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Ionic Imbalance

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1. Introduction

Seizures are accompanied by significant alterations in both intra- and extracellular ion concentrations (Hotson, 1973; Kager et al., 2000). These concentration gradients, in concert with the conductances of a variety of ion channels, determine the resting membrane potential, the degree of membrane excitability, and the strength of excitatory and inhibitory synaptic responses. Changes in these concentration gradients have profound effects on the signaling and excitability of cells and can therefore play an important role in seizure generation, maintenance and cessation (Kager et al., 2000).

In this chapter, we describe the network of pumps, channels, and exchangers that make up the ionic regulatory system (IRS). This system runs in a nearly steady state while the neuron is at rest and responds to increased neuronal signaling by reestablishing normal ion distributions. We give a brief description of the basic elements of the IRS and their role in ionic maintenance. The IRS has the ability to redistribute intra- and extracellular ions rapidly, but this system can be overwhelmed by excessive activity, allowing ion concentration to drift towards equilibrium permitting their effects to dominate neuronal dynamics. (Ullah et al., 2009; Ransom et al., 2004) In addition to excessive neuronal firing, the IRS can be compromised through a broad range of alterations to its constituent mechanisms. We give a broad overview of how malfunctions in critical elements of the IRS may influence seizure onset or duration and identify several motifs that may play a role in a wide range of seizure disorders.

We will present a brief review of the known etiologies for a small number of seizure disorders. We discuss the ways in which idiopathic causes of epilepsy such as channelopathies, as well as symptomatic origins such as structural malformations and scarring, interact with the IRS to modulate or even generate seizure activity. In the second part of this section we outline the role of the IRS in experimental seizure models, both acute and chronic. We conclude this section by evaluating experimental seizure models and mathematical models based on the mechanisms that comprise the IRS.

In the final section we discuss the action of common anti epileptic drugs and note whenever possible their proposed mechanism in seizure prevention or cessation. We discuss direct and indirect interactions of these drugs upon the IRS and evaluate potential consequences of these interactions.

2. The ionic regulatory system

2.1 Components of the ionic regulatory system

The neuron at rest is subject to continuous leakage of ions across the plasma membrane. It therefore requires a steady flow of energy to maintain ionic concentrations necessary for normal neuronal firing. Ions leak down their electrochemical gradients via a combination of diffusion through the membrane as well as channels whose conductances are relatively insensitive to voltage but highly selective to ionic species. These leak currents determine the resting membrane potential and serve to reestablish the resting membrane potential after perturbations, wiping out the effects of inputs received by the neuron in the distant past. It may even be said that leak currents allow the neuron to “forget” remote inputs. The conductance through other channels depends upon factors such as transmembrane potential, ionic concentrations, chemical ligands, and more sophisticated cellular processes. These channels are involved in neurotransmitter signaling and action potential generation. The electrical state of the neuron is determined by the flow of ions across the plasma membrane. The passage of ions through these channels is due to a competition between their charge flow down the electrical gradient and chemical flow down their concentration gradient. The potential at which these mechanisms are balanced is described by the logarithm of the ionic concentrations for a given ion outside and inside the cell and is known as the Nernst potential.

$$V = 26.6 \ln [C_o / C_i] \quad (1)$$

The further the actual membrane potential is from this Nernst potential, the greater the electrochemical gradient for that species of ion. The amount of charge that flows down this gradient can be approximated by Ohm's law, where resistance equals one over the membrane conductivity, σ , for the cell and the voltage is the difference between the membrane potential and the reversal potential for the ion. In reality, the conductivity is dependent on the ionic concentrations and is better modeled using the Goldman-Hodgkin-Katz equation. The approach we outline is a good approximation to the GHK analysis and is far more transparent.

$$I_i = \sigma_i (V_m - V_i) \quad (2)$$

At rest, the electric current produced by the leak of sodium, potassium, and chloride are balanced, and the resting potential, aside from osmotic effects and immobile ions, is determined by a conductance-weighted average of their reversal potentials. The net current through the ion channels is described as:

$$I = \sigma (V_m - V_{rev}) = \sum_i \sigma_i (V_m - V_i) \quad (3)$$

We can therefore express the total reversal as:

$$V_{rev} = \frac{\sum_i \sigma_i V_i}{\sum_i \sigma_i} \quad (4)$$

Similarly, the reversal potential for channels that are permeable to multiple ions, such as the NMDA, AMPA, and GABA channels, is roughly a conductance-weighted average of the reversal potentials for the permeable ions. In any case the flow of ions through a pore is proportional to the difference between the membrane potential and the reversal potential for the ion. This difference is the electrochemical gradient experienced by these ions.

Individual ions are not regulated independently, but rather the pumps, channels, and cotransporters providing steady state concentration gradients often exchange precise ratios of different ionic species therefore connecting their individual dynamics. Therefore, the IRS forms a driven-coupled-dynamic system that can display complex behaviors when forced from normal steady state conditions (Cressman, 2009). These emergent behaviors may play a role in seizure dynamics.

Ultimately the driving force behind all ionic gradients is a set of ATPases embedded in the cellular membrane that use the energy stored in ATP to move chemical species and charges against their electrochemical gradients. There are numerous electrogenic exchangers in the human brain, but a few of these play a disproportionately large role in establishing ionic gradients. The primary source of electrochemical gradients across the plasma membrane of neurons is the 3/2 sodium potassium ATPase. This pump extrudes three sodium ions into the extracellular space in exchange for the uptake of two potassium ions into the intracellular space, moving both elements up their chemical gradient as well as +e charge up the electrical gradient. The rate of exchange increases with increasing intracellular sodium and extracellular potassium concentrations, providing a mechanism that compensates for increased ionic drain produced by electrical signaling (Lennie, 2003; Attwell, 2001). It is also responsive to the membrane potential, magnesium concentration, and ATP availability. Pumping rates and ATP production are limited by glucose, oxygen and mitochondrial function, therefore there are multiple constraints upon the compensatory action of the pump.

Gradients are further tuned by the action of electroneutral cotransporters that move ions up their concentration gradient at the expense of a second, electrochemically favorable ionic gradient. For instance, chloride gradients are largely established through the cotransport of potassium and chloride ions through the KCl cotransporters (Payne, 1997; Stein, 2003). The action of this cotransporter allows potassium to exit the cell down its electrochemical gradient while forcing chloride up its electrochemical gradient. Therefore the steady state chloride gradients are directly influenced by the potassium gradients establishing more linkage between ion species.

