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Neuronal Circuits In Epilepsy: Do They Matter?

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Abstract

Seizures occur in groups of neurons and involve complex interactions across several regions. The focus of much epilepsy research has been on changes in single neuronal populations but the interpretation of the implications these changes is often limited by not being able to place those observed changes appropriately overall function of the brain. Understanding regional interactions at the beginning and during the evolution of a seizure may help place the changes in the appropriate context of the pathophysiology of epilepsy and guide us in identifying more effective therapies. In this paper we will focus on the circuits that support the different stages of seizures. Although we are far from knowing how the system works to initiate and spread seizures, we hope to provide a framework upon which we can place cellular changes. The concepts of seizure focus, initiating seizure circuits, paths of spread and neuromodulatory centers will be used to develop a systems view of epilepsy.

Keywords

Epilepsy; Seizure; Functional anatomy; Brain circuit; Cortical-subcortical interaction; Neuromodulation

Introduction

One of the great problems in understanding the pathophysiology of epilepsy is that it is really a collection of many disorders of the brain, some acquired as one goes through life and others inherited or congenital. Attempts to create a unifying theory or mechanism to allows us to identify the source of seizures or to develop more targeted therapies have been met, to date, with very limited success. One of the problems in this effort to understand the basis for epilepsy is that when we encounter a change in a particular region of the brain it is not clear how we should interpret the finding with regard to its role in epilepsy. The changes at the neuronal level in the expression of different isoforms of receptors and voltage gated channels associated with different types of epilepsy are often interpreted as pushing the system closer to seizure threshold. At the level of the single neuron or population of neurons, such an interpretation is usually appropriate. However, seizures do not arise in a

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single neuronal population, rather they begin, within regions or between regions with complex interactions. As suggested by the neuroscience uncertainty principle above, predicting overall system function from the activity of a single channel is, at best, chancy. There are too many relay stations from the channel to the whole brain to understand how one leads to the other. Similarly, explaining the pathophysiology of epilepsy from a scalp EEG reduces the brain to a black box, the workings of which are mysterious. Although we will likely never be able to connect all the dots from cell to brain to have a complete image of what is happening to start, maintain and spread a seizure, developing an understanding of what is happening at different hierarchical levels of the brain during the course of a seizure may allow us to interpret changes that are discovered at the neuronal level more appropriately. In this chapter we will focus primarily at the level of the circuits that may support the initiation and spread of seizures. Other articles in this volume describe in significant detail changes at the local level. We hope that you will be able to take the material in this collection and connect the dots in new and creative ways.

One of the major problems faced in placing a change in the physiology of a single neuron is not knowing where in the circuit this particular neuron lives and works. Is it an excitatory projection neuron that will increase excitatory output from one region to another? Is it an inhibitory neuron in which increased excitability results in overall increased inhibition? Is the change a contributor to the epileptic state or is it a reaction in an attempt to reestablish system homeostasis? Is the target of the region of increased excitatory output a region that is a net excitatory or inhibitory modulator that will increase or decrease the probability of a seizure? These are some of the issues that have to be answered to understand the effect of changes at the neuronal level. For the moment we will focus on some of the known circuit interactions so that we can build a basic wiring diagram into which the neurons can be inserted.

Basic Considerations

In considering the circuitry of a focal seizure, there are at least three stages in the evolution of a seizure that may involve different circuit components: seizure initiation (transition from interictal to ictal), seizure buildup (the early phase of activity that occurs within the initiating circuit) and seizure spread (the process of recruiting additional regions and circuits). The importance of breaking seizures down into these phases is that each is likely associated with different circuitry that involve different physiologies. At present we don't really understand the processes particularly well, but there are some data that give us insight into the components that support and spread seizure activity, and we will explore some of these data later. Although it would be ideal to use models of spontaneous seizures to examine the regional interactions, for the moment we don't know how or where to study the functional anatomy of these seizures. For this reason we have relied predominantly on induced seizures to define the components and how they interact, because in induced seizures one can determine the site of initiation and manipulate the hypothesized circuit components as seizures are induced to demonstrate the potential role these regions play. Identifying the components is essential for understanding the pathophysiology of epilepsy because once the key regions of the circuit are identified, one may focus on the unique physiology and pharmacology of those regions to target therapies that are more specific. The

effect of a drug can vary considerably depending on where in the circuit it is working most potently. For these reasons in vivo studies using intact seizure circuits are essential to understanding epilepsy and its mechanisms.

