



The Dentate Gyrus and Temporal Lobe Epilepsy: An “Exciting” Era

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Abstract

This review describes developments in epilepsy research during the last 3 to 4 decades that focused on the dentate gyrus (DG) and its role in temporal lobe epilepsy (TLE). The emphasis is on basic research in laboratory animals and is chronological, starting with hypotheses that attracted a lot of attention in the 1980s. Then experiments are described that addressed the questions, as well as new methods that often made the experiments possible. In addition, where new questions arose and the implications for clinical epilepsy are discussed.

Keywords

seizure, hilus, mossy cell, HIPP cell, adult neurogenesis, mossy fiber sprouting

Temporal Lobe Epilepsy Neuropathology and the Dentate Gyrus

One of the major concepts that dominated the epilepsy research community in 1980s was the importance of underlying neuropathology in the hippocampus. For the purposes of this review, the hippocampus is defined as areas CA1, CA2, CA3, and the dentate gyrus (DG). There was a common view that temporal lobe epilepsy (TLE) was characterized by a pattern of hippocampal neuronal loss that was originally called Ammon’s horn or hippocampal sclerosis and then, as neuronal loss in extrahippocampal areas became appreciated, mesial temporal sclerosis (MTS).¹ In the hippocampus, neuronal loss mainly included the DG hilus and pyramidal cell layers of areas CA1 and CA3. The DG and area CA2 cell layers were relatively resistant.¹

Notably, it was often assumed that MTS led to epilepsy. One argument was the finding that seizures in patients seemed to start in the sclerotic hippocampus.² Surgical removal often helped, supporting the hypothesis, but did not always stop clinical seizures. How the hippocampus could be important but its removal not provide a cure could be explained by the concept of secondary epileptogenesis,³ where secondary foci assume

the role of the primary focus if the primary focus is removed. Still, explaining hippocampal neuropathology continued to attract attention.

At the core of the issue is selective vulnerability, that is, why some neurons are vulnerable relative to others. Experiments began to focus on characteristics of individual hippocampal neurons to understand this issue, made possible by the increasing acceptance of the hippocampal slice preparation and with it, the ability to make stable intracellular recordings. Using improved markers of single cells such as biocytin, the basic neuronal properties and morphologies of hippocampal neurons were clarified, and an increasingly detailed map of their circuitry emerged. This understanding proceeded in parallel with cellular investigations of induced seizure-like activity in slices of normal animals, leading to predictions about how the characteristics of the cells and circuitry contributed to seizures. The techniques have now been superseded by more advanced imaging and recording methods, including recordings in awake head-fixed animals, as well as viral-based strategies and techniques to record simultaneously from many areas rather than one cell. Therefore, the understanding of cells and their circuitry continues, but the “neurocentric” view has given way to one that includes glia, the vasculature, and immune cells.



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Most studies were made of CA1 and CA3 initially because the DG didn't survive well after the slice procedure. Better equipment to section the brain and methods to limit damage during the slice procedure helped. In the DG, the relatively resistant granule cells (GCs) lay juxtaposed to vulnerable hilar neurons, making the DG attractive to understand reasons for selective vulnerability. At first GCs and hilar neurons were characterized. Hilar neurons became divided into 2 categories: the glutamatergic mossy cells (MCs) and diverse GABAergic neurons.⁴ Vulnerable hilar neurons were identified as the MCs and a subset of hilar GABAergic neurons that expressed the neuropeptide somatostatin. Later the DG GABAergic neurons were categorized by their axonal targets,⁵ and despite the developments of other classifications⁶ the nomenclature based on the axon has been widely adopted. Hilar somatostatin-expressing cells are now often referred to as the hilar cells with a terminal projection associated with the perforant pathway (the outer 2/3 of the DG molecular layer), or HIPP cells.