The neuronal environment is also highly regulated by the activity of glial cells surrounding the neurons. Glial cells help maintain a normal neuronal environment through a range of actions, including reuptake of extracellular glutamate and buffering of extracellular potassium concentrations. Astrocytes possess a high density of inward rectifying potassium channels (Kir). The phenomenon of rectification is produced by polyamines or magnesium ions that block the channel at positive potentials, preventing potassium from flowing down its electrochemical gradient into the extracellular space. As potassium is dumped into the extracellular space, its reversal potential increases towards zero and becomes greater than that of the glial membrane potential, thus leading to an inward flow of potassium (Butt, 2006). Once siphoned into the glial cell, potassium diffuses through the network of glial cells via gap junctions that allow networks of glia to form extensive functional groups. These glial networks can move potassium from areas of high to low extracellular potassium concentration. They may also serve to move ions into the vasculature by interacting with

specialized endothelial cells of the blood brain barrier (BBB). This buffering may mitigate the local excitatory effects of increased extracellular potassium, but it may also facilitate the spread of potassium over relatively large spatial networks (Somjen, 2004).

In addition to glial buffering, simple ionic diffusion and osmosis will blur ionic gradients in the extracellular space. On the scales of the extracellular space the diffusion constant for water can be assumed constant, however the effective diffusion is limited by the path the ions can take. This effect, or tortuosity, can be greatly influenced by the geometry of the extracellular space. Increased extracellular potassium concentrations leads to potassium uptake by glial cells and the subsequent absorption of water through osmotic action. This influx of water leads to cell swelling that in turn can cause the extracellular space to become more confined resulting in an increased tortuosity (Somjen, 2004; Sykova, 2005).

Finally, the brain needs a continual supply of energy, oxygen, and other building blocks as well as the removal of carbon dioxide and other waste. As in the rest of the body this role is provided by the vasculature, however endothelial cells of the central nervous system and gonads are far less permeable than the in the rest of the body. This increased regulation is provided by the BBB and the cerebral spinal fluid barrier (CSFB). Endothelial cells with tight junctions line the capillaries in grey matter to make the BBB, and similar cells line the blood vessels of the choroids plexus and pial and arachnoid spaces as well as the outer layer of cells of the arachnoid (Somjen, 2004; Zheng et al. 2005). These cells actively move ions, amino acids, glucose and more in and out of the vasculature and allow the passive diffusion of oxygen and carbon dioxide. The endothelial cells of the BBB and their tight junctions are influenced by the endfeet processes of the glial syncytium, interactions that are believed to play an important role in the glial buffering of potassium, as discussed above.

One should not think of the IRS as exerting strict control over ionic composition; rather this set of mechanisms supports certain fixed states towards which the system will evolve. However this system can potentially support multiple fixed points, and limit cycles as well as a range of long lived transient states. This lack of strict control could be viewed as a shortcoming of neuronal systems, but in reality it affords them a great degree of dynamics that can be used for changing neuronal function. For instance, calcium entering the buton after the arrival of an action potential is not immediately expelled, and this makes subsequent action potentials more effective at producing vesicle release (Eccles, 1941, Feng, 1941). This common mechanism of synaptic potentiation is utilized by some cells and has been proposed as the basis for information encoding. Other transient neuronal states, such as cortical up-states, may also make use of transient deviations from ionic balance(Lennie, 2003; Haider, 2006; Ullah et al., 2009).

2.2 Breakdowns of the IRS

Seizure disorders may be caused by a number of distinct etiologies. Causes are generally classified either as idiopathic, that is, of unknown but likely genetic origin, or symptomatic, that is, due to a lesion or structural malformation (Shimizu-Okabe et al., 2007). A number of genetic abnormalities have been identified as causing idiopathic epilepsy disorders, and for many of these abnormal protein structure and function have been identified. The genetic culprits tend to encode ion channels and receptors for neurotransmitters (Lu & Wang, 2009). For epilepsy due to structural changes or defects, the cause of the seizure is due to malformations or scarring that cause far less subtle changes in neuronal function. We will proceed by revisiting the main components of the IRS, discuss which components would

make the system vulnerable, and present examples of epilepsies that are influenced by these breakdowns. We will finish this section by discussing experimental and computational models of epileptic seizures and discuss how these are predicated on disruptions to the IRS. We will begin by describing some general effects of disturbances to the ionic environment on seizure generation and propagation. We will refer back to these motifs in each subsequent section. They are segregated into discussions of resting membrane potential, excitability and refractory periods, edema, acidosis, and synaptic release and response.

2.2.1 Resting potential

The magnitude of the resting membrane potential is approximated as the weighted average of the reversal potentials for the ions conducted at rest as described in the previous section. Reversal potentials decrease in magnitude with decreasing concentration gradients, and so decreases in potassium and/or chloride gradients will result in an upward shift of the resting membrane potential and can lead to increased excitability and spontaneous spike generation. On the other hand, decreases in sodium gradients have the reverse effect, making the cell less excitable. The membrane potential is more sensitive to absolute changes in potassium concentrations than absolute sodium concentrations, since potassium is more conductive than sodium. Therefore potassium is the most important ion for establishing the resting membrane potential (Kager et al., 2000).

The potassium reversal potential is also more sensitive to changes in potassium concentrations than are reversal potentials for sodium and chloride. Since reversal potentials depend on the ratio of the extra- and intracellular concentrations an absolute change to the smaller of the two concentration has a greater effect on the reversal potential than would the same change in the larger concentration. Ionic flow across the membrane also produces a larger concentration change in the exterior than in the substantially larger interior space. Since potassium concentrations are lowest in the extracellular space and sodium and chloride concentrations are lowest in the interior, the external potassium concentration is most easily altered. The physiological concentration of potassium (4mM) is low as compared to sodium (18mM) and chloride (6mM), making it more susceptible to large percent changes in concentration and therefore large changes in the its reversal potential.

2.2.2 Excitability and refractory periods

Neuronal excitability is a function of both the resting membrane potential as well as the threshold for firing. This threshold is determined by the voltage gated response of sodium channels as well as the electrochemical gradient for sodium. If sodium gradients are diminished they will cause the threshold to rise to higher voltages making the cell less excitable, providing some amount of negative feedback on continual firing. This mechanism is widely accepted as the means by which some bursting neurons intermittently cease their activity (Catterall, 2000; Hodgkin & Huxley, 1952).

