Mecanismos Básicos que Median las Crisis Convulsivas y la Epilepsia
A seizure (from the Latin sacire—to take possession of) is the clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. Epilepsy is a disorder of the central nervous system characterized by recurrent seizures unprovoked by an acute systemic or neurologic insult. Epileptogenesis is the sequence of events that turns a normal neuronal network into a hyperexcitable network. (Slide 2)

Recognizing the distinction between seizures and epilepsy is essential. Epilepsy may require chronic treatment (with antiepileptic medication and, in some cases, surgery) whereas therapy for an isolated seizure is directed toward the underlying cause and may not require antiepileptic drugs (AEDs). Furthermore, epilepsy often has profound psychosocial ramifications for the patient, and is thus a diagnosis to be assigned with care.

B. Overview

In order to understand the concepts of seizures, epilepsy and epileptogenesis, we will first consider some of the basic anatomic and electrophysiologic properties of the cerebral cortex, and the factors that determine the level of neural activity at the cellular and cell network level. We will then discuss the physiologic basis of the electroencephalogram (EEG), routinely used in assessing patients with seizures and other neurological disorders. Finally, we will address some of the main features of the abnormal physiological activity that occurs within a seizure focus, and present a few of the proposed mechanisms that may underlie certain seizure types.
Neurophysiology of the Cerebral Cortex

A. Basic Anatomy of Cortex

The human cerebral cortex consists of 3 to 6 layers of neurons. The phylogenetically oldest part of the cortex (archipallium) has 3 distinct neuronal layers, and is exemplified by the hippocampus, which is found in the medial temporal lobe. The majority of the cortex (neocortex or neopallium) has 6 distinct cell layers and covers most of the surface of the cerebral hemispheres. A particularly important cortical structure in the pathophysiology of one of the more common epilepsy syndromes is the hippocampus. This structure illustrated in Slide 3 is common in temporal lobe epilepsy. As seen in the slide, the hippocampus consists of three major regions: subiculum, hippocampus proper (Ammon’s horn) and dentate gyrus. The hippocampus and dentate gyrus have a three layered cortex. The subiculum is the transition zone from the three to the six layered cortex. Important regions of the hippocampus proper include CA1, CA 2 , CA3. The cortex includes two general classes of neurons. The projection, or principal, neurons (e.g., pyramidal neurons) are cells that “project” or send information to neurons located in distant areas of the brain. Interneurons (e.g., basket cells) are generally considered to be local-circuit cells which influence the activity of nearby neurons.
Interneurons (e.g., basket cells) are generally considered to be local-circuit cells which influence the activity of nearby neurons. Most principal neurons form excitatory synapses on post-synaptic neurons, while most interneurons form inhibitory synapses on principal cells or other inhibitory neurons. Feed-forward inhibition occurs when an inhibitory neuron receives collateral innervation from an excitatory projection neuron. Since the inhibitory neuron is activated closely in time with the principal cell, feed-forward inhibition serves to inhibit over-activation of the principal cell by the projection neuron. Recurrent inhibition can occur when a principal neuron forms synapses on an inhibitory neuron, which in turn forms synapses back on the principal cells to achieve a negative feedback loop. In this type of feedback inhibition, the excited principal cell recurrently excites interneurons to inhibit the firing of neighboring principal cells, thus preventing the pool of target principal neurons from becoming synchronously over-activated. Slide 4 illustrates schematically both types of inhibition in a local interneuron-granule cell dentate gyrus circuit.

However, recent work suggests that some interneurons appear to have rather extensive axonal projections, rather than the local, confined axonal structures previously suggested. In some cases, such interneurons may provide a very strong synchronization or pacer activity to large groups of neurons.
B. Basic Neurophysiology and Neurochemistry Governing Excitability:

