Chapter 3

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, in some cases leading to impaired consciousness. This chapter will outline basic mechanisms of epileptic discharges, particularly in terms of cellular electrophysiology.

Localisation-related (partial) epileptic activity.

Localisation-related epilepsies arise in the neocortex and limbic structures including the 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 ‘interictal spikes’ often found in the EEGs of humans with partial seizures. Theories on full-blown seizures are less well developed at present.

Cellular mechanisms.

Experimental interictal discharges are characterised by abrupt ‘paroxysmal’ depolarisation shifts 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 paroxysmal depolarisation shift:

• Has properties of a giant excitatory postsynaptic potential (EPSP), and depends on glutamate, the main excitatory synaptic transmitter in the brain. Essentially it is the sum of simultaneous excitation from many other neurons within the same population.
• Has contributions from voltage-sensitive calcium channels, which can produce slow action potentials.
• Drives neurons above the threshold for the fast action potentials, due to voltage sensitive sodium channels.

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 be connected 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 synapse and/or because of the firing pattern of the presynaptic neuron (burst firing 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. In experimental models the minimum epileptic aggregate can be as low as 1000–2000 neurons, but probably is larger in human epileptic foci.

Acute experimental epilepsies, using convulsant treatments on normal brain tissue, model symptomatic seizures. They usually modify synaptic networks by one or more of:
• Blocking inhibitory synapses (using GABA as their transmitter) that normally control the excitation of the excitatory synaptic network. This is typical of many convulsants used experimentally (eg PTZ and bicuculline), and can occur clinically (eg penicillin and quinolones, under certain conditions).
• Paradoxically, excessive activation of GABA\textsubscript{A} mediated synapses can switch them from inhibitory to excitatory and thus promote epileptic activity. This is due to a collapse of the gradient of chloride ions across the membrane, leaving bicarbonate ions as the main charge carrier at these synapses.
• Strengthening excitatory synapses, for instance with abnormally low levels of extracellular magnesium ions unblocking the NMDA subtype of glutamate receptor.
• Increasing neuronal excitability.

Other factors contribute to epileptic discharges:
• Electrical field effects produce rapid synchronisation of action potentials.
• Electrotonic junctions also lead to rapid synchronisation and can reduce seizure threshold.
• Spontaneous ‘ectopic’ action potentials in pyramidal cell axons can contribute to increasing excitability and generating seizures.
• Accumulation of neuroactive substances, notably potassium ions, in the extracellular space will increase and sustain neuronal excitability.

\textit{Cellular mechanisms in chronically epileptic tissue}. Epilepsy is, of course, a chronic condition in which the brain generates epileptic seizures without being exposed to convulsant drugs. Chronic experimental models, and where it is possible to make the appropriate measurements in human localisation-related epilepsies, reveal multiple changes which occur in various combinations in specific examples. Some of the better characterized include:
• Increased synaptic connectivity is a common feature, perhaps most famously in mossy fibre sprouting. At least in theory, this will promote the chain reaction recruitment of excitatory, glutamatergic neurons outlined above.
• 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 (often in parallel with a loss of sensitivity to carbamazepine).

- Synaptic receptors can also be different 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.

**Interictal discharges versus seizures.** While interictal discharges are commonly associated with localization related epilepsy, they probably are 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 interictal discharges may help prevent prolonged seizures getting started, by mechanisms yet to be determined. Other studies suggest that interictal discharges may come in more than one variety, some of which tend to precipitate seizures.

Perhaps the crucial question is what factors determine whether an epileptic discharge develops into a full-blown seizure.

During the first few seconds of a seizure discharge, concentrations of extracellular potassium ions increase from the normal 3-4 mM to 10-12 mM, which in turn excites neurons, with a relatively slow time course. The dynamics of the handling of extracellular potassium and other neuroactive substances by neurons and glia during seizures is an active area of research.

Extracellular potassium appears to accumulate too slowly to be the trigger for seizures, so the mechanisms that sustain synchronous activity for the first few seconds are potentially very important. Several hypotheses exist here. Increased involvement of slow, metabotropic glutamate receptors is one. Avoli’s group implicates the minority of interictal discharges that are associated with relatively large potassium transients. My group has been particularly interested in the roles of fast oscillations often found close to the seizure initiation site in human and some experimental epileptic foci. Such rhythmic activity can potentiate fast excitatory transmission, and can also promote the switch of GABA responses to their depolarizing, excitatory form.

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.
As is clear from this section, the basic mechanisms of seizures remain an active area of research.

Histopathology. Epileptic foci are often associated with focal lesions. It is clear that prolonged seizures cause neuronal death. 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 whether such lesions exacerbate the epilepsy over time.

Improvements in non-invasive imaging and in post-mortem histology have started to implicate subtle dysgenic abnormalities, at least as risk factors, in the development of idiopathic epilepsies. There is a great deal of interest in how these structural abnormalities translate into epilepsy, but a lack of good experimental models has slowed progress.

Generalised epilepsies

Absence epilepsy 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. It arises from the thalamocortical system, and appears to depend on the properties of both cortex and thalamus. Until recently there was a solid 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 low threshold calcium channels in thalamic cells. Recent evidence, especially from one of the better models of this condition, the Generalised Absence Epilepsy Rats from Strasbourg (GAERS), suggests that the thalamic T current may not be critical and that the frontal cortex may play key role, a point that contributes to blurring the distinction between localization related and primary generalized epilepsies.

Conclusions.

The basic neurophysiological mechanisms of some forms of epileptic activity 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