A common hypothesis in the 1980s to 1990s for MCs and HIPP cell vulnerability was based on the research being done at the time about excitotoxicity, and the common view that TLE was caused by a brain insult or injury. Based on these views, it seemed logical that neuronal death after brain insults is due to excitotoxicity induced by the brain insult.⁷ A critical step in excitotoxicity was the escalation of intracellular calcium levels during strong glutamatergic stimulation. The role of glutamate and calcium in excitotoxicity arose from experiments often in areas or systems besides hippocampus⁸ and the role of glutamatergic afferents to the DG arose from the repetitive stimulation animal model.^{9,10} In this model, afferent stimulation was triggered repeated in an anesthetized rat using a stimulating electrode placed into the perforant path, the major afferent to the DG. Neuroanatomical studies showed that vulnerable MCs and HIPP cells died after the stimulation, but not the DG GCs.¹¹ It was surprising that the primary type of GABAergic cell survived (called basket cells; now called perisomatic-targeting cells, often expressing parvalbumin (PV)) because it was often assumed that they were vulnerable, and deficient GABAergic inhibition was critical in seizure generation.¹²

Using antibodies to label different cell types, studies showed that there was a low expression of calcium binding proteins (calbindinD_{28K} (CaBP), PV) in the MCs and HIPP cells but high expression of CaBP in the GCs and PV in the perisomatic-targeting cells.¹³ Later it was shown that chelating intracellular calcium in MCs and other hilar interneurons could protect them in a slice model of repetitive stimulation.¹⁴ However, MCs and HIPP cells lack other proteins that GCs have (eg striatal-enriched protein tyrosine phosphatase; STEP), and new molecular techniques suggest that STEP is important for neuroprotection.¹⁵ The "calcium-binding protein hypothesis" is now discussed much less because, in part, selective vulnerability in other brain areas is not necessarily correlated with calcium binding protein content.¹⁶ The field has also become more complex with diverse roles and regulation of intracellular calcium and new interest in apoptosis of hilar cells.¹⁷

Other hypotheses arose to address selective vulnerability based on cellular and circuit properties, perhaps because of the wealth of new data arising from new improved methods such as patching visualized neurons. For example, GCs had resting membrane potentials (RMPs) that were hyperpolarized compared to most other neurons in the hippocampus.^{18,19} So called "tonic" inhibition and other aspects of the powerful GABAergic inhibition of GC firing emerged²⁰ as well as complex regulation of Gamma-amino-butyric acid (GABA) receptors.^{21,22} The GCs also express ion channels which make them stop firing if a persistent depolarizing input occurs, called spike frequency adaptation.^{18,19} Vulnerable MCs and HIPP cells showed more depolarized RMPs than GCs, and less adaptation, although the resistant perisomatic-targeting cells also had depolarized RMPs and little adaptation.²³⁻²⁵ There was an increasingly common view that the normal "quiescence" of GCs, rarely firing action potentials, explained the GC resistance to brain insults. Without as much action potential discharge, it was suggested that excitotoxicity would be unlikely. The relative quiescence of GCs was later supported by additional recordings *in vivo*²⁶ and is now considered a dogma. It appears critical to normal cognitive functions dependent on the DG. Conversely, MCs are highly active both *in vitro* and *in vivo*,^{24,27} and work has suggested that the normally high activity in MCs is also important for cognitive functions related to the DG.²⁸ Thus, what is good for normal functions seems to place the brain at risk for MTS-like pathology and possibly TLE.

Hypotheses to explain selective vulnerability are still an active area of research, in part because it is as important as ever to address the debilitating effects of brain injury. On the other hand, neuroprotective strategies have not been a "magic bullet" in preclinical epilepsy research.²⁹ This has led to new energy into other pressing questions. For example, the way genetics applies to epilepsy has become an area of increasing attention. One reason is that studies of "idiopathic" epilepsy have revealed the importance of genetics.^{30,31} Methodological advances have allowed both clinical and basic scientists to increasingly ask questions related to genes.