Given that the basic mechanism of neuronal excitability is the action potential, a hyperexcitable state can result from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra- or extra-cellular ion concentrations in favor of membrane depolarization. A hyperexcitable state can also result when several synchronous subthreshold excitatory stimuli occur, allowing their temporal summation in the post synaptic neurons (Slide 5). Action potentials occur due to depolarization of the neuronal membrane, with membrane depolarization propagating down the axon to induce neurotransmitter release at the axon terminal. The action potential occurs in an all-or-none fashion as a result of local changes in membrane potential brought about by net positive inward ion fluxes. Membrane potential thus varies with activation of ligand- gated channels, whose conductance is affected by binding to neurotransmitters; or with activation of voltage-gated channels, whose conductance is affected by changes in transmembrane potential; or with changes in intracellular ion compartmentalization.
Neurotransmitters are substances that are released by the presynaptic nerve terminal at a synapse and subsequently bind to specific postsynaptic receptors for that ligand. Ligand binding results in channel activation and passage of ions into or out of the cells. The major neurotransmitters in the brain are glutamate, gamma-amino-butyric acid (GABA), acetylcholine (ACh), norepinephrine, dopamine, serotonin, and histamine. Other molecules, such as neuropeptides and hormones, play modulatory roles that modify neurotransmission over longer time periods (Slide 6).
The major excitatory neurotransmitter is the amino acid glutamate. There are several subtypes of glutamate receptors. Glutamate receptors can be found postsynaptically on excitatory principal cells as well as on inhibitory interneurons, and have been demonstrated on certain types of glial cells. The ionotropic subclasses are the alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), kainate receptors, and N-methyl-D-aspartate (NMDA); these allow ion influx upon activation by glutamate (Appendix A, Table 1). They are differentiated from one another by cation permeability as well as differential sensitivity to pharmacological agonists/antagonists. All ionotropic glutamate receptors are permeable to Na+ and K+, and it is the influx of Na+ and outflow of K+ through these channels that contribute to membrane depolarization and generation of the action potential. The NMDA receptor also has a Ca++ conductance that is blocked by Mg++ ions in the resting state, but under conditions of local membrane depolarization, Mg++ is displaced and the channel becomes permeable to Ca++; influx of Ca++ tends to further depolarize the cell, and is thought also to contribute to Ca++ mediated neuronal injury under conditions of excessive neuronal activation (such as status epilepticus and ischemia), potentially leading to cell death, a process termed excitotoxicity. The other major type of glutamate receptor is the metabotropic receptor, which functions by means of receptor-activated signal transduction involving membrane-associated G-proteins (Appendix A, Table 2). There are at least 3 subtypes of metabotropic receptors, based on differential agonist potency, mechanism of signal transduction, and pre- versus post-synaptic localization. (Slides 7 & 8)
Experimental studies using animal epilepsy models have shown that NMDA, AMPA and kainate agonists induce seizure activity, whereas their antagonists suppress seizure activity. Metabotropic agonists appear to have variable effects likely dependent upon their different location and mechanisms of signal transduction.
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In the adult brain, GABAA receptors are permeable to Cl- ions; upon activation Cl- influx hyperpolarizes the membrane and inhibits action potentials. Therefore, substances which are GABAA receptor agonists, such as barbiturates and benzodiazepines, are well known to suppress seizure activity. GABAB receptors are associated with second messenger systems rather than Cl- channels, and lead to attenuation of transmitter release due to their presynaptic location. The second messenger systems often result in opening of K+ channels, leading to a hyperpolarizing current. Certain GABAB agonists, such as baclofen, have been reported to exacerbate hyperexcitability and seizures.
Mecanismos Celulares de la Generación de las Crisis Epilépticas

- **Excitación (mucha)**
  - Iónica—influjo de Na⁺, corrientes de Ca++
  - Neurotransmisor—glutamato, aspartato

- **Inhibición (poca)**
  - Iónica—influjo de Cl⁻, salida de K⁺
  - Neurotransmisor—GABA
Función Normal de SNC

Excitación

Inhibición

glutamato, aspartato

GABA

Modificado de White, 2001
La hiperexcitabilidad refleja tanto excitación aumentada como inhibición disminuida

↑ glutamato, aspartato

\[ \text{Inhibición} \]

↓ GABA

Excitación

Modified from White, ICEG, 2001
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Factors Governing Excitability of Individual Neurons:

The complexity of neuronal activity is partly due to various mechanisms controlling the level of electrical activation in one or more cellular regions. These mechanisms may act inside the neuron or in the cellular environment, including other cells (e.g., neighboring neurons, glia, and vascular endothelial cells) as well as the extracellular space, to modify neuronal excitability. The former may be termed “neuronal” or “intrinsic,” and the latter “extra-neuronal” or “extrinsic.”

