

## Basic mechanisms of epilepsy

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Epileptic seizures typically involve excessive firing and synchronisation of neurons. This interrupts the normal working of the parts of the brain involved, leading to the clinical symptoms and semiology of the specific type of epilepsy. This chapter will outline basic mechanisms of epileptic discharges, particularly in terms of the cellular electrophysiology of focal epilepsies.

### Focal epileptic activity

Focal epilepsies arise in the neocortex and limbic structures including hippocampus and amygdala. Work on a range of experimental models produced detailed theories on the generation of brief (~100–500 ms) epileptic events analogous to the ‘inter-ictal spikes’ often found in the EEGs of humans with focal epilepsy. Experimental inter-ictal discharges are characterised by abrupt ‘paroxysmal’ depolarisation shifts (PDSs) that occur synchronously in the majority of neurons in the local area. These are large depolarisations, 20–40 mV, which make the neurons fire rapid bursts of action potentials. The PDS has properties of a giant excitatory postsynaptic potential (EPSP), and depends on glutamate, which is the main excitatory synaptic transmitter in the brain. This giant EPSP is driven by the simultaneous excitation from many other neurons within the same population. The PDS also depends on the intrinsic properties of the soma-dendrite regions of the neurons, for instance voltage-sensitive calcium channels can produce slow depolarisations that drive multiple fast (sodium channel) action potentials.

Combined experimental and theoretical work on many experimental models show that the following features are necessary for this kind of epileptic discharge:

- Excitatory (usually pyramidal) neurons must make divergent connections into a synaptic network. The probability of such connections can be quite low – for instance between ~1–2% of randomly-chosen pairs of pyramidal cells in the hippocampus.
- The synapses need to be strong enough, because of the properties of the individual synapses and/or because of the firing patterns of the presynaptic neurons (burst firing due to slower voltage-sensitive depolarising channels means that synaptic potentials can summate). Essentially neurons need to have a good chance of driving their postsynaptic targets above threshold.
- The population of neurons must be large enough (the ‘minimum aggregate’ – analogous to the critical mass of a nuclear fission bomb). This minimum aggregate allows neurons to connect with almost all the others in the population within a few synapses, with the result that activity in a small subset of neurons can spread through the population very rapidly under the right conditions. The divergent connections mean that the neuronal population is recruited in a near-geometrical progression. In experimental models the minimum epileptic aggregate can be as low as 1000–2000 neurons, but is probably larger in human epileptic foci.

Other factors contribute to epileptic discharges. Electrical field or ephaptic effects produce rapid synchronisation of action potentials on a millisecond timescale. Electrotonic junctions also can contribute to synchronisation and can reduce seizure threshold. Accumulation of neuroactive substances, notably potassium ions, in the extracellular space will increase and sustain neuronal excitability, and may play a role in prolonging epileptic discharges. Finally glia may play active roles both through the control of extracellular ions and transmitters, and in releasing transmitters in response to activation.

The conceptual framework of the chain reaction of excitation through networks of glutamatergic neurons was mainly developed by an iterative combination of experiments on normal brain tissue exposed to convulsant drugs and computer simulations. Given this is normal tissue, the networks responsible for the epileptic activity exist to serve the normal operations of the brain, not to cause seizures. Under physiological conditions the risk of excessive synchronisation is controlled by several mechanisms, perhaps most notably the presence of inhibitory interneurons. These GABA-containing neurons represent under 20% of neocortical and hippocampal neurons, and come in a variety of types. Those, such as the basket cells, responsible for 'feedback inhibition' provide a conceptually straightforward mechanism: they receive excitatory input from many pyramidal cells, are relatively easily excited, fire action potentials at very fast rates, and inhibit many pyramidal cells. They are therefore ideally suited to detect the build-up of excitation in the pyramidal cell population and to respond by blocking the ability of those pyramidal cells to generate axonal action potentials in response to the excitatory synaptic input on their dendrites.

Acute experimental epilepsies model symptomatic seizures. The convulsant conditions often, but by no means always, work by blocking GABAergic inhibition.