Functional anatomy of epilepsy

When we speak of the circuitry underlying the different stages of a seizure, we often speak in terms of seizure functional anatomy which includes the physical and physiological substrate in which seizures arise and spread. The term implies that there are complex networks involved in the initiation of seizures and suggests that different different regions play particular roles in a seizure's evolution. In broadest terms we can identify four major components of seizure functional anatomy: 1) the seizure focus, 2) the initiating circuit, 3) the pathways of spread or recruitment and 4) the modulatory centers. The **seizure focus** is the site the provides the physiological spark the starts the seizure. It can be small or large, but without the focus, the seizures won't start. The **initiating circuit** is the set of interconnected regions that are necessary to support the spark from the focus and convert it to a seizure. If a seizure spreads outside the initiating circuit, it has to recruit other regions through defined pathways. A **modulatory center** is any region outside the initiating circuit or paths of spread that influences the seizure threshold. The location of all four components will vary from seizure type to seizure type, but there are data supporting their existence.

The **seizure focus** is generally considered as unified entity, the place a seizure starts and the target for surgical intervention. Remove the focus and the seizures are cured. The common belief is that the seizure starts the same way, and the entire focus acts in unison. However, there is much evidence to suggest that the focus is more of a region of seizure onset with a number of sites that can act independently to initiate seizures. The best evidence for multifocality within the seizure onset zone comes from surgical experience with intracranial monitoring. In some cases, people with a large abnormality may have seizures with different clinical phenotypes, and with intracranial recordings two clinically different seizures can have different patterns of seizure onset within the larger seizure onset zone (Figure 1). This concept of a distributed or multifocal focus also receives support from the observation that the best outcomes from surgery for mesial temporal lobe or limbic epilepsy occurs when most of the temporal limbic regions are removed (Thom et al., 2010). As with large neocortical seizure foci, mesial temporal seizures can have a broad, synchronized onset over multiple limbic structures as well as multifocal, independent onset from each of the sites (So, 1991; Spencer and Spencer, 1994; Bertram, 1997). For the moment the concept of the "seizure focus" is undergoing an evolution as our understanding changes, but it is probably safe to say that the single, synchronized entity that was once the conceptual model of the focus is no longer appropriate.

The **initiating circuit** is the separate neuronal populations that are necessary to support the start of a seizure. Although the seizure focus is the spark that starts the seizure, there is growing evidence that for the seizure to get started, a larger network is needed to support, organize and sustain the seizure activity. This concept was first promoted by Pierre Gloor and his colleagues for spike wave seizures (Avoli and Gloor, 1982), but there is growing evidence that an initiating circuit is also essential for focal seizures. At present the concept

of this circuit is built around cortical and subcortical (typically the thalamus) connections in which the first seizure activity appears, although we cannot exclude focal or regional cortical circuits that might assume this role. As will be described later, the role of these components is quite different, but they have to work together for the seizure to get started.

Pathways of spread or recruitment are the routes that seizures follow to extend beyond the initiating circuit. These patterns of spread can be quite stereotyped in any one individual and are the means by which seizures secondarily generalize. Although many explanations have been offered about how the seizures move from one region to another, there are little data to support the theories. They include seizure induced changes in the local extracellular environment, strength of existing pathways (local, regional, subcortical) and the propensity for one region to seize. This area has not received much attention, but if we could prevent seizures from spreading, we could keep the seizures confined to the initiating circuit and, in theory, minimally intrusive into a person's life.