1. Examples of neuronal (intrinsic) factors include: (Slide 14)

   • The type, number and distribution of voltage- and ligand-gated channels. Such channels determine the direction, degree, and rate of changes in the transmembrane potential, which in turn determine whether an action potential occurs. Voltage-gated sodium channels, for example, form the basis of the rapid depolarization constituting the action potential. Among ligand-gated channels, the GABA receptor complex mediates inflow of chloride ions which hyperpolarize the cell, forming the basis of neuronal inhibition, as described previously.

   • Biochemical modification of receptors. For example, phosphorylation of the NMDA receptor increases permeability to Ca++, resulting in increased excitability.

   • Activation of second-messenger systems. Binding of norepinephrine to its alpha receptor, for example, activates cyclic GMP, in turn activating G-proteins which open K+ channels, thereby decreasing excitability.

   • Modulating gene expression, as by RNA editing. For example, editing a single base pair of mRNA encoding a specific glutamate receptor subunit can change the ion selectivity of the assembled channel.
Epilepsia y Canalopatías

- Inherentes
  - Mutaciones de canales iónicos dependientes de voltaje
  - Mutaciones de canales que se acoplan a ligandos (receptores a neurotransmisores)
  - Diferentes mutaciones en el mismo gen puede resultar en tipos radicalmente diferentes de crisis y epilepsia

- Adquiridas
  - Auto-inmune (anticuerpos contra el canal de postasio)
  - Cambios en la expresión de los canales después de las crisis epilépticas
Mutaciones de Canales & Receptores a Neurotransmisores en la Epilepsia - I

dependientes de voltaje

- **SCN1A**
  - Epilepsia Generalizada & Crisis Febriles Plus (GEFS+) tipo 2
  - Epilepsia Mioclónica Severa de la Infancia (SMEI)

- **SCN1B**
  - GEFS+ tipo 1

- **SCN2A1**
  - GEFS+
  - Crisis Infantiles-Neonatales Familiares Benignas (BFNIS)

Mutaciones genéticas de canales de sodio

American Epilepsy Society 2008
Mutaciones de Canales & Receptores a Neurotransmisores en la Epilepsia - II

Mutaciones Genéticas de Canales de Cloro Dependientes de Voltaje

- **CLCN2A**
  - Epilepsia de Ausencia Juvenil (JAE)
  - Epilepsia Mioclónica Juvenil (JME)
  - Epilepsia con Gran Mal al Despertar (EGMA)
Mutaciones de los Canales de Potasio Dependientes de Voltaje

- **KCNQ2, KCNQ3**
  - Convulsiones Neonatales Familiares Benignas (BFNC)

- **KCND2**
  - Epilepsia del Lóbulo Temporal (TLE)

- **KCNMA1**
  - Epilepsia Generalizada con Disquinesia Paroxística (GEPD)
Mutaciones de Canales & Receptores a Neurotransmisores en la Epilepsia - III

*Mutaciones de Receptores a Neurotransmisores Mutaciones a Receptores*

- **GABRG2** (Subunidad gamma-2 del receptor)
  - GEFS+ tipo 3
- **GABRA1** (Subunidad alpha 1 del receptor a GABA)
  - JME
- **CHRNA4** (Subunidad alpha-4 del receptor a nicotina acetilcolina)
  - Epilepsia del Lóbulo Frontal Nocturna Autosómica Dominante (ADNFLE) tipo 1
- **CHRNB2** (Subunidad beta-2 del receptor a nicotina acetilcolina)
  - ADNFLE tipo 3
Some Synaptic Factors include:

Changes in the density, conductance or binding of neurotransmitter gated ionotropic channels which can have potent effects on the effectiveness of GABA or Glutamate at a given synapse.

