Exploring epilepsy

Partners in life and in research, Drs Kristina and Tim Simeone are investigating epilepsy, its comorbidities and novel therapeutics.

Can you introduce yourselves, explaining what inspired you to begin researching neuroscience?

KS: Health has always been very important to me. We are at a point in history in which we can articulate how to maintain our peripheral health, however, very little is known about our brain health. The brain is composed of complex neuronal-glia networks. These local and global networks are responsible for influencing peripheral physiology, knowledge processing, consciousness, personality and emotion. For multiple known and unknown reasons, some networks can become dysregulated affecting our cognitive faculties, memory, behaviour, and in some cases spontaneous seizures may develop. My expertise and techniques centre around neuroanatomy, neurobiology and mitochondrial bioenergetics. Throughout my training and career, I have studied how factors – such as age, experience, diet, sleep and pharmacology – influence brain health, pathology and function. Understanding the neuroplasticity of brain health will provide insight into how we should care for our brain throughout life and will assist us in the treatment of neurological disorders and diseases.

TS: The prevalence and variety of neurological disorders and mental health issues impacts each of us on a daily basis, frequently on a personal level. I recognised early in my graduate education that many therapies in use for diverse disorders originated as treatments for epilepsy. I concluded that devoting my research career to epilepsy had the greatest potential for influencing peripheral physiology, knowledge processing, consciousness, personality and emotion. For multiple known and unknown reasons, some networks can become dysregulated affecting our cognitive faculties, memory, behaviour, and in some cases spontaneous seizures may develop. My studies focus on the sleep disorder comorbidities associated with epilepsy.

How has learning about the ketogenic diet (KD) contributed to your investigations?

TS: The KD is high in fat and very low in carbohydrates and proteins. However, it is the most effective non-surgical treatment for refractory epilepsy (ie. uncontrolled seizures). Strict adherence to the KD is required for the beneficial effects to manifest, but the poor palatability of the diet means compliance is low, and clinical use limited. Our research is aimed at identifying the mechanisms of the KD that are responsible for these effects in the hope of identifying new targets for the development of pharmaceutical therapies. A novel approach that manipulates the same mechanisms, but does not require a high fat diet, could be highly beneficial.

KS: It is thought that the primary fuel source for the brain is glucose, but interestingly, treatment with the KD switches the primary energy source to fat. This transition from glucose to fat changes the excitability of an epileptic brain, which ultimately results in fewer seizures. This suggests that the excitability of the brain may be tethered to or controlled by its metabolic fuel. Thus, we aim to better understand the plasticity of the brain in response to different fuels and how these fuels influence brain health and function.

Do you collaborate with any other researchers or laboratories?

KS&Ts: We have been very fortunate to be trained by and work with outstanding basic and clinician scientists including Drs Jong Rho (University of Calgary), Patrick Sullivan (University of Kentucky), Charles Allen (Oregon Health & Science University), Rama Maganti (University of Wisconsin), Deepak Madhavan (University of Nebraska Medical Center), Jiri Adamec (University of Nebraska at Lincoln), Peter Abel (Creighton University), Steve White and Karen Wilcox (University of Utah) and Tallie Baram (University of California, Irvine).

Can you describe your research goals?

TS: My research focuses on detailing the mechanisms by which nutritionally regulated gene transcription factors can affect the biophysical properties of neurons of epileptic networks.

KS&Ts: When we collaborate, we each bring a different knowledge base, technical expertise and perspective to the table. This enables us to intellectually explore ideas more fully and encourages out-of-the-box thinking. Our differing techniques allow us to test hypotheses with a rather large tool kit.

You each have your own laboratory and are investigating different aspects of epilepsy. Can you describe your research goals?

KS: My studies focus on the sleep disorder comorbidities associated with epilepsy. Within this work, we examine the expression of different sleep regulating proteins in the brain and the interaction between sleep and seizures. These studies are also exploring the role of the KD and other dietary therapies in promoting sleep, and vice-versa, we are also researching the potential of sleep-promoting agents in reducing seizures.
Brain excitability: from networks to organelles

A husband and wife team based at Creighton University is investigating the epileptic brain. Using animal models to reveal the mechanisms underlying the disease, and its connections to sleep and diet, they hope to find new therapeutic targets.

**EPILEPSY IS ONE** of the most common serious neurological disorders, affecting approximately 65 million people around the world – yet despite its pervasiveness, it lacks effective treatment. Around 30 per cent of those with the condition are unable to control their seizures with currently available drugs. Clearly, new approaches to treating this condition are required.

Professors Kristina and Tim Simeone at Omaha’s Creighton University School of Medicine are investigating mechanisms of brain hyperexcitability using multiple platforms from network electrophysiology down to organelles and transcription factors.

The Simeone Labs collaborate on three major research avenues, which are beginning to intersect. Led by Kristina, one project focuses on sleep disorder comorbidities associated with epilepsy. Tim coordinates another project, which focuses on a novel transcription factor that may also hold anti-seizure properties. A final joint venture investigates the role of brain fuel, mitochondria and neurotransmission.

**BRAIN RHYTHMS: SEIZURES AND SLEEP**

Epilepsy has an important but underappreciated connection with sleep. At least one-third of epilepsy patients suffer from a sleep disorder, and this is significant as insufficient and poor quality sleep is detrimental to critical physiological functions. In patients with epilepsy, lack of sleep can not only exacerbate cognitive impairments and psychological comorbidities, but also worsen seizure frequency and/or severity.