After spike initiation, sodium influx, and depolarization, voltage gaited potassium channels open and release potassium from the cell, thus repolarizing the membrane. The rate of this repolarization is determined by the electrochemical potassium gradients and potassium conductance. If either of these mechanisms are impaired the duration of the depolarization is lengthened, resulting in increasing transmitter release. The magnitude of the hyperpolarization can also become diminished and cause a reduced or eliminated relative

refractory period. On the other hand, in neurons with inactivating sodium channels, the loss of hyperpolarization may lead to a prolonged absolute refractory period and therefore reduced potential for fast action potential generation (Catterall, 2000).

2.2.3 Synaptic release and response

Synaptic release is initiated when an action potential enters a buton and depolarizes its membrane. This depolarization activates voltage-gated calcium channels and allows calcium to enter the buton, producing a fusion of vesicles with the plasma membrane and the release of transmitter into the synaptic cleft. The amount of calcium entering the buton depends on the duration of depolarization by the action potential as well as the electrochemical drive forcing calcium into the cell. Therefore low extracellular levels of calcium work to inhibit synaptic release.

As stated in the previous section the reversal potentials for all mixed ion channels are approximated by the weighted average of the ions they conduct. This treatment can be applied to any ion channel. Here we will discuss the effects on the AMPA and GABA_A receptors. The AMPA channel is in general excitatory, and it conducts calcium, potassium, and sodium. Decreased potassium gradients will make these channels more excitatory while decreased calcium and sodium gradients will lead to decreased excitation (Kager et al., 2000).

The GABA_A receptor is permeable to both chloride and bicarbonate. The reversal is generally very low due to the chloride reversal potential. Maintenance of the chloride gradient is essential to produce strong inhibitory responses. If the breakdown in this gradient is significant, chloride can flow out of the cell upon receptor activation leading to excitation. As mentioned above the chloride gradient is intimately linked to the potassium gradients. Therefore, losses in potassium gradients are once more implicated in making neural networks more excitable.

2.2.4 Edema

Ionic imbalances can lead to transient osmotic gradients between neurons and glia and the extracellular space. These gradients are diminished by the flow of water towards regions of high concentration. When concentrations are higher in cells, as is the case during metabolic malfunction, or when glia absorb extracellular potassium, water movement into the tissue results in edema. This swelling can have detrimental effects on further potassium clearance through diffusion (Somjen 2004; Ragaišis, 2002; Park et al., 2008).

2.2.5 Acidosis and alkalosis

Acidosis (a lower than normal pH) and alkalosis (a greater than normal pH) can affect neuronal excitability. In general, acidosis lowers excitability, and alkalosis increases excitability. This is because H⁺ ions directly modulate ion channels, both voltage gated and ligand gated.

H⁺ ions inhibit all voltage gated ion channels, but not equally. If all channels were equally inhibited, there would be no impact on excitability, because inward currents would still balance outward currents. However, calcium channels (the most inhibited) and sodium channels are inhibited much more strongly than potassium channels. In fact, in pH ranges that are consistent with life, potassium is relatively unaffected by H⁺ ions. This means that

an increased concentration of H^+ ions (acidosis) inhibits inward currents (such as Na^+ and Ca^{2+}) while leaving outward currents unaffected. The overall net result is more outward current relative to inward current, and a hyperpolarized neuron. This is consistent with lower excitability. On the other hand, an absence of H^+ ions (alkalosis) would boost inward currents, and somewhat depolarize the cell, leading to excitability. In addition, at the synapse, an increased flow of inward Ca^{2+} results in an increased release of neurotransmitters, which also helps explain why alkalosis causes excitability (Somjen, 2004). H^+ ions also impact ligand-gated ion channels. Glutamate modulated ion channels are depressed by H^+ , resulting in inhibition. In contrast, GABA modulated ion channels are enhanced by H^+ , also resulting in inhibition (Somjen, 2004).

3. Epilepsies

3.1 Idiopathic

Out of the vast array of proteins expressed in the brain, only a small number are responsible for epilepsies. The complexity of the brain and its behavior may lead one to expect a greater variety of disorders. However, insensitivity to most parameters, redundancy, and the fact that phenotypes can only survive as long as their seizures remain transient, all limit the range of genetic variation that can lead to seizure disorders.

Familial hemiplegic migraines are associated with mutations in the genes encoding sodium/potassium ATPase and in rare cases patients exhibit epileptic seizures (Ashmore et al., 2009; Gallanti et al, 2008). With decreased pumping, normal neuronal activity results in the general loss of all ionic gradients. Complete loss of gradients will however more likely lead to spreading depression and perhaps migraine rather than seizures. In order to produce sustained seizure activity the pumps must remain at least partially functional.

In a similar fashion, without glucose, oxygen, and an intact metabolic system to produce ATP, sodium/potassium pumps are incapable of maintaining the resting potential and cells quickly depolarize once they drift above threshold and begin firing action potentials. If ATP is not produced in a relatively short time, loss of mitochondrial gradients as well as elevated calcium concentrations will initiate apoptotic pathways. There is then the potential for the creation of lesions whose spatial extent depends on the scale, duration, and severity of the metabolic deprivation.

Even though there are a large number of ion channels, only a small number have been found to be directly responsible for epileptic syndromes. Generalized epilepsy with febrile seizures plus (GEFS+) encompasses a number of disorders including severe myoclonic epilepsy of infancy (SMEI), border-line SMEI (SMEB), and intractable epilepsy of childhood (IEC) (Kapur 2002; Lossin et al. 2002). In total, there are four types of GEFS+, each defined by its causative mutation (Lossin et al., 2002). Three types of GEFS+ include mutations to either the alpha or beta subunit of the $Nav1.1$ or $Nav 2.1$ sodium channels (Fujiwara-Tsukamoto et al., 2004; Rosenberg et al., 1997). There are a number of different direct effects on sodium channel conductance, including changes in inactivation and frequency-dependent rundown. The loss of inactivation removes a strong governing effect on neuronal firing, increasing afferent signaling as well as ionic accumulation around the effective cells. The former obviously leads to greater excitation, but would also lead to greater inhibitory output. Ionic accumulation not only increases due to the increased activity, but also because the loss of inactivation allows higher sodium currents to keep the cell from repolarizing. This windowing effect will be discussed in greater detail below.