Modulatory centers are regions of the brain that project to key components of the seizure circuits (focus, initiating circuit or pathways of spread) and affect the level of excitability of those components and thus alter the likelihood that a seizure will happen or spread. These areas are not directly involved with the seizure activity, at least not in the early phases, but their roles have been suggested by the observation that seizures can vary in clinical intensity and duration. There is further support for circuit modulation because seizures happen sporadically even though the “epileptic substrate” of the focus is considered a fixed abnormality. Other observations supporting the concept of circuit modulation include the varying intensity and duration of seizures in one individual: at times seizures remain non-convulsive and at other times they evolve to full tonic-clonic events. For this reason we should consider these neuromodulatory centers as regions that shift the chances that a seizure will start or spread. These inputs to the focus are key to that process and are every bit a part of the functional anatomy, even if they do not directly participate in the electrographic seizure activity. At the moment these centers are not well known and may be difficult to identify although we will discuss the potential role of several regions later. The interplay of these four components is outlined in Figure 2.

Circuitry of Epilepsy

As noted at the beginning of this article, epilepsy has many causes and can arise in many different regions of the brain. For these reasons, the underlying pathophysiology and associated functional anatomy will also vary considerable. Because there is no prototype for the circuitry that supports the start and spread of seizures in all types of epilepsy, we will describe two common types of epilepsy, spike wave and limbic, and what is known about the underlying circuits that are involved in the different stages in the evolution of the seizure. Within each of these two types of epilepsy there is considerable variability in the neuronal physiology that causes the seizures, so in this discussion we will focus on what is known about the circuits and how they support the initiation and spread of seizures. For each seizure type we will discuss what is known about the four parts of the seizure circuit (focus, initiating circuit, paths of spread and modulatory circuitry)

Spike wave or generalized epilepsy—Absence or spike wave epilepsy is characterized by very regular spike wave discharges that often have an anterior predominance on EEG recordings. They are generally, but not always, brief (3 to 10 seconds), and, when they are done, the EEG and individual return to normal. Pierre Gloor with a number of colleagues (Avoli and Gloor, 1982) demonstrated that these seizures do not occur in isolated neurons, rather in an assemblage of neurons, local and remote. The key circuit for these discharges involves an interaction between the cortex and several nuclei of the thalamus. In a series of simple but elegant studies using the feline generalized penicillin epilepsy model, found that if the thalamus and cortex were disconnected from one another, the spike wave seizure activity stopped. The overlying cortex had frequent irregular and disorganized spiking and the thalamus showed normal oscillatory activity. They concluded that not only did the spike wave seizures depend on an intact thalamocortical circuit, but also that each component had a distinct and separate role in the discharge: the cortex supplied the excitatory drive and the thalamic nuclei organized this drive into an ictal discharge (Figure 3). This body of work created the prototype for epilepsy circuits that is still largely valid.

Is there a seizure focus in generalized spike wave epilepsy?: That question has been asked for decades. The communal answer has most often been that there is no focus or that it is multifocal, with multiple regions of the neocortex having the potential to initiate a seizure. Using our definition of seizure focus as the region or regions that provide the spark that starts the seizure, there is ample evidence that the cortex serves that role. Gloor and colleagues demonstrated that increasing excitation in the cortex, would induce the seizures, whereas a similar manipulation elsewhere would not (Avoli et al., 1990). But how focal is the focus in a “generalized” type of epilepsy? Most recordings in people with spike-wave epilepsy show a predominance over the frontal lobe, and between seizures the interictal spiking can shift in predominance between the left and right frontal lobes. All of these observations are made on signals recorded from the scalp, as intracranial recordings in these people are hard to justify. More recently data from Meeren and her colleagues (Meeren et al., 2002) have suggested that spike wave seizures in a genetic rat model of spike wave epilepsy begin focally in a restricted region in the frontal lobe, but rapidly recruited other regions. For the moment we can't be sure about how focal the seizure focus for this type of epilepsy is, but all of the data point to the cortex as the region that provides the spark, and thus fits our definition of focus.