### **Chronic epileptic foci**

Epilepsy is by definition a chronic condition. Chronic epileptic foci depend on abnormal functional organisation of the neuronal networks in the region. Many epilepsies are acquired. Perhaps the clearest example is post-traumatic epilepsy, where a severe head injury has a 20–30% risk of leading to spontaneous epileptic seizures after many months to years, both clinically and in the corresponding rat model. During the latent period, the process of 'epileptogenesis' takes place, which transforms normal brain networks into epileptic foci. While seizures directly triggered by the injury over the following week or so can be blocked by antiepileptic drugs, the process of epileptogenesis cannot. Recent experimental work suggests that it is possible to disrupt epileptogenesis, for instance by focal application of tetrodotoxin to silence the tissue, or administration of cannabinoid receptor antagonists. An effective treatment to prevent epileptogenesis is a major goal in current epilepsy research.

Several of the common chronic models of focal epilepsy, in particular temporal lobe epilepsy, also depend on epileptogenesis. Initial insults include several that trigger acute status epilepticus (e.g. kainic acid, pilocarpine, sustained electrical stimulation) and others that do not (e.g. kindling, intrahippocampal tetanus toxin). With the exception of kindling, which generally does not result in spontaneous seizures, these models have a latent period of 1–2 weeks before spontaneous recurrent seizures start.

*Cellular mechanisms in chronically epileptic tissue.* A key issue is the nature of the abnormalities in the functional organisation of brain tissue which makes it prone to generate epileptiform discharges, while in most cases sustaining relatively normal activity most of the time. Chronic experimental models, and where it is possible to make the appropriate measurements in human localisation-related epilepsies, reveal multiple changes in the structure and function of the neuronal networks. Some of the better characterised include:

- Increased synaptic connectivity. This is a common feature, perhaps most famously in mossy fibre sprouting, where the axons of the granule cells of the hippocampal dentate area can be located because of their high zinc content. The mossy fibres normally are restricted to the hilus and parts of CA3, but in temporal lobe epilepsy invade the molecular layer above the granule cell body layer. Other axons are more difficult to assess, but sprouting does occur in at least some cases. At least in theory, this will promote the chain reaction recruitment of excitatory, glutamatergic neurons outlined above, although their additional synapses onto interneurons complicate the pathophysiology.
- Intrinsic properties. Voltage-gated ion channels change in many epilepsies. This is very clear in the small minority of epilepsies that are genetic channelopathies: in some, potassium channels are weakened, in others sodium channels may become more persistent. In these cases the mutation is presumably a primary factor in epileptogenesis. Changes in voltage-gated ion channels also can be found in much more common epilepsies that do not have an obvious genetic basis, for instance temporal lobe epilepsy where sodium channel inactivation is delayed leading to increases in persistent sodium currents (often in parallel with a loss of sensitivity to carbamazepine).
- Synaptic receptors can also be abnormal in epileptic tissue. Again the inherited channelopathies have good examples of altered GABAergic receptors (tending to depress inhibitory potentials), and of changes in nicotinic receptors. Other studies of more common idiopathic epilepsies reveal alterations in expression of specific receptor subunits.
- Inhibitory transmission may be altered in more subtle ways than changes in receptors, such as: changes in chloride homeostasis (specifically chloride transporters) which can make IPSPs depolarising instead of hyperpolarising, changes in the responsiveness of interneurons to excitatory input, or in some cases selective losses of particular classes of interneuron.

*Inter-ictal discharges versus seizures.* While inter-ictal discharges are commonly associated with localisation-related epilepsy, they are probably generated by different, or at least non-identical, circuits from seizures. Moreover, their role in seizure generation is far from clear. Results from some experimental models suggest that inter-ictal discharges may help prevent prolonged seizures getting started, by mechanisms yet to be determined. Other studies suggest that inter-ictal discharges may come in more than one variety, some of which tend to precipitate seizures; these seizure promoting inter-ictal discharges typically have a large GABAergic component and lead to relatively large increases in extracellular potassium concentrations, which may be what prolongs the epileptic activity into the early stages of a seizure.