Epilepsies can arise from dysfunction to the inhibitory mechanisms. Mutations to GABA_A receptors are implicated in GFES+ type 3. In neuronal networks with these mutations, inhibitory currents are one-tenth of their normal strength. The direct loss of inhibition should be weakly compensated for by the reduction of potassium flowing out of the KCl cotransporters, as decreased potassium flow should reduce the potassium accumulation outlined above. This effect is most likely insignificant in comparison to the loss of inhibition and potential for uncontrolled excitatory discharge.

As previously mentioned, cotransporters are important for establishing chloride gradients. Unlike sodium, calcium, and potassium, chloride has no other means to produce a gradient than by utilizing cotransporters. There is evidence that reexpression of juvenile sodium-potassium-chloride cotransporters occurs after trauma (Shimizu-Okabe et al., 2007; Payne, 1997), and upregulation of the gene for the sodium-potassium-chloride cotransporter has been demonstrated in epileptic tissue (Shimizu-Okabe et al., 2007). In the adult form these cotransporters moves both potassium and chloride out of the cell functionally increasing the strength of post synaptic inhibitory currents. The juvenile form moves potassium sodium, and chloride into the cell. This juvenile form diminishes the strength of GABA and its reversal potential can even lie above the resting potential resulting in GABAergic excitation. On the other hand decreasing the potassium and sodium reversal potentials causes a relative inhibitory effect on the neurons.

It is interesting to note that there is no significant evidence that mutations to potassium channels leads to seizures disorders. It is easy to imagine that any source of significant change in potassium conductances would have a severe effect on both the resting potential, excitability, and synaptic strength. Perhaps it is because of this sensitivity that phenotypes with potassium channel dysfunction are not viable.

3.2 Symptomatic

Symptomatic epilepsies are caused by lesions, malformations, and tumors. Although these seizures are due to identifiable structures, the specific cellular alterations and therefore etiologies are quite different. These alterations can include structural and functional changes due to direct mechanical insult or genetic regulation due to more complex processes such as immunological responses.

Brain lesions can either be highly localized as in the case of traumatic injury or ischemia, spread across elements of extensive neuronal circuits like the limbic system, or present diffusely as in a systemic metabolic crisis. The tissue within and surrounding a lesion is different from normal brain. In certain severe lesions complete neuronal death occurs, leaving microglia and astrocytes to occupy the interior of the lesion. In other cases a reduced number of neurons remain within the lesion. In these cases, the behavior and morphology of these neurons can change. In the next section we will discuss experimental models aimed at investigate these post trauma alterations. They suggest that seizures may more easily arise and persist due to reduced potassium buffering by glial cells affected by the trauma, perforation of the BBB, and subsequent immune response.

Tumors, malignant and benign, can induce epileptic seizures. In many cases, these seizures appear to originate from the borders of the tumor (de Groot et al., 2010) and may not even present until the tumor is removed. In other cases the cells within the tumor are functionally active and may play a role in seizure generation themselves (de Groot et al., 2010). There are numerous types of tumors that can result in epileptogenesis. Some gliomas expand into the

surrounding parenchyma by releasing large quantities of glutamate. This glutamate excites local neurons, depolarizes them, inducing high levels of activity that eventually leads to neuronal death. As the neurons die off the cancer can expand into the vacated space. Prior to cell death the excessive excitation, in tandem with other modifications to the tissue can lead to seizure generation.

Seizures caused by malformations, such as cortical dysplasia, are associated with the presence of abnormal cells in the region of the malformation. The effects of these morphological and structural abnormalities on seizure generation is not well understood. However as has been discussed above in the context of edema, relatively large cellular volume can lead to reduced potassium buffering by the glial network. Similarly, structural changes associated with other diseases such as Sturge Weber syndrome can cause seizures. In this case vasculature malformations exerts stresses on the local neuronal and glial tissue.

As is often the case, it is straightforward to identify qualitative mechanisms whose actions could lead to epileptic behavior. However we are often presented with opposing mechanisms whose combined effects cannot be easily ascertained. As these systems are complex it is often impossible to analytically determine which effects will dominate and further investigation via computational modeling or experiments are necessary.

4. Models

As already mentioned, the IRS and neuronal dynamics in general can produce complicated dynamics. Therefore altered function of a specific mechanism cannot always be extrapolated to overall behavior. To this end it is often necessary to perform experiments or computational simulations.

4.1 Experimental models

4.1.1 In vivo

Most experiments aimed at understanding the electrophysiology of epilepsy are performed in rodent models. Most in vivo models involve producing damaged, or lesioned, neuronal circuits. Whether it be through electrical, chemical, or mechanical insult the resulting brain will show significant and stereotypical damage to susceptible regions and cell types. As in human epilepsy, the development of chronic seizures in these animal models is not immediate. Epileptogenesis is due to changes to the neuronal circuits that involve apoptotic and necrotic cell death, astrocyte and microglia migrations, and complex alterations to neuronal and astrocytic function. A complicated set of observable changes is well documented in the literature and we will only discuss a small number of them here.

It has recently been proposed that epileptogenesis occurs at least in part due to a breakdown in the BBB trauma, infection, or ischemia (Friedman et al., 2009). Animal models demonstrate that neuronal tissue undergoes a set of stereotyped alterations in response to albumin entering the extracellular space through the breached BBB. First, there is a reduction in the expression of Kir4.1 channels in glial endfeet. These channels as discussed above are one of the essential features of glia that allow them to buffer potassium from the extracellular space. Secondly, there is a reduction in the expression of gap junctions in glial cells. These gap junctions link together glial cells forming a syncytium that facilitates potassium buffering as discussed previously. As with a reduction in Kir channels the impaired syncytium limits the ability of the glia to remove potassium from the extracellular

space. Experiments on genetically modified animals confirm that these effects facilitate the generation of seizures (Binder & Steinhäuser, 2006; Djukic et al., 2007; Wallraff et al., 2006). Dysfunctional glutamate metabolism in glial cells is also implicated in epileptogenesis following trauma. As discussed above one of the primary functions of glial cells is to recycle glutamate. In addition glial cells can also release glutamate on their own and may play a more central role in seizure generation than previously thought (Tian et al., 2005). Of course tonic, or large releases of glutamate will lead to increased activity and therefore strain the IRS. Finally, transformed astrocytes release more inflammatory mediators than normal glia. The release of inflammatory mediators has been implicated in epileptogenesis (Hinterkeuser et al., 2000).