With a potentially diffuse (anatomically) cortical focus, what is the initiating circuit?:

The data point very strongly to a critical cortical-thalamic-cortical loop that is essential for the seizure to start in spike wave seizures. The key components are the pyramidal cells of the cortex, the GABAergic neurons of the reticular nucleus of the thalamus and relay nuclei of the thalamus. Gloor's work with the feline penicillin model showed that when disconnected from one another the cortex could only spike irregularly, and the thalamic relay neurons showed no abnormal activity. Only when the two were connected did rhythmic spike wave discharges arise. Both components had to be present, and if one were inactivated or missing, seizures would not occur. Just as in any electrical circuit, if there is a break somewhere, the circuit won't work, even if the primary components are present and functioning normally. The reticular nucleus of the thalamus, which provides much of the

GABAergic input to the thalamic relay nuclei, hyperpolarizes the relay neurons which activates the calcium T-currents (Crunelli and Leresche, 2002; Kostopoulos, 2001). The size of this initiating circuit (cortical area, thalamic nuclei) is not well defined, but, if the findings of Meeren can be generalized to the human disorder, it may be relatively restricted, and the pathways of spread become the critical issue in developing the more widely distributed discharge.

How do generalized spike wave seizures spread outside the initiating circuit?: All of the experiments to date support a model of cortical-cortical recruitment through regional or interhemispheric pathways. In the feline penicillin epilepsy model, separating the hemispheres through callosotomy or isolating a region of cortex prevented synchronization of activity, and, in some cases, the spread of seizure activity to other regions. In the WAG/Rij rat it was also demonstrated that cortical-cortical interaction was also important, but that recruitment of the additional nuclei of the thalamus played a role as well. Based on these observations, one may hypothesize that spread outside of the initiating circuit depends on the projections of the seizure focus to other regions as well as the participation of the nuclei of the thalamus that support those regions (Meeren et al., 2005).

Are there modulatory centers for spike wave seizures?: At present we really can only hypothesize that they exist. Although the substrate for seizures is permanent, the seizures don't occur non-stop. In fact they can be quite intermittent. This observation suggests that there are changes in the system physiology which allows the seizures to occur. In the feline penicillin model, manipulation of brain stem and midbrain projection nuclei increased and decreased seizure frequency. Enhancing thalamic GABAergic tone will also increase the number and duration of seizures. In some forms of spike wave epilepsy, the spiking increases significantly during sleep. At present, we are less certain about the exact nature of neuromodulation, but are certain that it happens. Neuromodulation may be the next major step in epilepsy therapy. The paths by which the seizure activity spreads to other regions have not been well studied either. These relationships have been reviewed more extensively elsewhere [Steriade, 2005] and also demonstrated in animal models of spontaneous spike and wave [Meeren et al., 2002].

Circuitry of limbic epilepsy—Unlike generalized spike wave epilepsy which does not have a well defined pathology or neuronal physiology, there are a number of changes associated with limbic (or mesial temporal lobe) epilepsy. Before entering into the discussion about the different circuits and components of the circuits, we will briefly review some of the key issues associated with this syndrome.

The Anatomy of Limbic Epilepsy

Limbic epilepsy is a common form of focal epilepsy and has abnormalities that have similar appearance across individuals [Thom et al., 2010]. Because there is a certain uniformity in limbic seizures we may be able to determine which structures are critical for seizure initiation, and the role they play in the seizure circuitry. A potential role of these structures in seizures was supported when surgical removal led to seizure control, with the implication that the mesial temporal regions were important for generating seizures. Kindling studies

that have shown that it is easy to initiate seizures in these structures in animals have further strengthened the concept that this region is important for seizure initiation [Goddard et al., 1969].

The quintessential pathology of limbic epilepsy has been hippocampal sclerosis, a combination of neuronal loss, atrophy and gliosis. The pattern of loss is usually in the hilus of the dentate gyrus and the CA1 region, but there are some variants. However, there are other limbic sites that also have changes, typically neuronal loss, atrophy and gliosis including the amygdala and the entorhinal cortex as well as specific nuclei in the thalamus [Juhasz et al., 1999; Natsume et al., 2003; Hudson et al., 1993; Du et al., 1993]. Animal studies in rats with post-status epilepticus limbic epilepsy have also revealed changes in the olfactory cortex, a region that is not regularly available in surgical specimens or examined in post mortem tissue [Bertram and Scott, 2000]. These observations suggest that the substrate for the seizures of limbic epilepsy is broader than just the hippocampus. The results of surgery for limbic epilepsy support the concept of a more distributed focus, as seizure control is more likely if multiple limbic sites are removed.