Focal seizures lasting tens of seconds typically invade relatively large areas of the brain, even if they do not generalise. The 're-entrant loop' theory argues that epileptic discharges need to cycle between several separate epileptogenic sites to sustain a seizure. Against this theory are observations that the delays between successive stages in potential loops are typically close to zero, and that slices containing a few thousand neurons can sustain seizure-like events. Hyperactivity in several interconnected brain regions will tend to increase the excitatory drive to each region, without the need for the sequential activation of the re-entrant loop model. The dynamic interactions of multiple parts of the epileptic brain probably play a substantial role in sustaining seizures.

*Histopathology.* Epileptic foci are often associated with focal lesions. It is clear that prolonged seizures cause neuronal death, which is why those chronic models of temporal lobe epilepsy that depend on an initial status epilepticus generally are associated with substantial losses of neurons. Excitotoxicity that results from the accumulation of intracellular calcium is in large part due to prolonged activation of glutamate receptors, notably the NMDA variety. What is less clear is how repeated brief seizures cause lesions in some individuals.

### **High frequency oscillations**

The classical EEG stops at 80–100 Hz, but work over the past couple of decades has shown that important insights can be gained at much higher frequencies. These high frequency oscillations (or activity) are often divided into sub-bands, notable ripples and fast ripples, with a demarcation at 200–300 Hz (the precise value differs between different studies). Ripples can be seen during some normal physiological states, while fast ripples seem to be pathophysiological.

Ripples and fast ripples appear relatively early after the initial precipitating insult in at least some experimental models, and provide a biomarker for whether individual animals will go on to develop spontaneous seizures. They presumably result from some of the earlier changes in the process of epileptogenesis and may provide clues on the underlying cellular and molecular mechanisms.

Fast ripples may provide a valuable marker for the ‘epileptogenic zone’. That is the volume of brain tissue that needs to be removed surgically to prevent seizures. The ultimate test is whether the seizures stop when the tissue is removed. This and the other zones identified in presurgical work-up are beyond the scope of this chapter. What is relevant is the use of fast ripples as one of the methods of defining the epileptogenic zone. Our own recent work suggests that fast ripples can be used in (at least experimental) cases where there is no hippocampal sclerosis to provide structural evidence.

Detecting fast ripples is not straightforward. Obviously the bandwidth of the recording system needs to be high enough – in the kHz range. But the recording electrodes also are critically important. Fast ripples are best detected with intracranial, preferably intracerebral, microelectrodes. A recent study has shown that the classical clinical macroelectrodes miss most high frequency oscillations faster than 100–200 Hz. This is probably because fast ripples in particular synchronise over very short distances, of the order of a few hundred microns, so they will be attenuated to below noise when recorded with electrodes with dimensions orders of magnitude larger. Their limited spatial extent and the small amplitude of fast ripples also make them difficult to record from the scalp.

### **Generalised epilepsies**

This chapter is centred on focal epilepsies, in part because less is known about the pathophysiology of the primary generalised epilepsies, with the exception of absence epilepsy, which will be outlined briefly here. It is the one class of generalised epilepsy where there is a plausible model of basic mechanisms. It differs from localisation-related epilepsy in many important respects. In particular it arises from the thalamocortical system, depending on the properties of both cortex and thalamus. Until recently there was a consensus on the mechanisms for the classic 3 per second spike-wave activity, which depended on synchronisation of the thalamus by rhythmic activity of networks of inhibitory neurons. The rhythm was thought to arise from the interaction of inhibitory postsynaptic potentials (IPSPs) with transient low-threshold (T) calcium channels in thalamic cells. Recent evidence, especially from one of the better models of this condition, the Generalised

Absence Epilepsy Rats from Strasbourg model (GAERS), suggests that the thalamic T current may not be critical. Work on this model also suggests that the frontal cortex may play a key role in initiating absence seizures, a point that contributes to blurring the distinction between localisation-related and primary generalised epilepsies.

## **Conclusions**

The basic neurophysiological mechanisms of some forms of epileptic activity now are understood in considerable detail. However many important issues remain, in particular on the basic mechanisms of prolonged seizures. Identifying specific cellular mechanisms playing crucial roles here should provide useful leads for novel and selective treatments.

## **Further reading**

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