On The Ignition, Propagation and Termination Of The Neuronal Bursting Activity During Ictogenesis In Epileptic Patients

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Abstract

Epilepsy creates a persistent increase in the probability of spontaneous seizures. An ictal episode evolves due to acute disturbance of the fine-tuned balance between excitatory vs. inhibitory inputs within a neural network in favor of excitation. The current literature that proposes the activity-dependent disinhibition as a valid mechanism of chronic epilepsy, does not provide clues on why this mechanism emerges only in epileptic patients and how the vicious circle resulting of an activity-dependent disinhibition in over-active ictogenic network would end. A new model, which presents chronic epilepsy as a disease of faulty architecture of the neural circuit, is discussed. Wherein; variable genetic or acquired predisposing factors drive abnormalities in the construction of multiple neural circuits resulting in an activity-dependent positive feedback excitatory loops which transform normal neural circuits into ictal foci. Such new mechanism, for igniting an activity-dependent unstable excitation with subsequent relatively stable disinhibition, leads to an ictal escape rhythm. The propagation of such bursting activity occurs either electrochemically via synaptic communication to remote susceptible circuits, or chemically via a trigger wave which recruits the non-connected proximal neurons. Termination occurs abruptly when the inhibitory interneurons functionally recover and reimpose their inhibitory effect on the ictogenic circuit to transform the escape rhythm into a normal, under-control output. The proposed model elucidates various enigmatic features of the disease; and illustrates both the end-result ictogenic mechanism arising from the wide variety of etiologies of human spontaneous and acquired epilepsy, and the timing of episodic transitions from normal activity to seizures.

Key words: Epilepsy; Ictogenesis, Excitatory Feedbacks; Competition Zone; and Escape Rhythm

Introduction

Brain electrical activity is non-synchronous (McPhee and Hammer, 1995) and regulated by factors within the neuron and the extraneuronal environment. Neuronal factors comprise the type, number and distribution of ion channels; changes to receptors of neurotransmitters and modulation of gene expression (Bromfield et al., 2006). The extraneuronal factors include ion concentration, synaptic plasticity and regulation of transmitters’ breakdown and reuptake (Blumenfeld, 2005).

During seizures; a discrete group of neurons begins abnormal excessive firing in a synchronized manner (Da Silva et al., 2003; Margineanu, 2010) which then can propagate to neighboring regions (Gotz-Trabert et al., 2008). The characteristics of said firing are high frequency bursts of action potentials and hypersynchronization (Fisher et al., 2005). At the level of single neurons, the ictal discharge shows a characteristic paroxysmal depolarization shift, which consists of a sequence of sustained neuronal depolarization resulting in a burst of action potentials, a plateau-like phase associated with completion of the action potential bursts, and then rapid repolarization followed by hyperpolarization (Misulis and Head, 2003).

The exact mechanism by which such smooth normal brain activity is suddenly shifted to the bursting ictal firing is still unclear (Noebels et al., 2012). The axiomatic mechanism, which involves an acute imbalance between the excitatory discharge and the inhibitory control, needs further elaboration on the cellular and molecular levels. Mutagenic neurochemical changes in the neurotransmitters, receptors and ion channels are a valid mechanism to address severe forms of epileptic encephalopathies wherein the brain activity is distorted with no or little normal epochs. Nevertheless; neurochemical changes on such a molecular level is time-invariant and don’t provide an explanation for the unpredictable episodic, and relatively rare, seizures (Schulze-Bonhage and Kühn, 2008) that occurs in...
chronic epilepsy. Besides; non-mutagenic changes in the number and distribution of ion channels and neurotransmitter receptors can not be asserted as a primary mechanism of epilepsy’s pathogenesis, or a reactive remodelling as a result of repeated ictal behavior of epileptogenic foci.

Models of activity-dependent disinhibition for ictogenesis solve the timing problem; wherein disinhibition occurred only at the extremes of network activity (Bracci et al., 2001; Wester and McBain, 2014). Therefore; the probability of ictal changeover would depend on the probability of that exceptional level of activity. Likely; the same range of probabilities characterizing spontaneous seizures can agree with the odds of these levels of activity (Staley, 2015). Once a seizure is induced by an activity-dependent disinhibition, the seizure itself can continue to produce activity levels that are sufficient to suppress inhibition, providing the necessary positive feedback to sustain the seizure. Yet; Said models do not provide the fundamental mechanism by which a robust input can transform a network with apparently normal activity into an ictal focus. Moreover; they do not give clues on how the vicious positive feedback circle will end, adding more ambiguity on the poorly understood mechanism of termination of an ictal activity.