Experiments over the last several decades have supported the concept that the thalamus, particularly the midline nuclei, is part of the limbic seizure circuit. The earliest studies showed that modulating inhibitory or excitatory function in the region of the medial dorsal nucleus had a profound effect on the behavioral expression of seizures, an observation that suggested that these nuclei had a role in seizure spread to other regions [Cassidy and Gale, 1998; Miller et al., 1989]. More recent studies have shown that either inactivating the midline nuclei pharmacologically or manipulating the excitability of this region has a profound effect on the seizure activity in the hippocampus as well [Bertram et al., 2001, 2008]. Further, although kindling of limbic seizures can occur with stimulation of the midline nuclei (and only the midline nuclei), the threshold for electrical current to induce the seizure is significantly higher than the threshold in the limbic sites [Bertram et al., 2008]. This observation draws a potential parallel between Gloor's model of spike wave seizures and limbic seizures in which the cortex provides the excitatory drive and the thalamus serves to organize and support the seizure. In both seizure types, seizures do not happen unless the thalamus and the cortical focus are involved.

The Physiology of Limbic Epilepsy

In human intracranial monitoring the goal has been to define the seizure generating zone sufficiently accurately so that seizure freedom is likely if that zone is removed. Overall, with some variability across the patients, there is a consistent finding of a broad regional seizure onset involving multiple limbic sites at seizure onset [So, 1991; Spencer and Spencer 1994]. This observation raises the possibility of a multifocal seizure focus or of a more centrally synchronized seizure initiation.

Data from animal studies raise the same possibility of a seizure focus that involves multiple limbic sites. Although the ease with which the seizures can be induced and the rapidity with which they spread depends on which site is stimulated, all of the limbic sites can induce the same seizure type. In recording multiple limbic sites in rats with limbic epilepsy, there is some variability from seizure to seizure with regard to where the seizure is first recorded,

but, just as in people, the overall the pattern of onset that is most commonly recorded is broadly synchronized over multiple areas [Bertram, 1997] .

In tissue taken from epileptic animals, multiple sites have neurons with clearly epileptogenic changes: hippocampus, amygdala, entorhinal cortex, olfactory cortex and the midline thalamic nuclei [Bertram et al., 1998; 2001; Mangan et al., 2000]. When synaptically stimulated these neurons have prolonged depolarizations, sometimes longer than 250 milliseconds with multiple superimposed action potentials[Fountain et al., 1998]. These observations suggest that there is a broad change in the limbic system with multiple areas that will have greater propensity to support seizure activity.

To summarize the information that is available about limbic epilepsy, there are four key points. First, the associated pathology involves a number of limbic and subcortical regions. Second, the neuronal physiology in this syndrome, at least in animal models, shows a widespread enhanced excitability. Third, specific midline thalamic nuclei that are widely connected to the limbic sites have a major influence on the initiation and spread of limbic seizures. Finally, the surgical control of limbic epilepsy is strongly tied to the extent of the resection, with the greatest success associated with a more complete resection of the mesial limbic regions. In the following paragraphs we will try to link those observations into a model of circuitry of limbic epilepsy.

How focal is the focus in limbic epilepsy?—As noted above the pathology associated with this syndrome is distributed across a number of limbic sites, including specific thalamic nuclei. Animal studies indicate that the neurons in these regions have enhanced excitability (Bertram et al, 1998; Mangan et al., 2000; Fountain et al. 1998) . Seizures in animal models was well as in people have a multifocal or broadly synchronized onset. Clinically there is the common observation that the success of surgery is associated with the removal of multiple limbic regions. The implication of these observations is that each of the sites could act independently to initiate a seizure or, potentially, to drive another site into a seizure. In other words, one seizure could be driven by the hippocampus, another by the amygdala. Thus, in limbic epilepsy, one may view the mesial temporal region as a broad seizure onset zone, with the potential that each of the structures (e.g. amygdala or hippocampus) acting as a seizure focus for any given seizure. This potential multifocal seizure onset zone is reflected in Figure 2 with three independent foci within a single seizure onset zone.