Animal Models of Epilepsy

Another area of major interest was to develop a bona fide animal model of chronic epilepsy. This quest began as the studies of normal animals were increasingly criticized as not necessarily being predictive of what occurs in patients. Although logical, there was a counterargument that many of the current epilepsy medications were based on drug testing in normal animals. Regardless, there is an increasing need for "high throughput" models such as zebrafish,³² organotypic hippocampal cultures,³³ patient-derived stem cells,³⁴ and organoids.³⁵ Advances in computational models have also led to new ways to study epilepsy.³⁶

One reason more work in animals with spontaneous seizures ultimately became the standard is that methods to induce epilepsy in rodents became available. The fact that the animals had spontaneous seizures was very exciting, and it also shed new

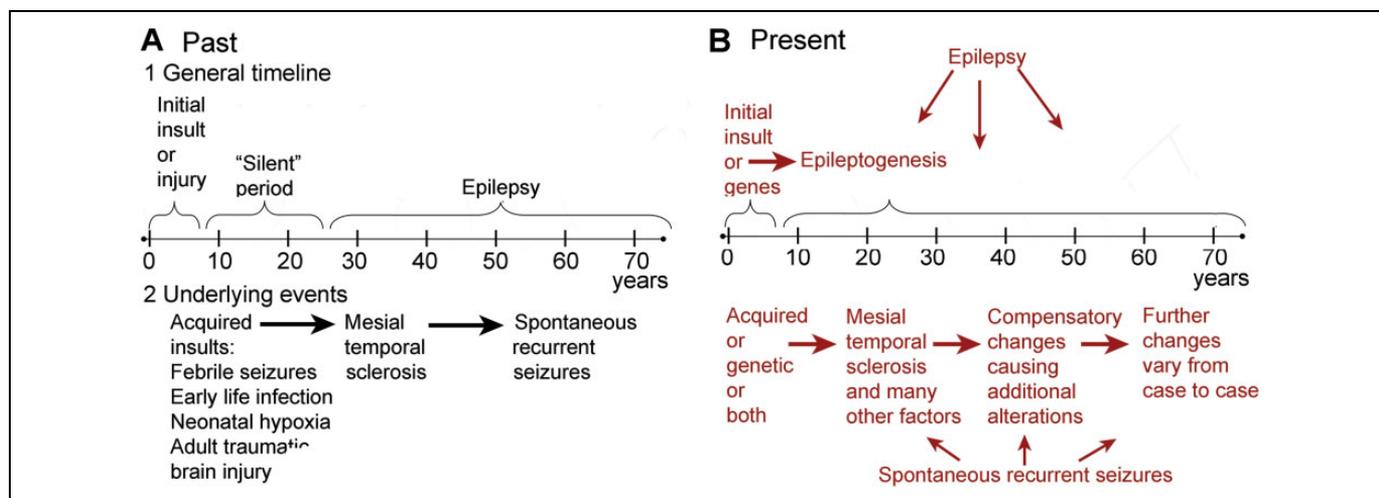


Figure 1. Concepts underlying epileptogenesis in TLE from the past and present. (A) Past concepts. 1. General timeline. Epileptogenesis had been suggested to occur in 3 phases,¹ the first typically occurring in early life and involving a brain insult or injury. A “silent” period follows the insult or injury and occurs before the first convulsive seizure. The first convulsive seizure is the start of the phase called chronic epilepsy or simply “epilepsy”. 2. Underlying events. The brain insult is typically an acquired event such as brain injury or infection, with examples listed. During the silent period, MTS develops and ultimately recurrent spontaneous seizures (defining chronic epilepsy). (B) Present concepts. 1. The general timeline is now considered with more appreciation for the role of genes. Therefore, after an initial insult or after altered genes exert effects (eg, on neurodevelopment), there is a progressive worsening of increased excitability (epileptogenesis). Spontaneous seizures can occur early or later in this progressive course of events. After 2 unprovoked seizures the term epilepsy is used³⁹ 2. Underlying events. Initial events include those that are not acquired. There is a rapid start in the reaction of the brain to the insult and ultimately a complex series of events unfolds, with some reactions leading to further changes. TMTS is one of the events that stimulates changes but others can also. Spontaneous recurrent seizures may occur before the brain stops changing.

light on MTS because a MTS-like pattern of damage occurred using one of the methods that has become most common—inducing status epilepticus (SE) by injection of the glutamate receptor agonist kainic acid³⁷ or cholinergic receptor agonist pilocarpine.³⁸ After the injection, SE occurred within about an hour, and in the ensuing days a MTS-like pattern of neuropathology developed. Within weeks or months, animals exhibited spontaneous limbic seizures in their home cages, and these seizures were convulsive and therefore very compelling. At the time, behavior was the way seizures were judged, so in an animal the most convincing evidence of a seizure was one that is convulsive; the standard now is video-electroencephalogram (EEG).