Kristina is studying this connection, aiming to elucidate the causes of sleep disorders and further understand contributing mechanisms underlying epilepsy. By investigating how seizures affect sleep, and how biological rhythms affect seizure occurrence in turn, her lab hopes to discover sorely needed new therapeutic targets that may improve both conditions.

**UNDERSTANDING NEUROPEPTIDES**

The Simeones’ investigations rely on kcna1-null mice, a genetic model of epilepsy with broad clinical relevance. Mice lacking the kcna1 gene normally develop seizures at a young age, exhibit the symptoms of sleep disorders.

In a National Institutes of Health (NIH)-funded project, Kristina is using these models to identify the mechanisms that connect sleep disorders to epilepsy. The project focuses on the lateral hypothalamus, the region of the brain involved in both hunger and wakefulness. Her lab is particularly interested in the neuropeptide orexin, the neurons of which drive wakefulness when firing. They hypothesise that hyperactive orexin neurons in the lateral hypothalamus may contribute to sleep disorder symptoms – including fragmented sleep, increased latency to sleep onset and reduced overall duration of sleep. Indeed, electroencephalogram (EEG) and electromyogram (EMG) analyses indicate the mice have reduced rapid eye movement (REM) and non-REM sleep, and increased arousals during rest.

Treatment with a drug that blocks orexin’s ability to act on its receptor improved sleep and importantly reduced the severity of seizures. In their continued research, the team aims to determine whether the reduced seizures were a result of improved sleep or the drug interacting directly with a seizure-generating mechanism.

**HIGH FAT FOR BRAIN HEALTH**

One interesting anti-seizure treatment that has shaped the Simeones’ research is the ketogenic diet (KD) – a diet high in fat and low in carbohydrates and proteins. This diet appears to be healthy fuel for the brain, and is the most effective non-surgical treatment for seizures that are resistant to drugs (refractory epilepsy). The KD has been shown to reduce seizures by 50 per cent in half of patients, and in a further third by 90 per cent.

In addition to decreasing seizures by approximately 75 per cent, Kristina has reported that the KD improves sleep. Furthermore, Tim demonstrated that the KD treatment significantly reduces the epileptic electrophysiological pathologies (high frequency oscillations known as fast ripples) in the seizure-generating hippocampus.

Together, the Simeones have observed that the KD increases longevity, which will have enormous implications for sudden unexpected death in epilepsy: “Thus, the KD holds the key to a broad-spectrum anti-seizure mechanism as well as potentially postponing or treating sudden unexpected death in epilepsy,” Tim articulates.

Despite its potential, the factors underlying the anti-seizure effects of the KD remain unclear. However, it is known that treatment with the diet restores mitochondrial function. Mitochondria are critical for neurotransmission, regulating synaptic and perisynaptic ATP and calcium levels. Mitochondrial impairment occurs in epilepsy and other neurological disorders, in which the KD is currently being investigated, including Alzheimer’s and Parkinson’s disease.

A collaborative effort by the Simeone Labs, and Drs Jong Rho and Patrick Sullivan, showed that the brain mitochondria of epileptic mice are dysfunctional: they produce less energy (ATP), more harmful reactive oxygen species, and have inferior calcium sequestration abilities. These collective
Around 30 per cent of people with epilepsy are unable to control their seizures with currently available drugs.

Impairments can alter neurotransmission and synaptic plasticity, injure brain cells and cause mitochondria to trigger cell death signalling cascades, resulting in pathology.

Accordingly, Kristina has designed a novel treatment to target mitochondrial dysfunction. The treatment is able to prevent kainate-induced status epilepticus in healthy mice, and reduce the incidence and severity of seizures by more than 50 per cent in over two-thirds of kcnat-null mice. Continuing studies are determining whether this treatment restores network activity and ultimately improves longevity in this model.

THE KEY PLAYER

Building on this, Tim’s NIH-funded project identified the mediator of the KD’s therapeutic effects. They found that the peroxisome proliferator-activated receptor gamma (PPARγ) transcription factor has similar genetic effects as the KD: ie. promoting anti-inflammatory signals, anti-oxidant pathways and mitochondrial health. In addition, long chain polyunsaturated fatty acids, which increase in the KD, are ligands for this transcription factor. “It therefore seemed logical to test whether PPARγ played a role in the anti-seizure efficacy of the KD,” Tim explains.

Using pharmacological and genetic tools, Tim showed that the KD actually increases levels of PPARγ in the brain of epileptic mice, and a blocker (antagonist) of PPARγ prevented the anti-seizure effects of the diet. Adding to this evidence, mice lacking PPARγ did not show the anti-seizure effects of the diet. Adding a blocker (antagonist) of PPARγ prevented an epileptic brain into a normal brain.

ASSEMBLING THE PUZZLE

Through their collaborative research, the Simeone Labs are beginning to piece together the puzzle – revealing the complex interplay between sleep, seizures, mitochondria, inflammation, homeostatic mechanisms and longevity.

The pair are also getting closer to new treatments. Orexin receptor antagonists are currently being studied for use in people with sleep disorders (without epilepsy). Treatments to promote mitochondrial health are currently available and more specific therapeutic combinations are actively being investigated. The results of Tim’s most recent work has potential for immediate impact, as PPARγ agonists are already used to treat type 2 diabetes and therefore would not require safety testing.

Furthermore, because cell death and inflammation are implicated in a range of neurological disorders, PPARγ could be used widely. This is also true for Kristina’s work. Many neurological disorders present with similar sleep disorder comorbidities and mitochondrial impairments. Together therefore, their research could change the lives of not only epileptics, but also those living with many other neurological conditions.

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