With a distributed focus, is there an initiating circuit?—The amygdala, hippocampus, parahippocampal gyrus, entorhinal cortex and, at least in animal models, olfactory cortex are implicated in the onset of limbic seizures. Although these structures are connected to a greater or lesser extent, they all have connections to the midline thalamic nuclei [Herkenham, 1978; Su and Bentivoglio, 1990; van der Werf, 2002]. Recordings from animal models show that the midline nuclei are involved synchronously with the onset of seizures in the limbic sites [Bertram et al., 2001]. In addition there can be onset from single regions, even though the most common pattern is diffusely synchronized across all limbic sites.. Finally, inactivating or inhibiting the midline region of the thalamus significantly ameliorates or prevents experimental limbic seizures, and these effects are specific to the midline nuclei, not the remainder of the thalamus [Bertram et al., 2008].

These observations suggest that the initiating circuit involves the limbic “cortical” regions (amygdala, hippocampus, etc.) and the midline nuclei (medial dorsal as the primary). This hypothesized functional anatomy creates many parallels between the initiating circuits of limbic epilepsy and Gloor's model for generalized spike wave epilepsy.

How do limbic seizures spread from the limbic system?—Less well established data exist for this question. In people frontal involvement are common, ipsilateral and contralateral and there is the less common convulsion, but what paths are followed are not well defined. Animal studies involving kindling and lesioning of possible input/output centers have raised the possibility that such regions as the perirhinal or entorhinal cortex are involved in “breakout” from the limbic system to the rest of the brain, and known pathways could support that hypothesis. That model is based on the concept of recruiting adjacent cortex and slowly recruiting neighbors until the entire brain is involved, much like Jacksonian march. However, it is a common observation that seizures originating in the limbic systems recruit larger areas of cortex in which the seizures begin synchronously with nearby cortex less involved. This observation suggests that the seizures spread through more regional connections. The data from kindled animals indicated that inhibition of the midline thalamus reduced the severity of the seizures, and, presumably, the spread [Bertram et al., 2008; Cassidy and Gale, 1998; Miller et al., 1989]. This observation suggested that the thalamus had a significant role in seizure spread, and the midline nuclei are connected not only to the limbic system but also to a number of neocortical sites. Such a scenario could create a functional anatomy for limbic seizures that has many similarities to the functional anatomy of generalized spike wave seizures developed by Gloor, in which there is a more complex interaction from cortex to cortex and from cortex to thalamus to new areas of the cortex. We will discuss the specific roles in the following section about the thalamus in epilepsy.

Are there centers that modulate seizure activity in limbic epilepsy?—The quick answer is that we don't know. However, there is much evidence to suggest that there is. The changes that predispose the system to seizures are always present, but the seizures occur only intermittently, often quite rarely. So it is likely that there are fluctuations in the intrinsic excitability of the brain that pushes the system, from time to time, over the seizure threshold. But what is happening is unknown. It is known that limbic seizures are far more likely to occur during the day than during the night but what leads to this diurnal variational remains unclear [Quigg et al., 1998]. Over the last several decades, the substantia nigra, and particularly the pars reticulata which contains many GABAergic projection neurons has been found to have a significant influence on limbic seizures [Bonhaus et al., 1991; Gale, 1992; McNamara et al, 1994; Moshé et al., 1995]. Others report other subcortical regions as having an influence on seizure expression [Deransart and Depaulis, 2002; Gale et al., 1993]. Where such neuromodulation occurs is also unclear (subcortical vs. cortical or both), but defining these centers may provide key insights into the mechanisms underlying seizures in a brain predisposed to them. Deep brain stimulation has been embraced as a therapy of great potential and defining these centers may provide new targets for stimulation.