A model for the pathogenesis of chronic epilepsy shall provide insights on the most enigmatic aspects of the disease: like the basic fundamental mechanism that emerges from the wide varieties of epileptogenic etiologies, propagation, and termination of ictal behavior; besides the unpredictable episodic timing of ictal episodes.

**MODEL:**

The ictogenesis process involves two main checkpoint steps; the initiation of the burst, and the propagation of the bursting activity. The initiation step involves abrupt imbalance between excitation and inhibition within the neural environment leading to the acute transition of normal brain activity to ictal rhythm. The proposed model functionally categorizes the origin of such abrupt imbalance into three different levels of neuronal hyperexcitability with ictal discharge, with special emphasis on the second intermediate level; the chronic epilepsy. While also proposes that the propagation checkpoint depends on the initial conditions; wherein if a large-enough number of neurons burst synchronously, the propagation of a depolarization wave becomes mandatory.

The first level is seizures in otherwise healthy brain tissue, which result from the simultaneous mass-excitation of large numbers of neurons by external insult or stimuli. Electric stimulation during ECT and chemical stimulation, either during acute overdosing or sudden withdrawal of a drug, are valid examples. During ECT; electrodes deliver an electrical impulse which traverses through intermediary brain tissue to simultaneously stimulate neurons by altering their internal electrical milieu and concentration of ions (Swartz, 2014). Chemical stimuli may involve toxic exposure to domino acid, which activates excitatory GluK1 glutamate receptors (Jett, 2012), or by overdoses of theophylline, which blocks the inhibitory adenosine A1 receptor (Boison, 2011). Also; abrupt withdrawal of GABAergic-acting sedative–hypnotic drugs can cause seizure due to chronic GABA receptor downregulation as well as glutamate overactivity, which lead to neurotransmitter sensitization and neuronal hyperexcitability (Allison and Pratt, 2003). Accordingly and as a result of both electrical and chemical stimulation; a large focus of hyperexcitable neurons bursts synchronously bypassing the initiation checkpoint to induce a depolarization wave which effectively propagates to induce an ictal episode, or series of episodes in case of chemical insults.

The third level comprises severe epileptic encephalopathies, which result from severe genetic abnormalities that compromise important inhibitory pathways. Such mutations are most frequently associated with continuous altering of brain functions; wherein there are no normal epochs of brain activity, with subsequent frequent seizures (Allen et al., 2013; Veeramah et al., 2013). Said seizures are usually multiform and intractable and usually accompanied by relentless cognitive, behavioral and neurological deficits (Khan and Al Baradie, 2012).

The second intermediate level is chronic epilepsy, which is emphasized in this model as it is responsible for the vast majority of seizures in humans. Chronic epilepsy can be subdivided into spontaneous, and acquired due to an acute injury of the normal brain tissue as trauma, strokes and infections. Despite different pathological origin; both subdivisions leads to extemporaneous activity-dependent shifts in the balance between inhibition and excitation in one or more neural circuits to increase the probability of seizures break out. This model tracks the poorly-understood initiation, propagation and termination of the ictal episode in chronic epilepsy.

Within a normal neural circuit; the excitatory output of principal cells is usually put under control by the interneurons which mainly exert an inhibitory effect on the incoming inputs; wherein the triggering of an action potential is determined by summation of excitatory and inhibitory signals. A neural circuit can be analyzed according to its neuronal content, to determine the feedback, feedforward balance between the inhibitory and the excitatory neurons, to yield a block diagram as shown in Fig. 1, wherein ($I$) represents the input excitatory signal, ($H$) represents the input inhibitory signal from the interneurons, ($e$) is the summation effect and represents the actual input, ($P$) is the number of excitatory principal neurons receiving the input ($I$) within the neural circuit, ($B$) is the average number of inhibitory interneurons for each excitatory principal neuron within the ne...
Fig. 1. A block diagram describes the architecture of the normal neural circuit vs. the ictogenic circuit.

