

Seizures and sudden death: When SUMO 'wrestles' potassium channels

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A gene crucial for brain and heart development may also be associated with sudden unexplained death in epilepsy (SUDEP), the most common cause of early mortality in epilepsy patients.

Scientists at The University of Texas MD Anderson Cancer Center have created a new [animal model](#) for SUDEP and have shown that mice who have a partial deficiency of the gene SENP2 (Sentrin/SUMO-specific protease 2) are more likely to develop spontaneous [seizures](#) and [sudden death](#). The finding occurred when observing mice originally bred for studying a link between SENP2 deficiency and cancer.

"SENP2 is highly present in the hippocampus, a critical brain region for seizure genesis," said Edward Yeh, M.D., chair of cardiology at MD Anderson. "Understanding the genetic basis for SUDEP is crucial given that the rate of sudden death in [epilepsy patients](#) is 20-fold that of the general population, with SUDEP the most common epilepsy-related cause of death."

Yeh's findings were published in this month's issue of *Neuron*.

Although it's not yet known what causes SUDEP in humans, inactivation of [potassium channels](#) genes have been linked to SUDEP in animal models. Potassium channels are found in most cell types and control a large variety of cell functions.

"These animal models demonstrated an important connection between

the brain and heart. However, it remains unclear whether seizure and sudden death are two separate manifestations of potassium channel deficiency in the brain and the heart, or whether seizures predispose the heart to lethal cardiac arrhythmia," said Yeh.

The study revealed that when SENP2 was deficient in the brain, seizures activated a part of the nervous system responsible for regulating the heart's electrical system. This resulted in a phenomenon known as atrioventricular conduction block, which effectively slowed down and then stopped the heart.

Yeh's team observed that the SENP2-deficient mice appeared normal at birth, but by 6 to 8 weeks, experienced convulsive seizures, and then sudden death. He believes the reason may lie with protein modifiers called SUMO. SENP2 deficiency results in a process known as hyper-SUMOylation, which dramatically impacts potassium channels in the brain.

"One of the channels, Kv7, is significantly diminished or 'closed' due to the lack of SENP2," said Yeh. "In mice this led to seizures and cardiac arrest."

In humans, the good news is that an FDA-approved drug, retigabine works by "opening" the Kv7 channel. The therapy was developed for treating partial-onset seizures. The findings in Yeh's new mouse model clearly demonstrate a previously unknown cause of SUDEP, which may open up new opportunities for study and treatment in the future.

Provided by University of Texas M. D. Anderson Cancer Center

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