Role of the Thalamus in Seizure Circuits

From the time of the work of Gloor and colleagues, the thalamus has been considered a key component of the seizure circuit for the initiation and spread of seizures, but its exact physiological role in the seizure was unclear. For spike-wave seizures, the drive to start the seizure came from the neocortex, and the spike and slow wave developed from the interaction among the cortex, the reticular nucleus of the thalamus and the relay nucleus that was reciprocally connected to the involved neocortex. The rhythms generated within the thalamus established the spike wave pattern, but how the seizures recruit additional regions was unclear. The work by Meeren and colleagues suggested, based on temporal relationships among the regions with regard to the appearance of seizure activity, that there was a complex interaction of cortico-cortical and cortico-thalamo-cortical circuits that were the center of the development and spread of the seizure. What the thalamus was actually doing remained unclear. In theory the excitatory projections of the thalamus could help drive the seizure in new areas [Bertram and Zhnag, 1999; Zhang and Bertram, 2002] , but there was no evidence about how a region that was a target of thalamic projections would become an active participant in the seizure.

In examining the thalamic role in seizures, one must first consider the anatomic connections among the different components of the limbic system (e.g. hippocampus to amygdala) and with the thalamus. There are numerous tract tracing studies that demonstrate projections from one limbic region to another (such as piriform cortex to entorhinal cortex or subiculum to cingulate or prefrontal cortex) as well as the reciprocal connections between the midline nuclei of the thalamus with the limbic system. In examining the connections in aggregate one can create a theoretical mechanism by which excitatory fibers from one limbic region diverge and then converge on another region, with one branch of the fibers stimulating the thalamus which in turn provides additional excitatory drive to the target limbic region. In this theoretical construct, the excitatory drive diverging through the thalamus would arrive later at the target region, thus prolonging the duration of the excitatory stimulation.

To test this hypothesis we broke these potential pathways into their physiological components to ascertain that each potential arm did function as hypothesized and then examined how these components worked together to enhance excitatory drive. We selected two limbic circuits in which the medial dorsal nucleus was, by anatomical studies, included. The two circuits were the piriform cortex to entorhinal cortex and the subiculum to the prefrontal cortex. Tract tracing studies had demonstrated that there were direct monosynaptic connections from the piriform cortex to the entorhinal cortex and medial dorsal nucleus and from the subiculum to the prefrontal cortex and the medial dorsal nucleus. Studies had also shown that the midline nuclei have projections to entorhinal cortex and prefrontal cortex as well [Sloan and Bertram, 2009; Zhang and Bertram, 2002].

Evoked potential studies confirmed that the monosynaptic connections were excitatory providing physiological evidence for excitatory divergence and convergence, but there was no evidence that these components actually worked this way. To demonstrate the potential existence of a divergent convergent excitation, it would be necessary to remove the influence of the thalamus from the responses and examine how the complex evoked potentials change when the thalamus has been inactivated. Stimulating in the piriform cortex

resulted in a complex multiphasic response in the entorhinal cortex, and stimulation in the subiculum induced a similar complex response in the prefrontal cortex. At both recording sites there was an early component to the responses which represented a monosynaptic response as well as a later multisynaptic thalamic component. We then inactivated the midline thalamus pharmacologically with tetrodotoxin which significantly attenuated the thalamic component of the evoked response. These observations suggested that the late arriving excitatory component of the thalamic response was a major factor in pushing the system into a seizure [Sloan et al., 2011a; 2011b].

Based on these results we developed a model for seizure circuits that involved the thalamus as a key component. Its role is to provide additional, late arriving excitatory drive that would prolong the duration of excitation that would push target region into a seizure. The monosynaptic, direct excitatory drive was insufficient to induce a seizure. The thalamus, and likely specific nuclei, amplifies the excitatory signal from the initiating site, and is, thus, a critical component of a divergent-convergent excitation amplification system without which seizures may not occur. These interactions are depicted in Figure 4.