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The output of the circuit is:

\[ O = eP \]

and the actual input after summation is:

\[ e = I - H \]

then, the output of the circuit can be described as:

\[ O(1 + BP) = IP \]

so, the ratio between the output and the input is:

\[ \frac{O}{I} = \frac{P}{1 + BP} \]

This equation represents a negative feedback system, wherein the emergent output of the circuit is lesser than the input signal by the effect of \( B \), the average number of inhibitory interneurons for each excitatory principal neuron within the neural circuit). Herein and as a consequence of all or none law; the \( \frac{O}{I} \) ratio actually represents the firing probability of each excitatory principal neuron within the neural circuit in response to the input \( I \).

\[ \frac{O}{I} < 1 \]

Negative feedback is a widespread inhibitory tuning mechanism within neural circuits, but negative feedforward usually augments a robust control as it’s characterized by inhibition certainty and minimal time lag. The inhibitory interneurons within a neural circuit not only put the excitatory output of the principal neurons under check, but also assure desynchronous firing of said neurons by decreasing the firing probability of each excitatory principal neuron within the neural circuit in response to a certain input. The presence of feed inhibition guarantees that the firing probability, of an excitatory neuron in response to an input signal, is usually less than one.

An ictogenic focus is characterized by defective neuronal architecture which leads to priming of positive feedback excitatory pathways consequential to interlaced excitatory interneurons or sprouting of axonal collaterals. Said defective neuronal architecture can result from the faulty neuronal arrangement due to dysgenesis guided by genetic predispositions, or as an end result of the compensatory reconstruction that occurs after brain injury. The positive feedback excitatory pathways are triggered off in
an activity-dependent manner. When an episodic surge of the circuit activity reaches a critical value, the positive feedback excitatory pathways are fully activated. Then, the system enters a positive feedback loop wherein the excitatory impulses reverberate to self-reinforce further excitation.

The activity-dependent positive feedback loop is extremely unstable, as the value \((O_j)\) is usually equal or more than unity \((O_j \geq 1)\), and collapses spontaneously; wherein \((j)\) represents the average number of excitatory feedback interconnections for each excitatory principal neuron within the neural circuit. Yet, as a consequence of impulses reverberation and self-reinforced excitation; the interneuronal inhibitory network enters a state of impulses reverberation and self-reinforced excitation; neuron within the neural circuit. Yet, as a consequence of impulses reverberation and self-reinforced excitation; the interneuronal inhibitory network enters a state of stupor. When the inhibitory control is defunct \((H = 0)\), the output of the ictogenic circuit is released. So; for each excitatory principal cell within the ictogenic circuit \((P = 1)\), each input will result in a subsequent output \((I = O)\) forming a synchronous escape rhythm; wherein all the excitatory principal neurons receiving the input \((I)\) within the neural circuit will burst simultaneously upon receiving the input \((I)\). However; such self-reinforced signal magnification and the subsequent escape rhythm (ictal discharge) occurs only at the extremes of the circuit activity; wherein the probability of output release would depend on the probability of an exceptional level of a vigorous activity that reaches the critical value.

The bursting activity resulting from the escape rhythm can be confined due to the integral surrounding zone of inhibition, which cannot be overcome by the current level of ictal discharge, to produce a focal abnormality of the brain electrical activity; or can propagate to distort the electrical activity of the whole or a large portion of the brain. The bursting ictal discharge will not overcome the zone of inhibition as long as the number of excitatory principal neurons, receiving an input \((I)\) within an ictogenic neural circuit, is small \((P = \text{small})\) leading to failure of electrochemical recruitment via synaptic communication; and/or failure of chemical recruitment of the non-connected proximal neurons as \((r \ll \phi_r)\); wherein \((r)\) is the radius of the recruited focus, and \((\phi_r)\) is the minimum critical focal radius from which the chemical recruitment can begin and the trigger wave can get off.

The propagation of the paroxysmal depolarization shift, as a characteristic bursting activity, can occur via synaptic transmission to the susceptible connected neurons of other remote networks; wherein the repetitive discharge from the presynaptic ictogenic neuron leads to \(Ca^{++}\) accumulation in the presynaptic terminals enhancing neurotransmitters release. Besides; it can propagate to the non-connected adjacent neurons by altering the extracellular ionic concentrations to produce a trigger wave which gradually recruits the neurons in the proximity to initiate a bursting activity by augmenting their excitability.