Many researchers promoted the “SE models” because SE often is noted in the history of patients with TLE. A counterargument is that SE is not extremely common, and the SE model in rodents leads to more brain damage than in TLE. Several modified versions of the original “SE” models were developed to improve them, but arguments continue. Nevertheless, the fact that MTS occurred, it did so long before the epilepsy, and animals with less damage did not develop epilepsy was viewed as strong evidence that brain damage causes epilepsy. Moreover, there were no convulsive seizures between MTS development and then chronic epilepsy in rodents, suggesting there is a “silent” period, as suspected in patients with TLE (Figure 1). The idea of a silent period eventually lost favor when data using video-EEG showed very early epileptiform spikes and bursts after SE that grow in duration and complexity until they ultimately are accompanied by convulsions.⁴⁰

Notably, other brain insults that are risk factors for TLE have been developed, and there also are genetic models.⁴¹ Although each animal model has its critics, there is no question that they have all been a huge boost to epilepsy research.

Dentate Gyrus Sprouting

An area of research that garnered great attention developed at about the same time that the SE models were first used. This research area started with the observation that axons of DG GCs, called mossy fibers (MFs), grew or “sprouted” after lesions in rodents.⁴² The MF sprouting was subsequently shown in rodents after SE and in sclerotic hippocampi.⁴³ The sprouted axons grew substantial distances and appeared to form new excitatory connections. When it was shown that SE in rodents led to MF sprouting, many researchers turned their focus to MF sprouting. It was shown that the sprouted axons made functional excitatory synaptic connections with other GCs in animal models,⁴⁴ which could elicit greater excitation of the GC population.⁴³ On the other hand, it was discovered that GCs in animals with epilepsy expressed GABA as well as glutamate,⁴⁵ and GABA itself could depolarize neurons (bring the RMP closer to action potential threshold) as well as hyperpolarize them (bring the RMP further from action potential threshold).^{46,47} Also, arguments were made that sprouted axons of GCs excited GABAergic neurons in the DG rather than GCs, and more inhibitory neuron activity would be likely to increase inhibition of the GC population, not decrease it.⁴⁸ Only when



inhibition was blocked by pharmacological use of GABA receptor antagonists was there evidence of underlying hyperexcitability in epileptic animals with MF sprouting.⁴³ The idea that individuals with TLE may have an inhibited hippocampus most of the time, but sometimes have seizures when inhibition fails, was a useful concept because many individuals with TLE have seizures only under certain conditions that are known to alter GABAergic inhibition, such as stress, the periovulatory or perimenstrual phase of the menstrual cycle, or sleep deprivation.

Ultimately the attention that had been given to MF sprouting turned to other ideas, motivated by new tools and hypotheses. In addition, some studies suggested that sprouting was not as important to epilepsy. One important source of support for this view used a drug to reduce MF sprouting in animals and it did not seem to block seizures in an SE model.⁴⁹ On the other hand, other researchers suggested that sprouting is found in many areas outside the DG and this “synaptic reorganization”, brain-wide, could be a factor in epileptogenesis.⁵⁰

Adult Neurogenesis in TLE

One of the biggest surprises over the last decades, at least regarding the selective vulnerability in the hilus, was the finding that many hilar neurons exist in SE models of TLE. It was also surprising to find that many of these hilar neurons were a type of GC.⁵¹ One explanation was suggested by a study published in 1997 showing that there was dramatic proliferation of neurons in the DG of the rat after SE.⁵² This study was timely because there was a growing appreciation that the DG was one of 2 brain regions where neurogenesis occurred in the adult animal, an idea that had not been widely appreciated in past decades.