Remodeling of synaptic contacts. For example, movement of an afferent axon terminal closer to the target cell body increases the likelihood that inward ionic currents at the synapse will bring the target neuron to threshold. The coupling between the pre- and post-synaptic elements can be made more efficient by shortening of the spine neck. In addition, previous synaptic experience such as a brief burst of high frequency stimulation (e.g., long-term potentiation-LTP) also increases the efficacy of such synapses, increasing their excitability.

• Modulating transmitter metabolism by glial cells. Excitability increases, for example, if glial metabolism or uptake of excitatory transmitters such as glutamate or ACh decreases.
Some extra-neuronal (extrinsic) factors include:

- Changes in extracellular ion concentration due to variations in the volume of the extracellular space. For example, decreased extracellular volume leads to increased extracellular K+ concentration, resisting the outward movement of K+ ions needed to repolarize the cell, thereby effectively increasing excitability. Glial cells buffer the extracellular space and serve to remove excess K+ ions as well as glutamate.
D. How Network Organization Influences Neuronal Excitability

Neurons are connected together in elaborate arrays that provide additional levels of control of neuronal excitability. An example of a very basic neuronal network is the well-studied dentate gyrus and hippocampus, as shown in Slide 23.
Mossy Fiber sprouting.

These are three photomicrographs from histological sections of the dentate gyrus (DG) stained with Timm histochemistry. Dark punctate granules depict the projection pattern of mossy fiber terminals that originate from granule cell axons. (A) The DG from a normal rat shows dense staining in the hilus (area within the U-shape of the DG) and in the CA3 region, with an absence of dark punctate granules in the molecular layer of the DG (arrow). (B) The DG from a rat that experienced status epilepticus-induced with kainic acid demonstrates prominent staining in the molecular layer. (C) Human DG obtained surgically during a standard anterior temporal lobectomy for the treatment of pharmacologically intractable mesial temporal lobe epilepsy. Note that the molecular layer of the DG has prominent staining, demonstrating mossy fiber sprouting into that region.
In the dentate gyrus, afferent connections to the network can directly activate the projection cell (e.g., granule cells). The input can also directly activate local interneurons (bipolar and basket cells), and these may inhibit projection cells in the vicinity (feed-forward inhibition). Also, the projection neuron may in turn activate the interneurons which in turn act on the projection neurons (feedback inhibition). Thus, changes in the function of one or more cells within a circuit can significantly affect both neighboring and distant neurons. For example, sprouting of excitatory axons to make more numerous connections can increase excitability of the network of connected neurons (Slide 24). Alternatively, loss of inhibitory neurons will also increase the excitability of the network. Inhibitory function can also be reduced by a loss of excitatory neurons that activate or “drive” the inhibitory neurons.
Mechanisms of epileptogenesis.

The schematic diagram describes the relationships between pathophysiological phenomena and brain location during epileptogenesis in mesial temporal lobe epilepsy. Partial onset seizures might initially originate in neocortical areas, but after the establishment of intractability, there is a vicious circle of interrelated pathophysiological phenomena within the hippocampal circuitry that self-sustains intractable seizures with propagation to neocortical structures.
The electroencephalogram (EEG) is a recording of the electrical activity of the cerebral cortex, through electrodes placed on the scalp. (Slides 26 and 27)
Sistema de Colocación de Electrodes 10/20 para EEG
The EEG measures the electrical potentials of cortical neuronal dendrites near the brain’s surface. Consider the electrical activity of a single pyramidal cell activated by an afferent pathway. The incoming excitatory signal at the synapse gives rise to a post-synaptic potential resulting from positively charged ions rushing into the cell. This leaves a relatively negative charge in the extracellular space in the vicinity of the synapse. The inward current at the synapse (referred to as the “sink”) flows down the dendrite and ultimately moves outward across the cell membrane at sites distant from the synapse (referred to as the “source”). The outward flow of positive charge leaves a relatively positive charge in the extracellular space. At this instant there is a dipole outside the dendrite, with a relatively negative charge at the distal part of the dendrite and a positive charge closer to the cell body. Thus, an extracellular electrode placed near the end of the dendrite detects a negative potential. (Slide 28)
An electrode placed at the scalp cannot detect these electrical changes in a single neuron because:

1) the potentials are small in magnitude (due to the low extracellular resistance), and 2) there is considerable distance from the cell to the scalp surface. However, two cortical properties permit us to record the brain’s electrical potential. First, pyramidal cells all have the same relative orientation and polarity. Second, many cells are synchronously activated. Slide 29 shows the changes in potentials generated by a layer of cortical neurons activated at the same time. The summation of the dipoles created at each of thousands of neurons creates an electrical potential detectable at the scalp. In practice, 20 or more scalp electrodes are placed at specific locations on the head to allow the simultaneous recording from the cortical regions of both hemispheres; each electrode can detect synchronous activity generated by approximately 6 sq. cm. of cortex, generally that found at gyral surfaces. The cortex that faces the cortical sulci generally does not contribute to the EEG potentials because the cortical dipoles generated in this location cancel each other.
In clinical medicine the EEG is an important diagnostic test in the evaluation of patients with seizure disorders, sleep disorders, and altered levels of consciousness (e.g., coma), and can help localize and diagnose certain infections and focal processes within the central nervous system (CNS). (Slide 30)
The EEG waveforms are divided into four major frequency bands: delta (0-3+ Hz), theta (4-7+ Hz), alpha (8-13+ Hz), and beta (>14 Hz) (Slides 31-33). At first glance, the normal spontaneous electrical activity detected by the EEG appears somewhat chaotic. However, there is a certain organization and rhythmicity of the activity that depends on the level of alertness or sleep and the age of the subject. The physiological basis of at least some of these rhythms seems to arise from intrinsic pacemaker cells in the cortex and thalamus. Several EEG rhythms can be characterized on the basis of the location, frequency and reactivity of the activity and the clinical state of the patient. For example, a symmetrical rhythm is observed over the posterior head regions during relaxed wakefulness with eyes closed, that undergoes amplitude attenuation with eye opening or mental alerting activities. It is called the posterior dominant rhythm or alpha rhythm, because in adults it has a frequency of 8-13 Hz; however, its frequency in children may be in the theta range.
Frecuencias del EEG

Despierto – ojos abiertos – beta - 18-25 ciclos por segundo (cps)

Relajado – ojos cerrados – alfa - 8-13 cps

Fase 1 – teta - 4-8 cps

Fase 2 – 12-14 cps – espigas de sueño y complejos K

Radtke, en Ebersole y Pedley, 2003
Frecuencias del EEG

Fases 3 y 4 – delta (sueño de ondas lentas) ondas 1-4 cps > 75 μV

Sueño MOR (REM) – 3-7 cps (como teta o fase I)

Radke, en Ebersole y Pedev, 2003
Alterations of brain function often result in abnormally slow frequency activity in the EEG. Pathologic slowing, when localized, often correlates with focal brain lesions; when diffuse, slow activity often signifies an encephalopathy. Epileptiform activity characteristic of people with epilepsy includes abnormalities such as spikes, sharp waves and spike-wave complexes, (slides 33 & 34).
Basic Mechanisms of Focal Seizure Initiation and Propagation

Initiation: The hypersynchronous discharges that occur during a seizure may begin in a very discrete region of cortex and then spread to neighboring regions. Seizure initiation is characterized by two concurrent events: 1) high-frequency bursts of action potentials, and 2) hypersynchronization of a neuronal population. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG (Slide 36). At the level of single neurons, epileptiform activity consists of sustained neuronal depolarization resulting in a burst of action potentials, a plateau-like depolarization associated with completion of the action potential burst, and then a rapid repolarization followed by hyperpolarization. This sequence is called the paroxysmal depolarizing shift.

Seizure propagation, the process by which a partial seizure spreads within the brain, occurs when there is sufficient activation to recruit surrounding neurons. This leads to a loss of surround inhibition and spread of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long association pathways such as the corpus callosum.

