

## Isovaline, a compound first identified in the Murchison meteorite, shows potential for treating Epilepsy

Epilepsy is a brain disease that affects 65 million people worldwide and is characterized by seizures that arise from hyper-active and hyper-connected brain cells. Typically, the first approach for managing seizures is treating individuals with pharmaceuticals. However, approximately 30% of individuals with Epilepsy do not respond effectively to drug treatment and many of these people have temporal lobe epilepsy. Therefore, the need to develop new drugs with better efficacy is an unmet need and has clear clinical utility.

In this study, the authors expand on their 2011 research paper which identified a novel compound called isovaline which may have potential to serve as an effective drug treatment for Epilepsy. Interestingly, this compound was first discovered in the Murchison meteorite that landed in Australia in 1969. Since isovaline has a similar chemical structure to gamma-aminobutyric acid (GABA), a common compound in the brain that inhibits brain activity, the study examined whether isovaline could attenuate seizures. To test this, rat brain slices containing the hippocampus and other temporal lobe structures were perfused with chemo-stimulants to elicit seizure-like events to mimic seizures occurring in temporal lobe epilepsy in humans.

Electrophysiological recordings were obtained in the hippocampus, which showed that isovaline could prevent or significantly reduce seizure-like events. This was accomplished by increasing activity specifically in brain cells of the hippocampus called interneurons which are responsible for controlling hippocampus excitability. A key finding was that isovaline effects became more pronounced and increased interneuron activity more robustly when these cells already had very active baseline activity. This suggests that isovaline-mediated control of hippocampus activity would likely occur when interneurons became more excited during seizures and would not affect normal hippocampal function such as memory and spatial navigation when normal interneuron activity took place. While the findings are exciting and point to a novel compound that decreases seizures in a unique manner, the experiments were conducted in brain slices and left open the question about its validity in intact seizing animals. Therefore, the present study investigated whether isovaline had anti-epileptic efficacy in a commonly used rat model of temporal lobe epilepsy.

Rats were administered a chemical called pilocarpine to elicit seizures in the hippocampus and other temporal lobe structures. Epileptiform activity was recorded in this area and also from the opposite part of the brain in the cortex to unmask when temporal lobe seizures evolved into generalized seizures that affect many brain areas. Pilocarpine caused generalized seizures to emerge 20 minutes after administration that lasted 37 seconds and recurred every 14 minutes. Isovaline was administered intravenously, which completely abolished hippocampal and cortex epileptiform activity 22 minutes later. Behavioral seizures were assessed using the Racine scale which characterizes seizure severity from 0 to 5 with generalized seizures denoted as 4 or 5 and the absence of seizures as 0. The authors administered isovaline in two ways. In one experiment,

isovaline was given 1 hr before pilocarpine treatment. Rats without isovaline had a Racine score of 5. In contrast, rats given isovaline before pilocarpine exhibited a Racine score of 0. In the other approach, isovaline was given after generalized seizures persisted for 90 minutes. Similar to findings in the first approach, isovaline reduced seizure severity from 5 to 0.

In conclusion, isovaline was first identified in the Murchison meteorite and can reduce seizures that begin in the temporal lobe. Although further work is needed to assess safety and tolerability considerations from acute and chronic isovaline administration and a better understanding is needed about its unique effects on interneuron activity, there is exciting potential for this compound as a novel type of drug treatment for Epilepsy.

## **Publication**

[Isovaline attenuates generalized epileptiform activity in hippocampal and primary sensory cortices and seizure behavior in pilocarpine treated rats.](#)

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*Neurosci Lett.* 2015 Jul 10