All in all these modifications to the glial tissue result in a compromised potassium buffering system, with the potential for greater excitation through poorly regulated glutamate trafficking and increased inflammatory interference.

4.1.2 In vitro

There is a large array of experimental models for seizures, that are in large part based on what is observed in epileptic seizures. Most experiments are carried out in brain slice preparations, usually dissected from rats or mice. Experimental models are designed to subject the neuronal tissue to conditions with combinations of ionic imbalance, excess excitation, reduced inhibition, or hyperactivity. For brevity, we will only discuss a few of these models and the role ionic imbalance plays in the behaviors seen.

Several seizure models are based on asserting ionic imbalances. Increasing extracellular potassium leads to the effects outlined above and is in almost all ways excitatory (Jensen & Yaari, 1997). Substantial increases in potassium can directly lead to seizure-like activity, and slightly elevated potassium is often used to promote activity in other models. Seizures can also be induced by reducing the extracellular calcium concentrations (Bikson et al., 2003). Both of these models are expected to exhibit reduced synaptic transmission, suggesting that these seizures are largely mediated by concentration dynamics.

Seizures are generally thought to be at least partially due to an imbalance between excitatory mechanisms and inhibitory mechanisms. A number of models attempt to produce these conditions by pharmacologically reducing inhibition with such agents as bicuculine or picrotoxin, or increasing excitatory mechanisms with agents such as carbachol. Not surprisingly these models produce uncontrolled excitatory output and seizure like events. Though the primary reason for these uncontrolled events is a tilting towards excitation, the dynamics of the seizures are undoubtedly influenced by the ionic imbalances produced by the hyperactivity.

There is some debate as to what degree inhibitory mechanisms are compromised in epileptic tissue. Some experimental models, such as 4-aminopyridine, are based on the assumption that it is not inherent loss of inhibition that leads to seizures but temporary loss due to the interactions between the networks of cells (Ziburkus et al., 2006). There it was demonstrated that prolonged seizure-like events can occur with intact inhibition. Excitatory output did not peak due to lack of activity in the interneuron network, but rather was accompanied by the interneurons being forced into a depolarized state through excess activity. This state, known as depolarization block, sets a threshold on cellular, especially inhibitory, output. Depolarization block, as will be discussed in the next section is influenced by, or even caused by, ionic imbalance. In addition to influencing the membrane potential, ionic imbalance will also shift the reversal potentials for synaptic transmission. Understanding

these effects may greatly enhance our understanding of the balance between excitation and inhibition during pathological states.

4.2 Mathematical models

Computational models are an efficient and relatively transparent method to investigate neuronal dynamics. For the sake of simplicity most computational models of neurons do not incorporate changes to ionic concentrations, even though one could argue that even small changes in the ionic distributions can influence network activity, and may in fact be used by the healthy brain to prime or suppress the responsiveness of the network (Frohlich et al., 2010). Either way there is no question that one must include concentration dynamics in order to understand the dynamics of seizures. This has been done on several different levels of complexity, from modeling individual neurons to networks of neurons (Somjen, 2004; Bazhenov et al., 2004; Cressman, 2009; Barreto & Cressman, 2011). Models are always approximations to physical systems, therefore results and predictions must be interpreted within the narrow scope of the models focus.

Although it is often possible to ascertain the general mechanisms involved in an epileptic disorder, the non-linearity of these mechanisms as well as coupling between different mechanisms often rules out a simple linear analysis. In these cases it is most often necessary to mathematically formulate these mechanisms and computationally evolve their dynamics in order to determine their effects.

4.2.1 Single cell models

Single cell models can either be optimized for the most transparent analysis, or be extremely complex in order to understand the detailed interactions of pumps, channels and transporters. Both of these approaches give their own insights into seizure dynamics.

The most detailed neuronal models include multiple compartments for the soma, dendrite, extracellular space, and glia (Kager et al., 2007). These models include numerous ionic channels, pumps, and cotransporters for potassium, sodium, chloride, and calcium, inserted at different densities for different compartments. This sophisticated model allows a detailed inspection of the mechanisms responsible for sustained after discharges.

One of the main results of (Kager et al., 2007) relates to the inactivation of sodium channels. They showed a strong relationship between seizure susceptibility and the permeability of the persistent sodium current. In their model, prolonged self sustained after discharges are maintained by a nearly balanced outward flow of potassium and inward flow of sodium. If sodium channels inactivate, this balance cannot be maintained and potassium flow will outstrip the sodium, and repolarize the cell. However with persistent sodium currents or incomplete inactivation of transient sodium this near balance can sustain long-term depolarized states. This incomplete inactivation is called windowing, due to the overlap between activation and inactivation curves for the transient sodium channels. Seizures finally subside as pump rates increase and currents decrease as ions approach equilibrium. They also show that the ionic imbalance produced leads to sustained depolarization and if severe enough, depolarization block.

On the other hand extremely simple models of single neurons have been employed to investigate the slow modulating effects of ionic changes with less attention paid to the individual currents responsible for the membrane potential and concentrations (Cressman et

al., 2009). In this study the authors investigated how seizures can arise from alterations to the IRS. The model was designed to replicate high potassium in vitro experiments described above. As the bath concentration in the model is increased to values used to produce seizures in experiments this model supports stable oscillatory behavior that could be the basis for seizures seen in experimental models. This model has also been utilized to investigate the role of depolarization block in seizure dynamics (Barreto & Cressman, 2011). Here the model was used to determine the parameters for glial function and potassium diffusion that produces the different patterns of neuronal firing and depolarization block seen in experimental models.

4.2.2 Network models

Of course seizures are the manifestation of activity that emerges from networks of interacting cells. There are several mechanisms that couple the activity of cells, namely synaptic transmission and extrasynaptic neurotransmitter release, gap junctions, and ionic flow through diffusion in the extracellular space as well as through the glia syncytium. A number of models incorporate these mechanisms (Frohlich et al., 2010; Park et al., 2008; Ullah et al., 2009).