The propagation of bursting activity is normally prevented by intact hyperpolarization and a region of surrounding inhibition created by inhibitory neurons. With sufficient activation there is a recruitment of surrounding neurons via a number of mechanisms. Repetitive discharges lead to: 1) an increase in extracellular K⁺, which blunts the extent of hyperpolarizing outward K⁺ currents, tending to depolarize neighboring neurons; 2) accumulation of Ca++ in presynaptic terminals, leading to enhanced neurotransmitter release; and 3) depolarization-induced activation of the NMDA subtype of the excitatory amino acid receptor, which causes more Ca++ influx and neuronal activation. Of equal interest, but less well understood, is the process by which seizures typically end, usually after seconds or minutes, and what underlies the failure of this spontaneous seizure termination in the life-threatening condition known as status epilepticus (see Clinical Epilepsy syllabus).
Onda Agudas

- Ejemplo de onda aguda (flecha) en el lóbulo temporal izquierdo
At the level of single neurons, epileptiform activity consists of sustained neuronal depolarization resulting in a burst of action potentials, a plateau-like depolarization associated with completion of the action potential burst, and then a rapid repolarization followed by hyperpolarization. This sequence is called the paroxysmal depolarizing shift. (Slide 37) The bursting activity resulting from the relatively prolonged depolarization of the neuronal membrane is due to influx of extracellular Ca++, which leads to the opening of voltage-dependent Na+ channels, influx of Na+, and generation of repetitive action potentials. The subsequent hyperpolarizing afterpotential is mediated by GABA receptors and Cl- influx, or by K+ efflux, depending on the cell type.
Seizures may also appear to arise from widespread cortical areas virtually simultaneously. The mechanisms underlying such generalized seizures (Slide 38) are incompletely understood.
The absence seizure, (also called petit mal) is a generalized seizure consisting clinically of a brief staring spell in conjunction with a characteristic burst of spike-wave complexes on the EEG (Slide 39).
Generalized spikewave discharges in absence seizures may result from aberrations of oscillatory rhythms that are normally generated during sleep by circuits connecting the cortex and thalamus. This oscillatory behavior involves an interaction between GABAB receptors, Ca++ channels and K+ channels located within the thalamus. Pharmacologic modulation of these receptors and channels can induce absence seizures, and there is speculation that genetic forms of absence epilepsy may be associated with mutations of components of this system.
Most common causes of epilepsy are acquired.
Most common acquired epilepsy, temporal lobe epilepsy, usually does not have a clear antecedent insult, but sometimes associated with early life prolonged seizures.
--The majority of epilepsy is acquired, but we may hypothesize that ion channel dysfunction is central just as in genetic epilepsy.

--The natural course of acquired epilepsy in humans follows a progression from insult (head trauma, etc.) to a latent period when no seizures are observed to the state of chronic epilepsy defined as two or more spontaneous seizures.

--During the latent period is epileptogenesis, a black box of cellular processes. In humans, latent period on order of months even years. What is going on inside this box during the latent period?
--it is certain that there are multiple cellular processes accounting for epileptogenesis
--one possibility is that the underlying insult sets into motion progressive changes in both voltage- and ligand-gated ion channels that produce net hyperexcitability in key neuron populations that support seizure generation
--a related but separate question is whether once spontaneous seizures occur, they may reinforce these changes, producing a vicious cycle of worsening epilepsy.
--this hypothesis, known as "seizures beget seizures" has some support from clinical evidence in humans and better support in animal models
--other factors likely at play include altered synaptic connectivity, expression of neurotrophic factors like BDNF, etc.
--unlike case in genetic epilepsy, unlikely that a *single* ion ch. defect explains development of epilepsy
An important experimental model of epileptogenesis is kindling, discovered by Goddard and coworkers in the 1960s. Daily, subconvulsive stimulation (electrical or chemical) of certain brain regions such as the hippocampus or amygdala result in electrical afterdischarges, eventually leading to stimulation-induced clinical seizures, and in some instances, spontaneous seizures. This change in excitability is permanent and presumably involves long-lasting biochemical and/or structural changes in the CNS. A variety of changes have been measured in kindling models, including alterations in glutamate channel properties, selective loss of neurons, and axonal reorganization. However, the exact mechanisms underlying kindling, and its applicability to human epileptogenesis, remain unknown. (Slide 41)