This potential role of the thalamus in divergent-convergent excitation amplification suggests that modulating the excitability of the thalamus could be a new target for therapy development. There was a trial of thalamic stimulation in epilepsy, primarily targeting the anterior nucleus that showed some benefit (Fisher et al. 2010). However, the study involved patients with focal seizures that were not well localized, suggesting that the different patients had seizures involving different circuits, not all of them limbic and not all including the midline nuclei. All of the work to date has suggested that efficacy is connected to positioning for drug infusions. If so, then electrodes that were not placed precisely in relation to a key circuit component are less likely to have an effect. The animal work indicates that understanding the circuitry is key to directing therapy appropriately.

Summary

In this paper we have emphasized that seizures occur in neuronal circuits and that different stages of seizures (initiation and spread) involve different circuits. In addition, although less well understood, there is good evidence to suggest that the excitability of any circuit is influenced by neuromodulatory centers that are often outside the regions of the brain that are involved in the seizures. As we consider developing new and better therapies, we must understand the seizure circuits so that we can direct the therapies to the parts of the brain that are most critical to the start and spread of the seizures.

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Highlights

Epileptic seizures arise in neuronal circuits

Neuronal circuits involved in epileptic seizures depend on site of onset

Understanding seizure circuits important for directing therapy

Heisenberg Uncertainty Principle

In atomic physics: It is impossible to determine accurately both the position and the direction and speed of a particle at the same instant.

In neuroscience: It is impossible to relate the activity of a single channel or receptor to the activity of the brain at the same instant.

Neuroscience corollaries:

The more one focuses on the activity of the channel, the less one understands about the activity of brain.

The more one focuses on the output of the brain, the less one can predict what is happening at a single channel.

Figure 1. Two patterns of seizure onset with different clinical expression within one region

A. Unilateral (contralateral) drawing of face without alteration of consciousness. EEG shows focal onset in two electrodes in the anterior temporal lobe that was followed by a rapid recruitment of the frontal lobe (recruitment not shown). MRI reconstruction with electrodes shows that onset is localized at the anterior pole of the temporal lobe.

B. Staring with impaired response and awareness without automatisms. EEG shows onset in different electrodes that the MRI reconstruction shows are along the medial aspect of the temporal lobe (subsequent spread, lateral temporal).

Patient was cured (seizure free off medications for five years) after complete resection of seizure onset zone. Pathology was pleomorphic xanthoastrocytoma.

Figure 2. Seizure focus, initiating circuit, pathways of spread and neuromodulatory centers
 The seizure focus is the region of the brain that provides the excitatory drive to start the seizure. Although considered a single entity, there may be subregions within the focus that operate independently to start seizures with different clinical manifestations (here A, B and C). The initiating circuit is the combination of the seizure focus and subcortical structures (often the thalamus) that are necessary for the seizure to begin. The pathways of spread may arise from the focus, thalamus (or both, see figure 4) to recruit new regions into the seizure. Neuromodulatory centers (NM) may act independently on the different components of the

initiating circuit (individually or together) to raise or lower the chances of a seizure's starting.

Secondary Spread

Figure 3. Circuitry of a generalized spike wave seizure

The initiating circuit consists of the neocortical focus that provides excitatory drive to the relay nucleus and reticular nucleus of the thalamus simultaneously. The stimulation of the reticular nucleus, which contains the majority of thalamic inhibitory neurons, enhances the inhibition of the relay nucleus which enters into a state of burst firing that is initiated as a result of the increased inhibitory drive from the reticular nucleus. The burst firing of the thalamic relay nucleus is reflected in the spike wave activity of the cortex. Once the seizure starts, it spreads through a combination of cortical connections from the focus and the organizing rhythmic activity of the thalamus. All pathways indicated are excitatory except from the reticular nucleus to the relay nucleus, which is inhibitory.

Initiating Circuit

Figure 4. Divergent-convergent excitation as a means of initiating seizures and recruiting new areas into the seizure

In this example, the initiating circuit consists of the entorhinal cortex stimulating the hippocampus directly and through the midline thalamic nuclei. Once the seizure is started, it may recruit new areas in a similar fashion. In this example, the now seizing hippocampus recruits the prefrontal cortex directly and also indirectly through a disynaptic pathway through the thalamus. The thalamic stimulation arrives in both circuits after the direct monosynaptic excitation and thus may prolong the duration of the stimulation.