Epileptogenesis, Post-stroke Epilepsy, Treatment, Depression, and the Importance of Quality of Life

A Review of Current Research in the Medical Field

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Abstract

The ADK hypothesis and the disruption of Ca2+ homeostasis in the brain are leading causes of epileptogenesis. These are the main underlying factors that lead to post-stroke epilepsy. In addition to this, epilepsy is known to cause a significant increase in risk for depression, which has been shown to be coupled with attenuation of the hippocampal region. This knowledge would lead one to think that epilepsy should be treatable, but current treatments do not address all of the issues at hand. The newest treatment, Levetiracetam, has been shown to reduce expression of synaptic vesicle protein 2A in order to control Ca2+ regulation but its side effects in terms of depression are controversial. Following is a culmination of new progress in treating epilepsy. Causes, diagnosis, comorbid depression, and levetiracetam specifics are included in search of an all-inclusive treatment.

Introduction

According to the Epilepsy Foundation, nearly 3 million Americans suffer from seizures as a result of some form of epilepsy. Despite the growing knowledge of how epilepsy affects the brain and an individual's quality of life, a conclusive treatment has not been discovered. For years we have known that the epileptic process is comprised of three phases: the initial insult, the latent epileptogenic phase, and finally epilepsy. Where in this process treatment should focus has not been thoroughly answered. Attempts at preventing the progression of epilepsy have been made without success. In searching for an answer, the quality of life of individuals suffering from the disease has been neglected. The following seeks to show new advancements in the medical field that are leading towards a seemingly elusive successful treatment, and to bring awareness the importance of the quality of life of epilepsy patients.

Underlying causes of Epileptogenesis

Epileptogenesis has been linked to many genetic factors. The Andenosine Kinase (ADK) theory of epileptogenesis links seizure occurrence and prevalence to the presence of Adenosine in neuronal astrocytes. The upregulation of ADK classifies as it as a key negative regulator in the attempt to solve the puzzle of epilepsy (Theofilas 2011). There are, however, many emerging theories which delve deeper into the inner workings of the brain. The abnormal presence of Ca2+ in the central nervous system has been linked to both the development of epileptogenesis and the condition of recurrent seizures (Becker 2008, Blair 2008). Transcriptional upregulation of Cav3.2, a T-type Ca2+ channel, has been shown to mediate epileptogenesis. The neuropathological symptoms of fully developed epilepsy, which include subfield-specific neuron loss in hippocampal formation and mossy fiber sprouting, were absent in Cav3.2 -/- mice (Becker 2008). Following the fact that alterations to Ca2+ homeostasis is observed during seizures, other Ca2+ mediating receptors have been distinguished. The Ca2+/ N-

methyl-D-aspartate receptor-dependent mechanism has been shown to heavily contribute to the molecular chain of events that leads to seizures (Blair 2008).

In order to further detail the causes of Epileptogenesis, we will next focus on Temporal lobe epilepsy as it is the most common drug resistant form of epilepsy (Herman 2002). Temporal Lobe Epilepsy (TLE) has been heavily linked to the over-excitability and spontaneous hyperactivity of the Entorhinal Cortex (Shah 2004). Furthermore, TLE has been linked to a decrease in Hyperpolarization-activated cation nonselective 1 (HCN1) (Shah 2004). When mice were tested with HCN1 genes, HCN1 -/- mice were found to be more susceptible to seizures and even showed more susceptibility to developing chronic TLE (Huang 2009).

Epileptogenesis and Stroke

Strokes have long since been recognized as a leading cause of epilepsy in human adults. The finer details of this debilitating condition, however, are only now being truly understood. EEGs (electroencephalograms) have been used to visually depict seizures but have not, until recently, been used for accurate diagnosis of post seizure patients. Findings show that periodic laterized epileptic discharges (PLED), which can be visualized in an EEG, are present in individuals with both early and late onset seizures. PLEDs are not present in seizure free patients. Frontal intermittent rhythmic activity (FIRA), also seen in an EEG reading, coupled with PLED show signs of early onset seizures, whereas FIRAs and diffuse slowing show high risk of developing late onset seizures. (Reuck 2006).

Acute seizures show a higher mortality rate both within 30 days after stroke (Szaflarski 2008) and in a 1 year post stroke period (Burneo 2010). Post-stroke seizures have shown to be very debilitating, showing considerable social and physiological implications which often lead to depression. Patients who suffer from seizures as a result of stroke show longer hospital stays and greater disability at discharge (Burneo 2010).

The visual premonitions seen upon close inspection of a test as simple as an EEG, in addition to post-stroke seizure statistics could be used to better treat stroke patients and prepare them for challenges they are to face in their near future, and perhaps save patients who have a higher mortality rate.

Depression and Epilepsy

Epilepsy patients have long since been known to have a greater risk of depression and suicide than otherwise healthy individuals. The underlying causes of these findings, however, have only recently become apparent. In a Canadian representative sample study, researchers showed that epilepsy creates a 43% increase in a patient's odds of suffering from depression. Risk groups were found to include: women, visual minorities, elderly, and individuals who experience food insecurities (Fuller-Thomson 2009). Early recognition of these risk factors should help physicians to become aware of the threat of depression in epileptic patients. The same study does also show a shocking statistic: of the epileptic patients included, 38% of those who suffered from both epilepsy and depression had not once consulted a mental health professional in regards to their feelings of depression (Fuller- Thomson 2009). If these individuals are not speaking of their depression, it becomes even more difficult to treat their symptoms.