In all of these models extracellular potassium concentrations play a role in coupling the activity of neighboring cells. This effect is investigated to varying degrees in a number of computational models (Park et al., 2008, Frohlich et al., 2010; Ullah et al., 2009). Durand's work focuses on the effect of extracellular coupling to synchronize bursting activity in networks of synaptically uncoupled neurons. Their main results suggest that larger networks require greater extracellular coupling to synchronize. Their work suggests that small networks with limited synaptic connectivity are more susceptible to synchronization. The works of Frohlich et al. and Ullah et al. focuses on the effect of potassium on the excitability and stability of activity within neuronal networks. Both of these models investigate one of the most difficult aspects to understanding seizures. Namely, how do networks only occasionally support seizure like states? In Ullah et al., 2009 the authors demonstrate that finite sustained activity, such as that implicated in short term memory (Gutkin et al., 2001), can be stabilized or destabilized by changes in glial function.

Frohlich et al. present a different form of multistability in networks of neurons with ionic and synaptic coupling. They demonstrate that networks can be forced into one of two dynamic states by varying the degree of perturbation. The two stable dynamic states in their model represent normal and pathological function. They demonstrate that the transition between these two states can be tuned through modifications to their ionic regulatory system. Both of these models implicate glial function and ionic balance in general as powerful modulators of network function as well as possible culprits in establishing pathological conditions.

5. Anti epileptic drugs

There are over 50 million diagnosed cases of epilepsy throughout the world, and many people are able to live without seizures thanks to the availability of a wide array of antiepileptic drugs. The first rudimentary antiepileptic drug was introduced in the mid-1800s, and numerous more have been developed since, each acting via a slightly different

set of mechanisms that lend them their anti-convulsant capacity. However, despite the advancement in antiepileptic drugs, as many as 30% of patients suffer from refractory epilepsy, meaning that no combination of drugs render them completely seizure free. This fact, along with an array of serious negative side-effects conferred by some drugs, provides incentive for continued research in AED development.

The basic goal of AEDs has been to dampen excitatory networks (or amplify inhibitory networks) in seizures without impacting day-to-day healthy behaviors. Broadly speaking, there are four major categories of anticonvulsant mechanisms. Most of these mechanisms are firmly rooted in basic ionic processes. Unfortunately for the scientists studying AEDs, in many cases these drugs do not have a single mechanism, but rather rely on multiple mechanisms that could be used to explain the anticonvulsant behavior. The majority of AEDs modulate sodium ion channel activity. Another group of AEDs modulate calcium ion channel activity. Both these mechanisms are effective in part because they limit Sustained High-Frequency Repetitive Firing (SRF). A third group comprises those AEDs that modulate the GABAergic system, particularly through the GABA_A receptor. Finally, the fourth category of AEDs limit the effectiveness of the excitatory neurotransmitter glutamate. There are a variety of additional minor mechanisms of AEDs, including modulation of potassium channels, inhibition of carbonic anhydrase, modulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, and even modulation of Na⁺/K⁺ ATPase pumps.

5.1 Inward cations

5.1.1 Voltage-gated Na⁺ channels

Many AEDs selectively decrease current through voltage-gated sodium channels. These AEDs include carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproic acid, and zonisamide, and possibly a new drug, Carisbamate (Liu, 2008). Evidence strongly supports the idea that these AEDs bind to voltage-gated sodium channels when they are in an inactivated state brought on by an action potential (AP). Because these AEDs bind voltage-gated sodium channels only in the inactivated state, they become more bound (and thus more effective) during repetitive APs. This use-dependent effect is critical to these AEDs having increased activity during rapid firing, as in seizure activity, but little or no effect during non-pathologic neuronal firing.

Once bound, these AEDs delay the sodium channel recovery from an inactivated state to a resting state and shift gating to a more negative voltage. For example, a normal voltage-gated sodium channel may recover from the inactivated state in an average of 2ms, but in the presence of phenytoin this recovery may take as long as 90ms (Delorenzo & Sun, 2002). With the sodium channel in an inactivated state, the neuron becomes refractory to subsequent APs until the AED becomes unbound. In this way, AEDs that modulate sodium channels significantly reduce SRF, which is thought to be a major component of seizure formation and spread. Hyperpolarization of the membrane removes all bound AEDs and allows the sodium channel to fully recover to a resting state. While most drugs that modulate voltage-gated sodium channels utilize this mechanism, there are slight variations from drug to drug. For example, while Topiramate modulates voltage-gated sodium channels in a voltage and use-dependent way, it does not fully block SRF (White, 2002). It is also believed that each drug acts at a different binding site on the sodium channel protein.

These AEDs act in a similar manner as the frequency dependent rundown mechanism compromised in GEFS⁺ type I. The role of sodium inactivation as a control parameter for

seizure susceptibility is also highlighted by the models of Somjen et al. There they suggest that the seizure length is very sensitive to the persistent sodium channel conductivity. Their and other models show that it is the persistent or windowed transient sodium channels that enable the self regenerating discharges. Therefore the main action of these drugs is most likely not the direct reduction on excitatory output, rather it is through limiting the self regenerative period for the active neuron itself.

5.1.2 Ca⁺⁺ channels

Many AEDs modulate voltage-gated calcium channels, all having the effect of inhibiting calcium current. However, different AEDs target different calcium channels. For example, lamotrigine inhibits high-voltage gated N/P type calcium channels, which are associated with neurotransmitter release at the synapse. By inhibiting these channels, lamotrigine is probably diminishing neurotransmitter release. Similarly, levitacetam inhibits N-type Ca²⁺ channels. However, by contrast, Succinimides (such as thosuximide), valproic acid, phenytoin, and zonisamide have been shown to inhibit T-type calcium channels, and are widely used for their anti-absence affects. T-type calcium channels are implicated in the generation and spread of bursts, particularly in absence seizures (Kito et al., 1996).

In addition to inhibiting T-type calcium channels, phenytoin is also thought to inhibit calcium uptake into mitochondria, which serve as a buffering system for intracellular free calcium. This inhibition can increase the intrasynaptosomal Ca²⁺ and cause hyperexcitability through an increase in miniature end-plate potentials. In fact, phenytoin is known to cause hyperexcitability at high concentrations, a reversal from its normally anticonvulsant behavior. This buildup of free calcium in the intrasynaptosomal space may explain this aspect of the drug (Delorenzo & Sun, 2002).

Studies suggest that topiramate targets L-type high-voltage calcium channels and decreases the peak current through the channel. In addition, it has been suggested that gabapentin inhibits high-voltage calcium channels with a particular specificity to the $\alpha_2\delta$ subunit. This subunit specificity allows gabapentin to modulate some neuronal types more than others (Rogawski, 2002).

