Seizure Initiation and Termination

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Introduction

A seizure is defined as an episode of excessive, synchronized neuronal activity associated with disturbance of sensation, loss of consciousness, convulsive movements, or combinations of these clinical signs. The precise combination is thought to reflect the brain regions that are synchronized in the discharge. Ever since electrical activity has been recorded in the brain, there has been reference to ‘spontaneous’ activity, the most dramatic form of which is seizure activity. Normally, brain activity does not appear to be highly synchronized. However, during a seizure, there is abnormal synchronization of brain circuits. Importantly, however, the occurrence of a seizure does not mean that the brain is abnormal. For example, seizures can be triggered in ‘normal’ brain by metabolic abnormalities such as hyponatremia and hypoglycemia, or by infection or inflammation. Every brain has a capacity to express a seizure.

The brain produces a variety of transient oscillations – synchronized activity in populations of neurons – that do not initiate seizures. This observation can be viewed in two ways. One is that there is a specific type of ‘trigger’ necessary to initiate a seizure. This trigger – such as an electrical shock – may itself produce excessive synchronization or may lower some threshold for seizure initiation. Alternatively, one could view the brain as having mechanisms that control the degree of synchronization; if these limiting factors fail, a seizure may begin. An example of such a process would be loss of inhibitory function in the cortex. Interestingly, if initiation. Alternatively, one could view the brain as having mechanisms that control the degree of synchronization; if these limiting factors fail, a seizure may begin. An example of such a process would be loss of inhibitory function in the cortex. Interestingly, if initiation. Alternatively, one could view the brain as having mechanisms that control the degree of synchronization; if these limiting factors fail, a seizure may begin. An example of such a process would be loss of inhibitory function in the cortex. Interestingly, if...
This observation suggests that, most likely, more than one mechanism underlies seizure onset. Indeed, even in these animal models of reduced inhibition, the seizures are episodic – they start and stop. Reduced inhibition would not be predicted to contribute to seizure termination.

Increases in excitation, either intrinsic excitability or synaptically-mediated excitability, could contribute to seizure initiation. Seizures depend on circadian rhythms as well as minute fluctuations of ionic concentrations, such as increases in extracellular potassium and decreases in calcium, which both increase excitability. Since astrocytes are thought to play a major role in the regulation of the extracellular environment, an increase in excitability due to changes in the ion concentrations could be due to glial dysfunction. Consistent with this idea, gliosis and/or reactive astrocytes are frequently found in epileptic tissue, and other investigators have described various abnormalities in the normal function of these astrocytes. Other ways in which an increase in excitation might contribute to seizure initiation include an acute increase in glutamate release, a transient inhibition of glutamate transporters on glial cells, or a transient increase in neuronal firing which could result in recruitment of surrounding neurons and, ultimately, in excessive synchronization.

Changes in the characteristics of a number of ion channels could increase intrinsic excitability, which could in turn contribute to seizure initiation. For example, the presence of a small persistent sodium current has been proposed (based on computer modeling) to be necessary for the generation of spontaneous activity in the CA1 region of hippocampal slices exposed to zero-calcium perfusing solutions. The sodium current is necessary for the generation of an after-depolarizing potential, and prolongs the neuronal firing in an individual neuron. A number of modifications in ion channels (channelopathies) have been described in inherited epilepsies. It is possible that a change in expression of genes that encode the same (or different) ion channels could account for other types of epilepsy that do not now appear to be inherited. However, it seems unlikely that a change in channel function that makes it more likely that a neuron will fire an action potential can be the sole mechanism behind seizure initiation. Seizures require multiple neurons to fire synchronously.

Most seizures begin in a small group of neurons and then spread. One theory has been proposed that irregular action potential discharge, which may or may not be synchronized across a small population of neurons, progresses into rhythmic synchronized discharges. These low frequency discharges, often expressed as interictal activity, then ‘fuse’ into larger aggregates. This process can then spread locally and/or to synaptically-connected brain regions. Recurrent excitatory connections, such as in the CA3 region of the hippocampus, provide a mechanism for synchronizing neuronal activity when only one, or a few, neurons fire. Noteworthy, however, in an animal model of temporal lobe epilepsy, an increase in recurrent excitation in the temporal lobe was not found to contribute to neuronal excitability. If a population of neurons in a brain region begins firing spontaneously, then the probability that two or three neurons might fire simultaneously is dependent on the frequency of firing. Once a small group of neurons begins to fire simultaneously, then these cells will be more likely to fire together again – and to recruit local or synaptically-connected neurons into the discharge. The presence of interictal activity is also proposed to lead to the formation of new, or abnormal, excitatory connections, promoting further changes in the brain. However, the idea that interictal activity actually begins the process of synchronization is debated. Indeed, interictal activity could reduce the likelihood of synchronization. The relative anatomy and physiology of the brain region in which the interictal activity is present probably determines the outcome.

