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Anti-seizure medication has a new target

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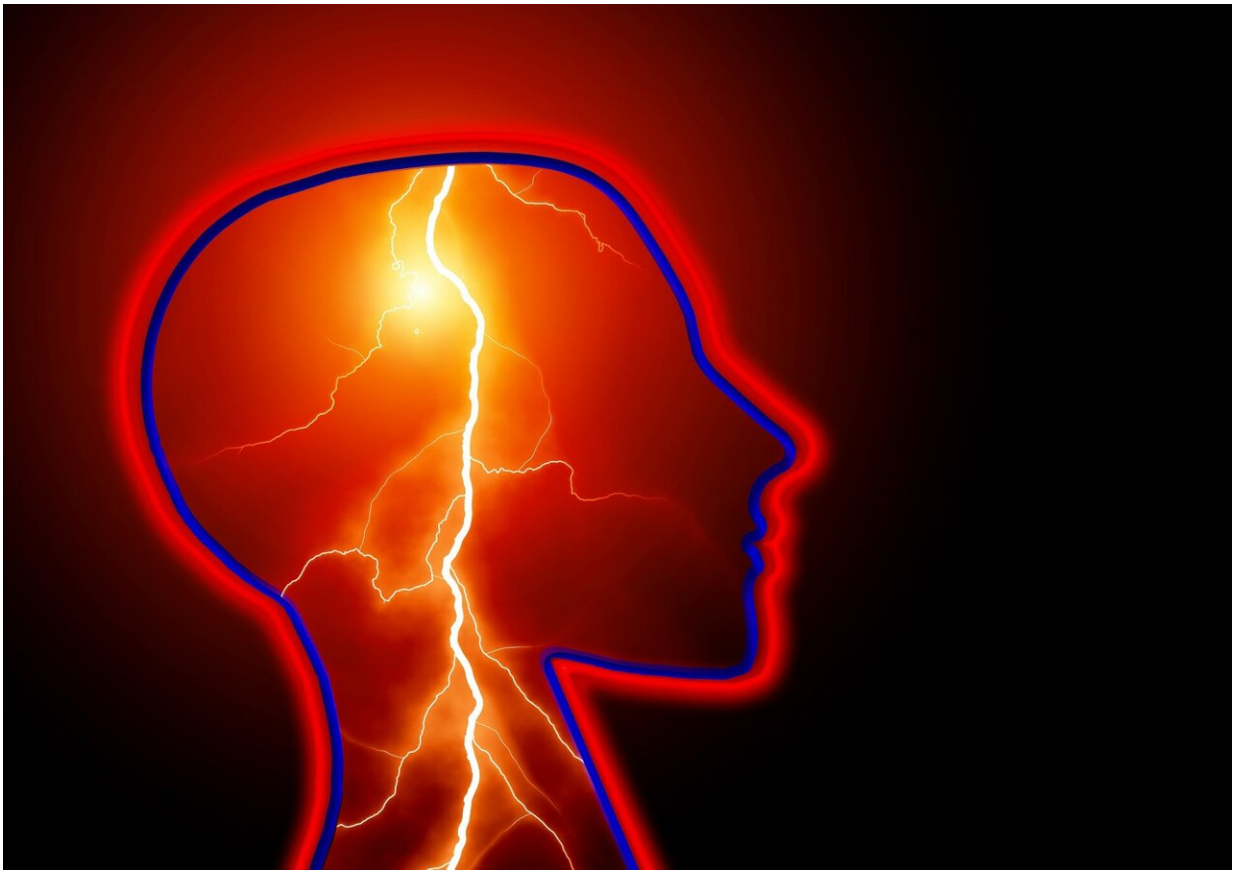

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An anti-seizure medication acts on unexpected molecular targets, according to a Northwestern Medicine study published in the *Journal of Neuroscience*.

Designed to target AMPA receptors in the brain, the medication—called perampanel—turns out to also modulate kainate receptors, according to Geoffrey Swanson, Ph.D., professor of Pharmacology and senior author of the study.

"The drug was thought to be highly specific for one type of excitatory receptor, but we found it was not as selective as previously described," Swanson said.

Perampanel, sold under the brand name Fycompa, is an anti-seizure medication used to treat epilepsy and similar disorders. The drug has significant side effects and is typically prescribed to patients who don't respond to safer drugs, Swanson said.

"As many as 35% of patients with epilepsy aren't treated effectively with existing first-line drugs, so there's always a drive to find new anti-seizure medications," Swanson said.

Perampanel works differently than many other anti-seizure medications, by reducing activity in AMPA receptors which are among the primary sources of excitatory signaling in the brain. Rampant excitatory signaling is a signature feature of epilepsy.

However, a recent study of perampanel's binding structure revealed its binding pocket—the specific molecular connections between the drug molecules and target receptors—are very similar in both AMPA and kainate receptors. Kainate receptors are another neurotransmitter receptor, responsible for balancing excitatory and inhibitory transmissions.

In the study, Swanson and his collaborators examined if perampanel was also acting on kainate receptors. Using AMPAR and kainate receptors expressed in cell cultures and in mouse neurons, Swanson applied

perampanel and measured activity in both types of receptors, finding that the drug indeed inhibits kainate receptors that contain one of the five types of subunit proteins.

Now that the identity of new molecular targets have been established, more work is required to establish how this unexpected inhibition affects treatment efficacy, according to Swanson.

"We have to untangle to what extent inhibition of kainate receptors contribute to both its anti-convulsive and adverse effects," Swanson said.

If perampanel can be more precisely targeted to either AMPA or kainate receptors, it could improve performance of the drug, giving patients with epilepsy another front-line option.

"In principle, we could improve its therapeutic profile—it also has the potential to tell us more about how these receptors contribute to basic mechanisms underlying epilepsy," Swanson said.

More information: Sakiko Taniguchi et al, The antiseizure drug perampanel is a subunit-selective negative allosteric modulator of kainate receptors, *The Journal of Neuroscience* (2022). DOI: 10.1523/JNEUROSCI.2397-21.2022

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