Regarding the reason for hilar GCs after SE, it was suggested that SE induced new GCs to mis-migrate away from their normal location in the GC layer. Afterwards, an explanation for mis-migration was proposed: It was shown that HIPP cells secrete reelin, which normally prevents cells from migrating to the source of reelin, whereas after HIPP cell death, hilar reelin was reduced.⁵³ Many years later, it was also shown that the GCs might emerge from the septohippocampal zone,⁵⁴ or the hilus itself, because progenitors and young GCs appear to be present in the hilus normally.⁵⁵

When recordings were made of the hilar “ectopic” granule cells (EGCs), it was shown that they have axons that innervate normal GCs and CA3 pyramidal cells, possibly mediating the synchronization needed for a seizure focus.⁵⁶ Therefore, there was a new reason to think of the epileptic DG and CA3 as a potential focus. However, to test this hypothesis took many years. Ultimately methods developed to express a toxic enzyme specifically in progenitors so that they would die selectively. With this method⁵⁷ and others,⁵⁸ it was shown that a mouse with reduced numbers of EGCs had greatly reduced chronic seizures. In addition, EGCs were shown in a different animal model of epilepsy⁵⁹ and humans with TLE.⁶⁰

Do Granule Cells Cause Seizures?

Although work described above reflected substantial progress in understanding the DG in TLE, an essential assumption about the DG in TLE was untested: It had not been shown that the GCs could ever initiate a seizure *in vivo*. The first hypotheses along these lines developed in the early 1980s when it was suggested that the GC population was similar to a gate or filter, normally preventing seizures from entering CA3 and CA1.^{61,62} Many supportive studies of this “gate” hypothesis have been done over the decades, but no recordings have been made *in vivo* showing the GCs initiate a seizure. On the other hand, it appears to be possible for hypertrophied GCs to initiate seizures, making this type of GC (and the mammalian target of rapamycin pathway that controls their formation), assume new importance in TLE.⁶³

Recent studies suggest how GCs could cause a seizure. One hypothesis has emerged from 2 lines of research that have attracted a great deal of attention: (1) one research area defined the potential mechanisms underlying the transition to seizures, and (2) another research area clarified characteristics of GC transmission to area CA3 pyramidal cells. Regarding the transition to seizures, the arguments about a single transition have been supplanted by the view, based on observations in clinical recordings, that there are multiple types of seizures in TLE and therefore different types of transitions.⁶⁴ Notably, one seizure type has been identified as primarily initiating in area CA3, and it may be no coincidence that these pyramidal cells have a very special type of synapse from GCs that can promote seizures. This type of seizure has been named hypersynchronous or HYP.⁶⁴ It begins when principal cells begin to synchronize, and an important contribution is failure of inhibition in the local circuit that typically keeps the principal cells from synchronizing. In separate experiments, it has been shown that, despite the quiescence of GCs normally, when they begin to fire they can have dramatically excitatory effects on their target neurons in area CA3. One of the reasons is the axon of the GC which has a “massive” axon bouton. The boutons of the GCs are packed with glutamatergic vesicles and peptides like brain-derived neurotrophic factor (BDNF) that facilitate more glutamate release, leading to even more excitation of GC targets than glutamate alone.⁶⁵ In fact, BDNF itself has been suggested to be critical in TLE.⁶⁶ The massive boutons of GCs are largely on the pyramidal cells, with smaller ones on inhibitory cells.⁶⁷ Therefore, based on this view, there is potential for GCs to strongly excite pyramidal cells more than inhibitory cells, although there are other views.⁶⁷ It is noteworthy that pyramidal cells in CA3 form recurrent excitatory connections normally, and even the discharge of one pyramidal cell can lead to a population discharge, a finding that was highlighted many years ago because of its relevance to TLE.⁶⁸ In summary, GCs can powerfully excite CA3 and have often been called potential “detonators.” Thus, the characteristics of GCs and CA3 (and perhaps EGCs) appear to be ideal to underlie a HYP seizure transition.