The neuronal resting membrane potential \(V_{\text{resting}}\) is mainly maintained by the role of \(K^+\) and \(Na^+\) leak channels \((\text{Purves et al., 2001})\). Due to the high concentration level of \(Na^+\) ions in the extracellular fluid and diminished membrane permeability; the effect of changes of the ion concentration in the extraneuronal environment on the resting membrane potential, differs greatly between \(K^+\) and \(Na^+\) ions. Such effect can be represented by the following two equations:

\[
V_{\text{resting}} \propto -\frac{K^+ - K_{\text{out}}^+}{K_{\text{out}}^+}
\]

\[
V_{\text{resting}} \propto +\frac{Na^+_{\text{out}} - Na^+_{\text{in}}}{Na^+_{\text{out}}}
\]

Both equations show the two different effects of fluctuations in the extraneuronal concentration of \(K^+\) and \(Na^+\) ions on the resting membrane potential. Accordingly and regardless of the osmotic effect; while the electrochemical effect of hypo/hypernatremia is negligible; neuronal resting membrane potential is very sensitive to trivial fluctuation of extraneuronal potassium concentration. The bursting activity resulting from the escape rhythm leads to a transient increase in the extraneuronal \(K^+\) concentrations within the proximity of the neural network. Said \(K^+\) fluctuations increase the excitability of adjacent neurons due to depolarizing the resting membrane potential. An increase in the neuronal excitability sets the affected neurons into bursting activity, leading to the propagation of the PDS through the brain tissue. As a trigger wave, each affected neuron augments further propagation, so that the propagation of PDS doesn’t slow down or lose amplitude as it travels through the brain tissue. The rate of recruitment of neurons into the bursting activity, propagation of the trigger wave, can be represented by the following equation:

\[
\frac{d(N)}{dt} = \rho_n\left(\frac{d(V_{\text{out}})}{dt}\right)
\]

or

\[
\frac{d(N)}{dt} = 4\pi.\rho_n\left(\frac{r^2}{4}\frac{d(r)}{dr}\right)
\]

wherein

\[
r \geq \phi_r
\]

wherein \((N)\) is the number of recruited neurons in unit of time \((t)\), \((\rho_n)\) is the neuronal density per unit of volume \((V_{\text{out}})\), and \((r)\) is the radius of the recruited focus, or the radius of the propagating trigger wave. \((\phi_r)\) is the minimum critical focal radius from which the chemical recruitment can launch. The bursting activity of the ictogenic circuit ends abruptly when the inhibitory interneurons within the ictogenic focus become functionally effective to transform the stable escape rhythm into a normal, under-control output.
RESULTS:

Many results can be inferred from the proposed model, but hereinafter are some that elucidate various enigmatic features of chronic epilepsy. By presenting epilepsy as a disease caused by mal-architecture of the neural circuits within the brain tissue; the probability of formation of spontaneous ictogenic foci increases within the brain regions characterized by high-rate of continuous active modulation of tissue micro-structure. Additionally; the model probes into the genesis of the ictal activity in epileptic patients; wherein the initiation involves ignoring an activity-dependent unstable positive feedback excitatory loop which spontaneously collapses, yet leads to a synchronous escape rhythm forming a bursting activity.

The action potential generated by uninhibited ignition tends to have echoic reverberations; so that the resulting escape rhythm shows the characteristic multi-spiking paroxysmal depolarization shift as a hallmark of epilepsy on the cellular level. The ictal bursting activity can be either confined by an intact zone of inhibition, which can’t be overcome by the current level of ictal discharge ($P$ is small and/or $r \ll \phi_r$), to produce a focal abnormality of the brain electrical activity; or propagating to distort the electrical activity of the whole or a large portion of the brain. The propagation of the bursting discharge occurs either electrochemically via synaptic communication to remote susceptible circuits, or chemically via a trigger wave which recruit the non-connected proximal neurons. Termination occurs abruptly when the inhibitory interneurons functionally recover and reestablish their inhibitory effect on the ictogenic circuit to transform the escape rhythm into a normal, under-control output.

