TSC Research summaries

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Title: Excitatory/inhibitory synaptic imbalance leads to hippocampal hyperexcitability in mouse models of tuberous sclerosis

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Neuron. 2013 May 8;78(3):510-22.

doi: 10.1016/j.neuron.2013.03.017

What is the topic? Tuberous sclerosis complex (TSC) is a genetic disorder that is caused by mutation in genes called *TSC1* and *TSC2* - this causes over-activation of a protein complex called mammalian target of rapamycin complex 1 (mTORC1). TSC is associated with numerous complications –the neurological ones being developmental disorders and seizures.

Neuronal (nervous system) networks are made up of neurons (nerve cells) that are connected to each other via synapses (connections between nerve cells). One of the defining properties of the brain is its capacity to undergo activity-dependent alterations in synapses. This capacity of the brain to 'rewire' (also known as 'plasticity') is what helps us form new memories, retain old ones and regain functionality after an injury such as a stroke. Activity-dependent plasticity of neuronal networks depends on a fine balance between excitation and inhibition, and aberrations in this balance can cause neurological disorders.

What did the researchers hope to learn? TSC is associated with seizures and neurodevelopment disorders; the authors wanted to find out whether alterations that are seen in TSC are sufficient to cause hyperexcitability in experimental subjects. The reason for examining this is that if we know the mechanisms that can cause seizures in TSC, we can potentially target them to stop seizures.

Who was studied? Two approaches were taken in this study – *in vitro* (meaning 'outside of the living organism') and *in vivo* (meaning 'inside the living organism'). The authors studied a part of the brain called the hippocampus because of its importance in seizure generation and propagation. The *in vitro* approach consisted of hippocampal neurons that were removed from the brain of transgenic (genetically modified) mice with reduced levels of the protein TSC1. In the *in vivo* approach, scientists studied the seizure properties of experimental mice with reduced levels of TSC1.

How was the study conducted? The authors used the dissociated hippocampal cultures to study electrical properties of neurons. Drugs that cause seizures in the lab are called chemoconvulsants – one of them is kainic acid (KA). KA was given to mice that had reduced TSC1 to see how these mice with mutated TSC respond to seizures.

What did the researchers find? Neuronal hyperexcitabity or the phenomenon in which neurons are excessively excitable is thought to underlie seizure generation and propagation. The *in vitro* studies

show that when levels of the protein TSC1 were decreased, there was a greater level of hyperexcitability. In experimental mice, administration of KA in animals with lower TSC exhibited more seizures. The reason behind this was that there was an imbalance between excitation and inhibition.

What were the limitations of the study? This study was done in experimental animals, and despite the interesting and exciting results, more studies need to be performed in tissue from human subjects with TSC to confirm that the same biological mechanisms are at play.

What do the results mean for you? Up until now, it was known that mutations in TSC genes interact with mTORC1 to eventually cause seizures and developmental disorders. This study takes this a step further because it shows the exact mechanism by which TSC can cause seizures and developmental delay i.e.by altering the excitation / inhibition balance.

This summary was written by Sloka Iyengar, PhD, epilepsy researcher at the Northeast Regional Epilepsy Group studying aspects of brain tumor-related epilepsy, mood disorders in epilepsy and special issues in women with epilepsy. She is also a science writer and contributes regularly to numerous websites to make neuroscience research more accessible to non-scientists. (December 2014).