIMITED (FOR A WHILE) BY THE POWERFUL FORCES OF SURROUNDING INHIBITION

Modular Propagation of Epileptiform Activity: Evidence for an Inhibitory Veto in Neocortex. Trevelyan AJ, Sussillo D, Watson BO, Yuste R. *J Neurosci* 2006;26(48):12447–12455. What regulates the spread of activity through cortical circuits? We present here data indicating a pivotal role for a vetoing inhibition restraining modules of pyramidal neurons. We combined fast calcium imaging of network activity with whole-cell recordings to examine epileptiform propagation in mouse neocortical slices. Epileptiform activity was induced by washing Mg^{2+} ions out of the slice. Pyramidal cells receive barrages of inhibitory inputs in advance of the epileptiform wave. The inhibitory barrages are effectively nullified at low doses of picrotoxin (2.5–5 μM). When present, however, these inhibitory barrages occlude an intense excitatory synaptic drive that would normally exceed action potential threshold by approximately a factor of 10. Despite this level of excitation, the inhibitory barrages suppress firing, thereby limiting further neuronal recruitment to the ictal event. Pyramidal neurons are recruited to the epileptiform event once the inhibitory restraint fails and are recruited in spatially clustered populations (150–250 μm diameter). The recruitment of the cells within a given module is virtually simultaneous, and thus epileptiform events progress in intermittent (0.5–1 Hz) steps across the cortical network. We propose that the interneurons that supply the vetoing inhibition define these modular circuit territories.

Feedforward Inhibition Contributes to the Control of Epileptiform Propagation Speed Trevelyan AJ, Sussillo D, Yuste R. *J Neurosci* 2007;27(13):3383–3387. It is still poorly understood how epileptiform events can recruit cortical circuits. Moreover, the speed of propagation of epileptiform discharges *in vivo* and *in vitro* can vary over several orders of magnitude (0.1–100 mm/s), a range difficult to explain by a single mechanism. We previously showed how epileptiform spread in neocortical slices is opposed by a powerful feedforward inhibition ahead of the ictal wave. When this feedforward inhibition is intact, epileptiform spreads very slowly (100 $\mu m/s$). We now investigate whether changes in this inhibitory restraint can also explain much faster propagation velocities. We made use of a very characteristic pattern of evolution of ictal activity in the zero magnesium (0 Mg^{2+}) model of epilepsy. With each successive ictal event, the number of preictal inhibitory barrages dropped, and in parallel with this change, the propagation velocity increased. There was a highly significant correlation ($p < 0.001$) between the two measures over a 1,000-fold range of velocities, indicating that feedforward inhibition was the prime determinant of the speed of epileptiform propagation. We propose that the speed of propagation is set by the extent of the recruitment steps, which in turn is set by how successfully the feedforward inhibitory restraint contains the excitatory drive. Thus, a single mechanism could account for the wide range of propagation velocities of epileptiform events observed *in vitro* and *in vivo*.

COMMENTARY

While much is known about how epileptic activity is generated and the ionic and synaptic mechanisms underlying seizure susceptibility, relatively little experimental attention has been paid to the mechanisms by which epileptic activity recruits adjacent neural circuits and spreads across the cortex. Clinically, epileptic activity propagates at widely varying speeds covering several orders of magnitude, from the relatively slow propagation rate in Jacksonian march (1) and in some neonatal seizures (2) to rapidly spreading activity in some secondarily generalized seizures. Numerous factors might govern propagation speed, including the extent and magnitude of local inhibition, the degree of myelination, or the level of maturation of ionic channels. Whatever local physiological factors affect neuronal recruitment and activity spread, abnormally synchronized discharges must overcome local inhibition to recruit adjacent

and distant neurons into the hypersynchronous firing pattern. How neuronal circuits manage to counteract an oncoming wave of hyperexcitation is a matter of considerable importance because it might be possible to target propagation mechanisms in future therapeutic development.

In these two papers, Trevelyan et al. used a combination of ingenious and innovative techniques to study the propagation of epileptic activity in slices of mouse occipital neocortex. Their goal was to investigate how inhibition limits the propagation of epileptic activity across the cortex and how the collapse of inhibition allows that activity to continue on its inexorable march. Previous studies using cortical slices in which inhibition was reduced by use of GABA_A receptor antagonists, such as picrotoxin or bicuculline, showed that propagation speed was very rapid (3). In contrast, Trevelyan et al. used the zero- Mg^{2+} model, in which excitation is increased and inhibition remains intact. When Mg^{2+} is omitted from the bathing medium, epileptiform discharges are produced in numerous brain regions, recordable in slices as paroxysmal depolarizations with superimposed rapid spike oscillations (4). In nominally zero Mg^{2+} , epileptiform

activity is generated with the facilitation of neurotransmitter release and activation of NMDA receptors, as Mg^{2+} blockage is relieved. These discharges spread slowly across the slice (at <0.3 mm/sec, compared with 50–90 mm/sec in slices partially disinhibited by GABA_A receptor antagonists), possibly as a result of preserved inhibition (5).

After obtaining whole-cell recordings of layer V pyramidal neurons, Trevelyan et al. induced epileptiform activity by washing out the Mg^{2+} . They found that prior to the onset of massive bursts of depolarization (the epileptiform waves), pyramidal neurons were barraged by bursts of hyperpolarizing currents for several seconds. Then, a transition occurred whereby the inhibitory current bursts were replaced by intense depolarizing current bursts (corresponding to the onset of the epileptiform activity). By recording simultaneously from pairs of nearby neurons, the relative timing of spontaneous neuronal activity could be compared; that is, excitatory bursts appeared in one cell, while inhibitory bursts were still present in its neighbor, which in turn developed excitatory bursts. In addition, utilizing concurrent, fast confocal imaging with the Ca^{2+} -sensing dye Oregon Green 488 Bapta 1 (OGB1), the appearance and propagation of epileptiform activity could be followed over time and space. The epileptiform activity propagated in a discrete, stepwise fashion across the cortex. The stepwise transition from inhibitory to excitatory activity occurred as the inhibitory “restraint” failed at each successive site (confirmed with whole-cell recordings) rather than because of an abrupt increase in excitatory drive. Addition of a small amount of picrotoxin essentially nullified the inhibitory barrages that precede the excitatory bursts. Furthermore, with successive ictal bursts, neurons exhibited progressively less inhibitory barrage, coincident with progressively faster propagation speeds. That is, during epileptiform activity, a given area of cortex is increasingly less able to generate feedforward inhibition and resist the progression of excessive excitation. These findings can account for the varied

propagation speeds of epileptic activity seen both in vivo and in vitro.

The authors concluded that the recruitment of neurons into an epileptiform firing pattern and the failure of inhibition occur simultaneously, suggesting that these events are linked mechanistically. In addition, the presence of strong intrinsic inhibition allows the cortical circuit to oppose epileptic spread and withstand the onslaught of extremely powerful excitation until the point at which inhibition finally gives way. The mechanisms of that transition need to be delineated before therapeutic strategies are devised. The stepwise procession of epileptic activity across cortex implies the progressive involvement of modules of cortical circuits and supports the long-held notion of the inhibitory surround as an important restraint on the march of epileptic activity across the neocortex (6).

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References

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