Two architectural factors contribute to the aggressiveness of an ictogenic focus; a major factor which is the average density, or average number, of the excitatory feedback pathways for each excitatory principal neuron within the neural circuit ($j$), and a minor factor which is the ratio between the neuronal density to the synaptic density ($\frac{\sigma_n}{\rho_s}$) within the ictal focus. Additionally; the velocity of the chemical neuronal recruitment via a trigger wave is proportional to the neuronal density of the affected brain region.

Moreover; the model shows that spontaneous epilepsy is a dynamic non-static chronic disease; wherein untreated recurrent attacks can lead to formation of neo-foci or exaggeration of the principle one via mal-architecting resulting of ectogenic excito-toxicity and subsequent faulty re-wiring driven by genetic predispositions. On the other hand; a rare possibility of long-term decomposition of an ictogenic focus, due to neural plasticity, can occur if consolidation with further ictal attacks is prevented. Besides; paradoxical therapeutic effect of combined anti-epileptic drugs, which enhance the GABAergic hyperpolarization, can occur, due to the higher probability of main input magnification, if the synaptic plasticity between the main presynaptic input and the postsynaptic membrane within the competition zone is anti-Hebbian.

DISCUSSION:

Several decades of experiments, which depend on pharmacologically-induced seizures, have established the idea that an imbalance between inhibitory and excitatory activity leads to ictal episodes (Scharfman, 2007). An acute imbalance between excitation and inhibition is thus a valid ictogenic mechanism. Problems arise when such mechanism is extended to cover the chronic process of epileptogenesis, which creates a persistent rise in the probability of spontaneous seizures (Staley, 2015). The timing of seizures in chronic epilepsy is unpredictable and ictal episodes are relatively rare, representing much less than 1% of the total brain activity (Moran et al., 2004). Thus; in chronic epilepsy, an ictogenic mechanism shall also explain the timing of episodic transitions from normal to ictal brain activity.

Additionally; another difficulty arises when applying the model of imbalanced inhibition and excitation to the etiology of chronic epilepsy, which does not usually suggest a chronic imbalance. In genetic predisposed epilepsy, analyses of the genetic etiology have occasionally found causal loss-of-functions mutations in inhibitory pathways (Macdonald and Kang, 2012), but loss-of-function mutations are also found in several excitatory pathways (Frank et al., 2006) (Carvill et al., 2014), and the majority of causal mutations involve genes that do not directly alter the balance of inhibition and excitation (Ran et al., 2014). In the acquired epilepsies, seizures start after an insult to a normal brain tissue as a result of stroke, trauma, or infection. Steady-state imbalances in excitation against inhibition, in established animal models of acquired epilepsy, are difficult to demonstrate. In the Pilocarpine model; a damage to the inhibitory neurons is compensated by an increase in GABAergic synaptogenesis before the onset of seizures (Zhang et al., 2009). Compensatory glutamatergic synaptogenesis also happens (Buckmaster, 2014), but steady-state network imbalances, between excitation and inhibition, are not evident in experimental and human epilepsy (Sutula and Dudek, 2007).

The current literature that proposes the activity-dependent disinhibition as a valid mechanism in chronic epilepsy, does not provide clues on why this mechanism emerges only in epileptic patients and how the vicious circle resulting of an activity-dependent disinhibition in over-active ictogenic network would end. The proposed model presents chronic epilepsy as a disease of faulty architecture of the micro-structure of the brain tissue;
wherein variable genetic or acquired predisposing factors drive abnormalities in the construction of multiple neural circuits resulting in an activity-dependent positive feedback excitatory loops which transform normal neural circuits into ictal foci. Such new mechanism for igniting an activity-dependent unstable excitation with subsequent relatively stable disinhibition leads to an ictal escape rhythm. Additionally; Said model provides insights about the mechanism of propagation and termination of such bursting activity. Besides; it illustrates both the end-result ictogenic mechanism arising from the wide variety of etiologies of human spontaneous and acquired epilepsy, and the timing of episodic transitions from normal activity to seizures.