Our understanding of the mechanisms underlying seizure termination is minimal. One of the earliest theories was that the intense neuronal activity depleted the stores of readily available ATP. Essentially, the theory suggests that running out of energy results in loss of the ion gradients across the membrane, making it impossible to generate action potentials. Such a condition would effectively end the synchronous discharge, and would account for the refractory period seen after a seizure. Short of a complete loss of ATP, there is also the possibility that the ion gradients are lost, or sufficiently reduced, that action potential firing is limited until the gradients can be restored. For this theory to hold true, action potential discharge during seizures would need to be frequent enough that the ion gradients cannot be regenerated. A less extreme hypothesis is that there is inactivation of ion channels underlying action potentials, resulting in blockade of action potential generation – and explaining the refractory period. Other theories for seizure termination include the proposals that the elevated extracellular potassium produced by the seizure activity causes a depolarizing block of neuronal activity, and that the sodium/potassium ATPase activity is enhanced by the seizure. Inactivation of sodium channels by the neuronal activity would also be predicted to terminate action potential firing. Computer modeling suggests that increases in intracellular sodium during seizure activity is linked to seizure termination. It has also been suggested that pacemaker failure is responsible for termination of ictal events in the cortex.

Before and during seizures there is an increase in the concentration of glutamate in the extracellular space. Such an increase could result in desensitization of the glutamate receptors. If the receptors were no longer sensitive to stimulation by glutamate, then neuronal excitability would be reduced. Cyclothiazide, a compound that inhibits desensitization of ionotropic glutamate receptors, has been shown to increase the frequency and prolong epileptiform discharges induced in rat hippocampal slices with low magnesium. This observation suggests that receptor desensitization could contribute to seizure termination. However, in the absence of synaptic transmission, epileptiform activity is also periodic, suggesting that receptor desensitization is not the only mechanism.

In the CA3 region of the hippocampus, the recurrent collateral synaptic connections are postulated to underlie the epileptiform activity that can be easily initiated by reduction of inhibition. Investigation of the burst discharge in this region has shown that exhaustion of the releasable pool of glutamate is a mechanism behind the termination of the individual bursts. When extracellular calcium is replaced with strontium, there is a reduction in the rate of glutamate release and prolongation of the bursts in disinhibited CA3. Replenishment of this pool would account for the interval between the short bursts of action potentials that characterize this epileptiform activity. Another possible mechanism that could contribute to termination of a burst of action potentials is a short-term depression of synaptic function induced by the electrical activity in the burst.
Methods

The major approach to the study of initiation and termination of seizure activity has been electrophysiological – to record from individual neurons and from populations of neurons in specific brain regions. This approach can be combined with pharmacological or genetic manipulation of excitability. Because of the ease of precise localization and identification of cell type in vitro, this type of experiment is typically carried out in acute brain slice preparations.

Epileptiform activity can be produced in hippocampal slices by a variety of methods. Short (<1 s) bursts are readily produced by raising extracellular potassium concentrations, lowering extracellular calcium or magnesium, adding blockers of GABAergic transmission, adding drugs which increases excitability, or a combination of these manipulations. Prolonged epileptiform activity (>5 s), which more closely mimics seizures in vivo, can be produced in vitro in the absence of synaptic transmission in both CA1 and the dentate gyrus. The discharges can be quite long, and consist (at the extracellular level) of a negative shift of the DC potential upon which population spikes are superimposed (indicating synchronous neuronal activity). The bursts recur at fairly regular intervals, suggesting the presence of some type of pacemaker activity. Epileptiform activity can be induced in cortical areas using many of the same manipulations.

There are some limitations of the currently available in vitro models for the study of seizure initiation and termination. In the intact brain, synaptic transmission is rarely, if ever, completely blocked. Therefore, the mechanisms that underlie onset and termination of the prolonged bursts in the absence of synaptic transmission may or may not be the mechanisms behind seizures in vivo. Similarly, the short bursts seen in in vitro models are more characteristic of interictal spikes than of seizures in vivo, leaving open the question of what allows, or stimulates, the more prolonged discharges in vivo. It is also possible that isolation of tissue from the whole brain alters the mechanisms that work to initiate and provide early synchronization of epileptiform activity. Mechanisms behind termination of synchronized activity are also probably different in the presence and absence of synaptic transmission.