5.2 Synaptic modulation

5.2.1 GABAergic inhibition

As GABA is the primary inhibitory neurotransmitter in the brain, it is a common target for AED drugs. There are two primary ways that AEDs can modulate GABAergic transmission: 1) By modulating either GABA_A or GABA_B receptors, or 2) By increasing the amount of GABA in the synapse.

Most drugs that modulate GABA receptors do so via the GABA_A receptor. Drugs such as benzodiazepines, topiramate, and barbituates such as phenobarbital allosterically enhance the GABA_A receptor. Since the GABA_A receptor is linked to chloride ion channels, enhancing these GABA_A receptors enhances the chloride ion current, hyperpolarizing the neuron. These chloride channels open in bursts that have a short, medium, or long duration (corresponding to 0.5ms, 2.5ms, and 7.3ms) (MacDonald, 2002). Phenobarbital will increase burst time (favoring longer bursts) without impacting burst frequency (Olsen, 2002). Conversely, benzodiazepines will increase burst frequency without impacting burst time (MacDonald, 2002). Despite subtle differences in mechanism, the end result is the same: an increase in

chloride ion current. Barbituates are not widely prescribed as anti-convulsants because of sedative side effects. Benzodiazepines are largely free of these side effects, probably because they target a specific sub-type of GABA_A receptors, limiting their effect throughout the brain. Barbituates are non-selective, and thus widely effective in all areas of the brain. This probably explains the notable sedative side effects compared to benzodiazepines (Olsen, 2002).

Presynaptic GABA_B receptors inhibit calcium channels (which prevents neurotransmitter release, while postsynaptic GABA_B receptors open potassium channels (which hyperpolarize the neuron). Baclofen is a non-selective GABA_B agonist, and so increases activity at both presynaptic and postsynaptic receptors. This can result in both anti-convulsant, and pro-convulsant behaviors. The pro-convulsant behaviors are thought to be caused by the presynaptic GABA_B receptors, which inhibit neurotransmitter release. While baclofen results in a reduction of excitatory neurotransmitter release, it can also reduce GABA release from inhibitory neurons, which play an important role in seizure prevention. There is some evidence that gabapentin modulates postsynaptic GABA_B receptors, however this is still debated. By activating only postsynaptic receptors, the pro-convulsant effects of baclofen are eliminated (Meldrum & Rogawski, 2007).

In addition to modulating GABA receptors, some AEDs also modulate the amount of GABA in the synapse. Tiagabine blocks the uptake of GABA back into the neuron by blocking the GABA transporter, GAT-1 (Giardina, 2002). This has the effect of leaving GABA in the synapse longer, prolonging inhibitory postsynaptic potentials. Valproic acid increases GAD activity, an important synthesizing enzyme for GABA. Increased GABA synthesis results in increased GABA in the brain (Löscher, 2002). Finally, vigabatrin is an irreversible GABA-T inhibitor. GABA-T catalyzes the conversion of GABA to succinic semialdehyde, and so reduces GABA levels in the brain. By inhibiting GABA-T, GABA is increased in the brain (Ben-Menachem, 2002).

5.2.2 Glutamatergic transmission

Glutamate is the most abundant excitatory neurotransmitter, and acts by binding to NMDA, AMPA, and kainate receptors at the synapse. Some AEDs target these receptors as a means to limit excitatory transmission. For example, felbamate and valproic acid act as antagonists of the NMDA receptor, thus inhibiting glutamatergic transmission. This is indirectly an ionic effect, because an activated NMDA receptor opens a nonspecific cation pore, which allows K⁺ to flow out of the cell along its gradient, and Na⁺ and Ca²⁺ to flow in. This has the effect of depolarizing the cell, contributing to excitability. Many traditional AEDs that inhibit glutamatergic transmission have intolerable side effects, and so are not used. However, felbamate is a drug that is well tolerated, despite acting on NMDA receptors. It has been shown that felbamate is a much more successful antagonist of NMDA receptors containing NR2B subunits, as opposed to NR2A. NR2B subunits are mainly found in forebrain areas, while NR2A subunits are found throughout the brain. Felbamate's tolerability may be owed to it is focused antagonism of NMDA in the forebrain areas of the brain, which play an important role in seizure generation, while other areas are left relatively unaffected (Rogawski, 2002). Kainate and AMPA receptors are also targets for AEDs. For example, topiramate is thought to inhibit Kainate receptors.

5.3 K⁺ channels

While voltage-gated sodium and calcium ion channels have long been targets of AEDs, targeting voltage-gated potassium channels is relatively new. A new AED, Ritagabine, has

been shown to modulate voltage-gated potassium channels. Research also indicates that lamotrigine gets some anti-convulsant properties by modulating potassium channels (Czuczwar et al, 2010).

Ritagabine increases current through the Kv7.2-7.3 subunits of the voltage-gated M-type K⁺ channel. This is done by lowering the activating potential required to open these ion channels down to levels close to the resting membrane voltage. This is either done by stabilizing the M-type channels in their open state, or destabilizing them in their closed state. Evidence suggests that the binding site is exposed when the channel is in the open state, and thus the channels are stabilized in their open state (Czuczwar et al, 2010; Scherer et al., 2005). Binding of Ritagabine probably interferes with the closing of the channel until lower voltages.

Opening these potassium channels allows potassium to flow out of the cell due to its gradient. This has the effect of lowering the membrane potential back towards resting or even hyperpolarizing levels, thus reducing excitability. Ritagabine has been shown to hyperpolarize neurons, which supports this explanation for some of its anti-convulsant properties.

5.4 Carbonic anhydrase and acidosis

Research suggests that some AEDs, such as topiramate and zonisamide derive their anti-convulsant properties in part from their ability to modulate the pH in the brain. This is done by inhibiting Carbonic Anhydrase (CA), the enzyme responsible for interconverting CO₂ and H₂O with protons and bicarbonate. The inhibition of CA results in the buildup of H⁺ ions from the metabolic process, and mild acidosis results. This is significant because the presence of an excess of H⁺ ions modulates ion channel activity, and causes inhibition, as explained previously (Mizra et al., 2009).