**MOLECULAR MECHANISM OF IGNITION:**

Either genetic predispositions drives defective wiring in spontaneous epilepsy or after-insult dysgenesis in the acquired one; both lead to architectural flaws in one or more neural circuits transforming them into ictal foci: wherein positive feedback excitatory loops are formed via sprouting axonal collaterals and/or interlaced excitatory interneurons. Consequently; a competition zone is formed, which comprises presynaptic long-term potentiated main excitatory input synapse(s), presynaptic inhibitory synapse(s) (formed by feedback or feedforward inhibitory interneurons), presynaptic long-term depressed feedback excitatory synapse(s) (formed by positive feedback interneurons or axonal collaterals), and a postsynaptic membrane of a principle neuron. The competition zone is not an anatomical but a functional entity; wherein a dynamic contest among synaptic plasticities determine the polarization of the postsynaptic membrane and further generation of an action potential. Normally; when a main excitatory input comes into the competition zone, the activity of the inhibitory feedforward or feedback control dictates the probability of action potential generation and firing of the postsynaptic neuron, whereas the long-term depressed excitatory feedback plays a negligible role.

Spike-timing-dependent plasticity causes a difference in the homosynaptic plasticity between the presynaptic main excitatory input, which evolves a long-term potentiation, and the presynaptic excitatory feedback(s), which evolve long-term depression. Due to time lag; the presynaptic feedback excitatory synapse(s) are long-term depressed because they always fires immediately after the firing of the supplied postsynaptic principal neuron, hence this particular feedback excitatory stimulus is made weaker (Song et al. 2000) (Debanne et al. 1994). Additionally; the rise in the synaptic weight of the presynaptic main excitatory pathway dictates a reduction in the synaptic weight of the presynaptic feedback excitatory synapse(s) to keep the average synaptic weight approximately conserved (Lynch et al. 1977) (Chistiakova et al. 2014).

A strong input form the presynaptic main excitatory pathway can be cumulated via spatial or temporal summation to surpass a threshold that ignites an ictal activity. Upon receiving a robust input, the activity-dependent depressed positive feedbacks are fully activated, due to Ca++ rush, and the accumulated vesicles fuse into the presynaptic membrane to release an excessive amount of excitatory neurotransmitters into the competition zone. The positive feedback excitatory loops are unstable and collapse spontaneously; yet the excitatory neurotransmitters released into the competition zone render the presynaptic feedback or feedforward inhibitory synapse(s) functionally obtund. Additional molecular mechanism can also contribute to sudden inhibitory stupor within the competition zone; excessive unstable positive feedbacks that ignite the ictal behavior cause the inhibitory feedbacks, not the inhibitory feedforwards, to oscillate rapidly. Intensely activated, dendritic GABA_A receptors excite rather than inhibit the postsynaptic membrane (Staley et al. 1995) of the principal neuron(s) with the competition zone.

The molecular mechanism of GABA-mediated membrane depolarization involves differential anionic concentration shift during intense GABA_A receptor activation. The membrane potential is positive to the Cl^- reversal potential (Bormann et al. 1987), so that the Cl^- ions flux is inward and the intracellular Cl^- concentration increases, but the membrane potential is negative to the HCO_3^- reversal potential (Huguenard and Alger 1986), so that the intracellular HCO_3^- concentration decreases due to the efflux of HCO_3^- ions. The decrease in the intracellular HCO_3^- concentration, drives the diffusion of CO_2 across the dendritic membrane, allowing continual regeneration of intracellular HCO_3^- ions by carbonic anhydrase at a rate that exceeds the removal of intracellular Cl^- ions (Staley 1994). Accordingly; The electrochemical gradient for Cl^- collapses more significantly than does the HCO_3^- gradient, producing a shift in the GABA_A reversal potential toward the HCO_3^- reversal potential that is sufficient to explain the depolarizing response.

Due to the functional stupor of the inhibitory pathways; the presynaptic main excitatory input is released to simultaneously activate the postsynaptic principle neurons forming an escape rhythm. The action potential generated by uninhibited ignition tends to have echoic reverberations along the neuronal membrane. NMDA receptors are very sensitive to changes in the membrane potential; wherein extracellular Mg^{++} and Zn^{++} ions bind to specific sites on the receptor, blocking the passage of other cations through the ion channel. Reverberating depolarization of the neuronal membrane, mainly the somatic and dendritic membrane, dislodges and repels the Mg^{++} and Zn^{++} ions from the pore, thus allowing a voltage-dependent flow of Ca^{++} and Na^{+} ions into the cell and K^+ out of the cell (Cull-Candy et al. 1990).
MOLECULAR MECHANISM OF PROPAGATION AND TERMINATION:

If the number of principal neurons of an ictogenic focus is not large enough to overcome the zone of inhibition exerted onto their axon terminals, the bursting activity would not be electrochemically transmitted via synaptic communication to the connected remote brain loci. Additionally; the synchronous activity of said small number of neurons would not significantly disturb the extraneuronal ionic environment, thus a trigger wave would not be created leading to failure of recruitment of adjacent non-connected neurons of nearby loci. However; when the number of principal neurons of an ictogenic focus is large enough, the bursting activity makes its way through the confinement and tends to propagate. Said large number of neurons will likely overcome the zone of inhibition and transmit the ictal activity via synaptic communication to the connected remote loci.

Besides; synchronous activity of a large number of principal neurons within an ictal focus can potentially disturb the extraneuronal ionic environment, generating a trigger wave which recruits adjacent non-connected neurons of the nearby neural networks. Ictal activity, of a large number of neurons within an ictogenic focus, induces regional elevation of extracellular $K^+$ ions due to persistent efflux. As mentioned before; neuronal resting membrane potential is very sensitive to changes in extracellular $K^+$ concentration. Regional rise in the levels of extracellular $K^+$ ions reduces the magnitude of potassium gradient across the cell membrane of the adjacent neurons; and therefore, shifts the absolute value of the resting membrane potential to depolarization. The adjacent neurons become hyperexcitable and respond by producing an ictal activity. The process of recruitment is self-reinforced generating a trigger wave that promulgates spatially with a defined speed. Active synaptic clearance brings about rebalance among the opposed neurotransmitters within the competition zone, so that the inhibitory control reimposes its effect and decrease the probability of firing of the principle neurons within the ictal circuit demolishing the synchronous escape rhythm; consequently the ictal episode is terminated. Reactive inhibitory reposition contributes to the altered state of consciousness after an epileptic seizure.

EFFECT OF ANTIEPILEPTICS ON THE COMPETITION ZONE:

The competition zone is a functional, not an anatomical, entity; wherein the mechanism of action of antiepileptics can be applied to. This subsection discusses the effects of antiepileptics on the competition zone because of the paradox that results from a molecular mechanism that is believed to contribute to the functional stupor of the inhibitory synapse(s), which results from the excessive unstable positive feedbacks that ignite an ictal behavior. The mechanism implicates that an intensely activated, dendritic $GABA_A$ receptors excite rather than inhibit the postsynaptic membrane (Staley et al., 1995).

Accordingly; drugs that enhance the effect of the neurotransmitter GABA at the $GABA_A$ receptors, as benzodiazepines, can effectively prevent seizures as they prevent the main input summation, so they prevent the ignition of the activity-dependent positive feedback excitatory loops in the first place. But; if the main input bypasses such inhibitory effect and ignites the unstable positive feedbacks, the overstimulated $GABA_A$ receptor, by the drug, would enhance the excitation of the postsynaptic membrane of the principal neuron(s) and functionally contribute, and further prolong, the presynaptic inhibitory stupor.

Consequently: drugs that enhance the effect of the neurotransmitter GABA at the $GABA_A$ receptors, as benzodiazepines and the like, exacerbate epileptic seizures that develop during using them as a preventive anticonvulsant. Whilst paradoxically; such medications are more effective if they are used to terminate an active attack as they boost the effect of inhibitory synapse(s) on the stable escape rhythm; which results after spontaneous collapse of the unstable excitatory positive feedbacks. Besides, they inhibit the electrochemical propagation of the ictal activity by consolidating the integrity of the inhibitory zone on the synaptic terminals of the ictogenic principal neurons of the primary ictal focus.

CONCLUSION:

In short; chronic epilepsy is a disease of mal-architecture of the neural circuits that results from genetically-predisposed, defective wiring in the spontaneous type; or neural dysgenesis in the acquired type. Said mal-architecture leads to formation of activity-dependent excitatory positive feedbacks that can ignite an ictal activity in response to robust stimulation. Such ictal activity tends to propagate electrochemically via synaptic communication to the connected distant loci, and chemically via a trigger wave to the adjacent non-connected loci. The ictal activity is terminated upon reimplantation of the functionally obtunded inhibitory control over the competition zone within the primary icetal focus.
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