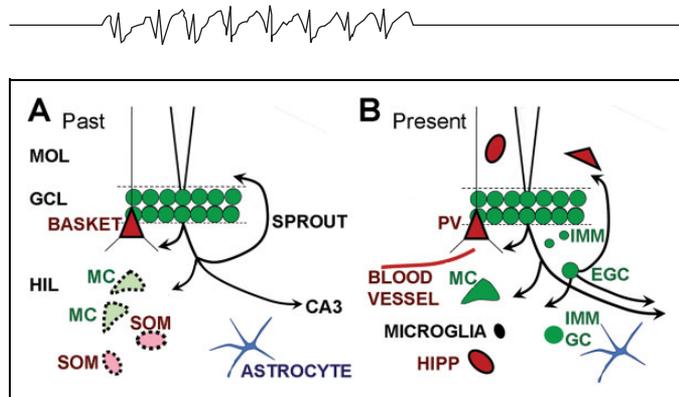


Figure 2. Past and present perspectives on the role of the dentate gyrus (DG) in temporal lobe epilepsy (TLE). **A.** Past views. A simplified schematic of the DG in TLE is shown with the major layers on the left (MOL, molecular layer; GCL, granule cell layer; HIL, hilus). Glutamate neurons are green; GABAergic neurons are red. In TLE, hilar MCs and SOM cells are reduced (dotted lines). The axons of GCs sprout in the epileptic brain and innervate dendrites in the MOL (SPROUT). **B.** Present views. An updated schematic shows that some MCs and SOM cells are lost in TLE. In addition to reactive astrocytes in the hilus, there are microglia, reflecting new appreciation of the diverse roles of glia and inflammation. New branches of blood vessels emerge because of new appreciation of angiogenesis in TLE. There are progenitors (IMM for immature) in the area next to the GCL which can divide in adulthood, giving rise to new GCs. Ectopic GCs (EGC) arise in the hilus. They contribute to sprouting that previously had been considered to be a characteristic only of cells in the GCL. Immature GCs arise from progenitors that are mainly beneath the GCL but can be in the hilus.⁵⁵ Many types of GABAergic neurons (red) are added to the diagram because of the greater understanding that they normally are present. GABAergic neurons are named using a different classification system. PV (parvalbumin) or perisomatic-targeting neurons replace the term basket cells; HIPP cells replaces SOM cells.

Research with selective new methods such as optogenetics are now addressing these ideas, although there is not always support for the idea that GCs initiate seizures.⁶⁹ Therefore, there is still a lot to be done. This is an “exciting” time to be conducting epilepsy research.

Conclusions

In summary, TLE is no longer considered a single type of epilepsy but a constellation,⁷⁰ reflecting multiple forms of TLE. Basic scientists no longer discuss TLE after brain insults or injury alone, instead referring to epilepsy after a brain insult as acquired TLE and other cases of epilepsy as genetic or multifactorial. Thus, there is more to MTS than the hippocampus (or DG) and more to TLE than MTS (Figure 1).

Regarding selective vulnerability, all the reasons for the vulnerability are not yet known. Instead, the plethora of brain changes that occur either when there is a brain insult or there is a genetic alteration during development can greatly change the brain (and the DG; Figure 2). This makes animal models of epilepsy very important.

Within the DG, there is more evidence than ever that GCs could be “detonators” and together with CA3 form a focus for seizures. However, the evidence is primarily from

animals—not humans. An important consideration is whether the DG is only one area where “detonators” exist, that is, more “ticking time bombs” exist outside of the DG. These additional sites could all be “brain gates,” and targeting these “gates” in epilepsy could be fruitful.

What are the “take home” messages for the clinic? There is a need to do more to understand the DG in patients with TLE. Advances in neuroimaging should provide the resolution to do so. There also is a need to control the changes in the DG that develop in TLE. Focal targeting of brain “time bombs” may be possible either by viral delivery, use of closed-loop silencing, or new methods that are on the horizon.⁷¹

Highlights

- The concepts underlying TLE have changed, especially with respect to the role of the DG.
- Mesial temporal sclerosis and selective vulnerability of hilar cells are still discussed but we know that there is more to TLE than MTS. Concepts like MF sprouting are still important but the role of glia, inflammation, and diverse aspects of genetics are increasingly appreciated.
- The advent of animal models with spontaneous seizures has been a boost to epilepsy research, but also creates debate about what is the best model.
- More evidence has been gathered to support the DG “gate” hypothesis but much more needs to be done. Fortunately, improved methods have provided exciting new opportunities for both empirical and computational approaches.

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