Even when individuals present their symptoms, neurologists have proven reluctant to treat depression for fear of increasing seizure frequency with the use of antidepressants (Cotterman-Hart 2010). This common misconception has only been supported with mice trials, and has never been thoroughly supported with evidence through human studies. In fact, the treatment of depression present in epilepsy patients has shown to increase the controllability of seizures, given that norepinephrine and serotonin have shown anticonvulsant neurotransmitter properties (Jobe 2005).

New research has sought to pinpoint a pathologic process that leads to this increased risk

of depression. The hippocampal region of the brain has been shown through both EEG and MRI volumetric analysis to be significantly smaller in both epilepsy patients and individuals who suffer from depression. Studies show, however, that patients with both depression and a right temporal seizure focus showed left hippocampal reduction that could not be explained by one condition alone (Shamim 2009). This pathologic reduction process of the hippocampus shows a biological link to the increase in risk for suicide and depression found in the majority of epilepsy patients.

Interactive Depression Treatment

In response to the prevalence of depression in epilepsy patients, the PEARLS depression treatment has been created. In order to deal with the specific challenges epilepsy patients are faced with, the PEARLS treatment is an entirely home-based program designed to manage depression. Rather than simply treating patients with anti-depressants, which is of high concern in patients with epilepsy due to the myriad of potential drug interactions, PEARLS treatment consists of in-home sessions where a heavy focus is placed on behavioral techniques.

In a controlled trial PEARLS has been proven to effectively reduce symptoms of depression in adults with epilepsy. In comparison to epilepsy patients who received normal care for their depression, PEARLS patients showed lower depression severity and suicidal ideation over a 12 month period (Ciechanowski 2010). In a follow-up study the permanence of these results was proven as the effects of the PEARLS program were proven to be maintained for a year after the end of the home visit PEARLS sessions (Chaytor 2011).

Levetiracetam

How and Why it Works

The specifics of levetiracetam's functions in quelling epileptic seizures have previously been a mystery. The pieces are, however, now beginning to come together. Reduced expression of Synaptic Vesicle Protein 2A (SV2A) has been linked to epileptogenicity, and SV2A has been linked to the homeostasis of synaptic vesicle components such as Ca2+ regulation as discussed previously. SV2A has been found to be the binding site for levetiracetem (Gorter 2009). In addition to this, lab rat studies also show that levetiracetam attenuates afterdischarge duration, thus allowing it to reduce the severity and length of seizures (Christensen 2010). Levetiracetam does however show fascinatingly novel properties. In the same study where scientists discovered its ability to attenuate discharge, Levetiracetam has been shown to inhibit the immediate early transcriptional responses which occur in response to neuronal spiking in the hippocampus. These immediate early transcriptional responses eventually lead to synaptic plasticity as a result of brain trauma, and Levetiracetam's IEG mediating properties make it a candidate for inhibiting the structural changes that cause the furthered development of epilepsy in the brain (Christensen 2010).

Levetiracetam and depression

The findings in regards to levetiracetam treatment and comorbid depression treatment have proven themselves contradictory. In 2008 an uncontrolled study showed that Levetiracetam treatment could have the ability to improve depression and anxiety in epileptic patients. Of the 25 patients involved, the majority showed significant improvements in depression during Levetiracetam treatment, and none of them showed an increase in depression. (Mazza 2008). It must be taken into account, however, that this study did not account for the placebo effect as all patients were given Levetiracetam.

These promising findings are essentially negated by a case study which shows, quite blatantly, the

depression risks involved with Levetiracetam treatment. In 2009, a 5- year-old epileptic boy was treated with Levetiracetam after all other treatments failed. Levetiracetam successfully treated his seizures, but he soon developed irritability, loss of appetite, loss of interest in previously pleasurable activities, aggression, and an unrelenting tiresome feeling. As a result, the boy was diagnosed with major depressive disorder. Levetiracetam treatment was discontinued and within two weeks the child's symptoms of depression completely disappeared. (Tamarelle 2009). When dealing with the life of a human, one study such as this one is enough to make Levetiracetam a less favorable solution to the problem of epilepsy.

Discussion

The medical world has come a long way in its understanding of epilepsy. There has not, however, been a clear answer as to how to treat epilepsy. Many antiepileptic drugs are currently in use, with Levetiracetam being the newest and foremost tool in the fight to control seizures. Levetiracetam's side effects are controversial, making it a potential threat to the mental stability of the patient at hand. Post-stroke epileptogenesis and depression in epileptic patients has been the focus of many studies over the past 10 years and has lead to many new understandings. Despite the growing knowledge of the subject, no treatment has been able to solve all the problems epilepsy presents.

Perhaps the one factor of epilepsy that we can presently treat successfully is the quality of life of epilepsy patients. Post-stroke EEG monitoring can allow for early diagnosis (Reuk 2006), and Levetiracetam shows promising results of being able to prevent the development of severe chronic epilepsy (Christensen 2010). This combined with knowledge of the severity and prevalence of depression in epilepsy patients can give neurologists the ability to help patients deal with their struggle to cope with their seizures until a fully adequate treatment is available.

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