5.5 HCN channels

There is recent evidence that gabapentin and lamotrigine increase the inward I_H current in some neurons. The I_H current is an important part of the ability of cardiac cells and neurons to control rhythmicity. Hyperpolarization-Activated, Cyclic Nucleotide-Gated K⁺ (HCN) ion channels are responsible for the I_H current. As the name would suggest, these ion channels are hyperpolarization activated, and allow Na⁺ and K⁺ to flow into and out of the cell respectively (K⁺ is four times more permeant than Na⁺) (Clapham, 1998). While the role of HCN channels in cardiac tissue is more clearly understood, the distribution and effect on neurons in the brain is still a matter of research and debate. However, it is clear that I_H plays a role in both pyramidal cells and inhibitory interneurons in the hippocampus, and may help to control the synchronized firing that is important for information processing. Studies show that HCN channels are active at the resting membrane potential for many hippocampal neurons. This net inward flow has the effect of depolarizing the neuron slightly, thus increasing excitability. At first glance, it would seem that I_H-induced excitability of inhibitory interneurons would cause overall inhibition, while I_H-induced excitability in pyramidal cells would cause excitation. However, research shows that the overall effect of increased I_H currents is inhibition.

The reason for this is more obvious in interneurons. An increase in I_H currents in inhibitory interneurons has a slight depolarizing effect by about 5-10mV (George et al., 2009), making it easier for these cells to fire. In fact, research indicates that this is one way gabapentin and

lamotrigine get their anti-convulsant properties (Peng et al., 2011). Despite having a similar effect, lamotrigine and gabapentin modulate I_H currents differently. Lamotrigine changes the activation potential of HCN channels (Poolos et al., 2002), while gabapentin increases the conductance while leaving the voltage gating unchanged (Surges et al., 2003).

The impact on pyramidal CA1 cells is perhaps less obvious. Interestingly, increasing I_H current in CA1 pyramidal cells has a nonlinear effect. Increasing I_H currents in conjunction with weak, subthreshold Excitatory Post-Synaptic Potentials (EPSPs) results in an overall excitatory effect. The peak voltage achieved by the EPSP is increased by the I_H currents, though still not enough to cause an action potential. However, strong subthreshold EPSPs have an overall inhibitory effect. The peak voltage achieved by these stronger EPSPs is actually lessened by I_H currents. If increased I_H currents have a depolarizing effect on neurons, how does this lead to inhibition? The answer rests with M-type voltage-gated K^+ channels. These channels are activated by modest depolarizations of the neuron, and allow K^+ to flow out the neuron along its concentration gradient. M-type K^+ channels thus have a hyperpolarizing (inhibitory) effect on neurons. Weak EPSPs are not enough to fully activate M-type K^+ channels, and excitation results. However, as the EPSPs get stronger, K^+ channels are activated, and inhibition results. Thus, the overall impact of gabapentin and lamotrigine is to make it more difficult for EPSPs to reach the action potential threshold, and thus is inhibitory (George et al., 2009).

5.6 Na^+/K^+ ATPase pumps

Some research indicates that AEDs, such as phenytoin, can increase the activity of the sodium potassium pump. Increasing the sodium potassium pump draws more potassium into the cell, and forces more sodium out, hyperpolarizing the cell. (Guillaume et al., 1986) There is also some evidence that this effect is dependent on the K^+/Na^+ ratio in the extracellular space. When there is a higher ratio of K^+/Na^+ , phenytoin is more effective at increasing Na^+/K^+ -ATPase activity. Because extracellular K^+ levels can often rise during seizures, this provides a mechanism where phenytoin can modulate seizure behavior without influencing healthy behaviors (Delorenzo & Sun, 2002). This is one of the few targets which is aimed at interacting with the IRS directly.

6. Summary

Although the importance of ion concentrations in seizure dynamics has long been established (Green & Petsche, 1961), the effects of ionic imbalances are still not well understood. Mounting experimental and computational results are beginning to untangle the role of the IRS in seizure dynamics. These findings suggest that seizure initiation, evolution, and termination are all highly influenced by changes in the ionic balance. The knowledge gleaned from this body of work should be used to better understand current pharmacological agents as well as used to inform new pharmacological targets, and other forms of treatment such as electrical or magnetic stimulation.

We have presented the basic mechanisms responsible for ionic regulation as well as their role in maintaining normal ion concentrations. We also described a number of common interactions between neuronal activity and ionic concentrations that directly influence neuron behavior and signaling. By influencing a wide array of neuronal properties, including, membrane excitability and synaptic potency, ionic imbalance can play a large role in establishing the behavior of networks of neurons.

In order to further establish the relevance of ionic imbalance in epilepsy we looked at the role of these mechanism in known etiologies. For known idiopathic epilepsies the function of the implicated proteins will often suggest a mechanism for seizure susceptibility. For instance, the loss of sodium channel inactivation may lead to prolonged depolarization and a greater increase in ionic imbalance. Even in diseases where the obvious culprit is inhibitory malfunction the effects of ionic imbalance are still highly relevant to the dynamics of these seizures.

In symptomatic seizures the alterations to neuronal and glial cells in and around lesions lead to a variety of abnormal behavior. Glial cells are highly implicated in many symptomatic seizures. Seizure susceptibility in some of these cases could be due to the diminished ability of glial cells to maintain ionic balance.

We concluded by looking at the major classes of antiepileptic drugs and their effects on the IRS. Though all of these pharmacological agents effect, to some degree, ionic balance, only a few directly act on it.

Experimental and mathematical models strongly suggest that glial malfunction is implicated in seizure dynamics. To this point, there are no drugs targeted at glial function. This could be a promising avenue for new antiepileptic agents. Since the IRS composes a coupled system it important to realize that no target is entirely specific. Therefore one cannot expect to solely interact with any one ionic gradient. It is therefore essential to make use of experimental and theoretical models to evaluate the effectiveness of pharmacological manipulations.

7. Conclusions

It was our goal to inform the reader of the importance of ionic imbalance in seizures, both to better understand the nature of seizures and their manifestations, as well as to think of better ways to directly interact with the Ionic Regulatory System to maintain normal neuronal states.

8. References

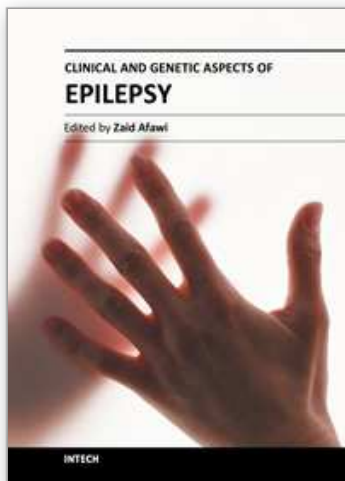
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