Recent Results

Mechanisms of seizure initiation under various conditions have been studied, but relatively few studies have addressed seizure termination. In particular, it is unclear how seizures are terminated in the absence of synaptic activity, where there is no loss of excitatory drive or augmentation of inhibitory inputs. We studied dynamic activity-dependent changes of intracellular pH in the dentate gyrus, in the absence of synaptic transmission, in acute hippocampal slices, using a fluorescent pH indicator. Slices were incubated in 40 μM SNARF-1 AM for 3 h. SNARF-1 is taken up into cells, where it is hydrolyzed by an endogenous esterase. Recurrent epileptiform activity was initiated by perfusing the slices with 0 mM-added calcium and 8 mM potassium solution. After 20–30 min in this solution, prolonged epileptiform activity (20–40 s discharges) recurs at regular intervals in the dentate gyrus. The epileptiform activity consists of a negative shift of the DC potential, with superimposed population spikes. Each burst of epileptiform activity was found to be associated with intracellular acidification, while between seizures the intracellular pH recovered. The average magnitude of the change in intracellular pH was 0.025 pH units; this average includes intracellular pH changes in non-bursting cells. These pH changes begin early in the discharge, suggesting that a particular level of intracellular pH during the prolonged epileptiform activity is associated with termination of the activity. This hypothesis was tested with antidromic stimulation during the recovery period. Early in the recovery period, stimulation could not initiate a prolonged burst. When the stimulation was applied in the middle of the recovery period, it could evoke a burst, but the duration of this burst was shorter than the regularly recurring bursts. This experiment demonstrated that the duration of the burst correlated with the degree of recovery of the intracellular pH. A recovery of the intracellular pH to at least ~50% of the baseline was required before the antidromic stimulation could initiate a prolonged burst (Fig. 1).

To further explore this relationship, a variety of conditions were tested. Experimental conditions that shortened the epileptiform discharge correlated with more rapid intracellular acidification, and experimental manipulation of intracellular pH altered the duration of the seizure discharge; acidification resulting in early termination of the epileptiform activity. Altogether, these data show a direct relationship between the level of intracellular acidification and the duration of the seizure-like discharge, suggesting that an intracellular pH-dependent process can terminate nonsynaptic neuronal synchronization. Many cellular processes are dependent on pH and it is not known which process terminates the seizure-like activity in this model.

When considering possible mechanisms of seizure termination, these data demonstrate that neuronal excitability is not reduced at the end of a prolonged discharge. Immediately after termination of the bursting, an antidromic stimulation can elicit a population spike whose amplitude is not reduced compared to control conditions. Thus, loss of ATP, enhanced sodium pump activity, inactivation of sodium channels or depolarizing blockade are unlikely to be involved in terminating the burst discharge activity in this model. There is clearly no decrease in neuronal excitability and, since there is no synaptic transmission in this model, there is no change in synaptic function which would explain burst termination. It would appear that the intracellular acidification inhibits cellular processes that are necessary for continued neuronal firing or bursting.

As suggested above, this model of epileptiform activity, in the absence of synaptic transmission, does not accurately model seizures in vivo. However, there are some significant similarities which make this correlation between intracellular pH and seizure termination quite compelling. First, the dentate gyrus provides a gating function in the transmission of seizure activity into and through the hippocampal circuits. The dentate gyrus appears to have a high seizure threshold and to be resistant to the initiation of seizure activity. However, once the seizure activity in the dentate gyrus has begun, all parts of the hippocampal circuit discharge as...
Early in the synchronization of the activity in the dentate gyrus, there is no alkalinization of the extracellular space suggesting that the seizure onset does not involve synaptic activity. In addition, maneuvers that increase or facilitate nonsynaptic mechanisms of synchronization increase the likelihood that discharges will begin in the dentate gyrus. Finally, the only way to mimic the prolonged discharges in an \textit{in vitro} system is to block synaptic transmission. Together, these observations suggest that nonsynaptic mechanisms are likely to be critical in the initiation and termination of epileptic discharges in the dentate gyrus, a structure that is thought to ‘gate’ the spread of seizure activity throughout the hippocampal circuit.

**Future Goals**

If intracellular acidification in the dentate gyrus represents a critical mechanism in control of seizure activity, in at least one brain region important in seizure spread, then determining the source of the acidification – and the cellular processes that are influenced or modulated by the acidification – will be important steps in understanding seizure control. Augmentation of the process, or processes, underlying seizure termination might help control seizures. In addition, understanding how changes in pH affect neuronal function would contribute to our insight into cellular control of neuronal excitability.

One thing that is not clear, and will need to be investigated, is whether the mechanisms that allow initiation and those that terminate synchronized neuronal activity are the same in normal and epileptic brains. Further, it will be important to investigate whether the mechanisms that underlie seizure initiation are the same in all brains with epilepsy – no matter what the type of epilepsy. One would guess that the mechanisms are, in fact, quite diverse. There could also be multiple mechanisms involved in seizure termination. Finally, one must ask whether we can therapeutically reduce the likelihood of seizure onset and augment the mechanisms underlying seizure termination. One could argue (based on what we do know about their mechanisms of action) that the currently available antiepileptic drugs reduce the likelihood of seizure onset. However, whether they (or other drugs) augment termination mechanisms is unknown.

**Further Reading**


