Neuroscience has irrefutably established NPY mutation as the primary cause of epilepsy. With that said, however, the fact that NPY interacts with pancreatic polypeptide (PP) and PYY has not been pursued as a causal path for epilepsy if their intersections are disrupted.

The thread of documents affixed to this article can be used by qualified computational biologists to verify how NPY is mutated.

https://neurosciencenews.com/peptide-epilepsy-brain-tissue-15426/

Peptide reduced epileptic seizures in human brain tissue

NEUROSCIENCE NEWSJANUARY 8, 2020

Summary: *The neuropeptide NPY reduces seizures in human brain tissue.*

Source: *Lund University*

Researchers at Lund University in Sweden have used a neuropeptide to successfully reduce seizure-like activity in tissue from patients with drug-resistant epilepsy.

One challenge facing researchers who study brain diseases is that for understandable reasons it is difficult to obtain human brain tissue for experiments. For that reason, experimental models are used, such as rodent studies, but one problem is that these often cannot be directly translated to human conditions.

However, sometimes researchers get the opportunity to study donated brain tissue from patients who have undergone surgery for the treatment of epilepsy. The tissue can then be used to investigate if it is possible to affect the seizure-like activity, and try new treatments. However, this resected tissue rapidly loses its viability.

Just over a year ago, researchers at Lund University in Sweden developed a method that solves this problem, making it possible to keep and use human brain sections alive in a more standardised way. The result is that donated brain tissue can be studied for 48 hours, compared with the previous 12. This longer period means, among other things, that the researchers can study the effect of different gene therapy treatments on the tissue, and that more data is obtained from a small number of patients.

“This provides a unique opportunity to test new treatments, as we get so close to the actual condition in the patient, without conducting the experiment directly on the patient”, says My Andersson, who leads a research team at the Epilepsy Centre at Lund University and who led the development of the method.

The researchers have now used this method to test a neuropeptide, NPY, which in previous rodent studies was shown to alleviate seizures in a drug-resistant variant model of epilepsy, a form of the disease that cannot be treated with available medicines.

“We saw that the neuropeptide also reduced seizures in human brain tissue, which is an important step forward”, says Merab Kokaia, professor and leader of the peptide study at Lund University.

The neuropeptide helps to maintain the balance, homeostasis, in the brain, which among other things means that the peptide is released during an epileptic seizure and can reduce it – acting like a circuit breaker.

“What we want to do now is to see if we can use gene therapy to insert an extra gene for the peptide in affected patients and thereby reduce the excitability that leads to the epileptic seizures”, explains Merab Kokaia.

The idea is to use viral vectors to deliver the gene for the neuropeptide in order to treat the area in which the epilepsy arises. The genetic material of the viruses is emptied and replaced with the gene that produces the neuropeptide. The researchers hope that these viral vectors can deliver the gene that produces the neuropeptide to the right place in the brain – a bit like a Trojan horse.

“There is still a long way to go before we know if it works well enough so that the peptide can be used as a treatment for drug-resistant patients, but as we have now seen that it works in human epileptic tissue and in gene therapy studies in animals, we have reason to continue working on this track”, says Merab Kokaia.

The method that enables the brain tissue to live longer could be used by other researchers to validate if other promising molecules have the same effect in human brain tissue as they have in laboratory tests.

“In this way, the tissue that researchers get access to, thanks to donations from epilepsy patients who have undergone surgical treatment, can be used to validate treatments established in other animal studies in which an effect against epileptic seizure has been observed. If positive results are also seen in human epileptic tissue, there is then a greater confidence for advancing towards the very expensive and extensive clinical studies”, concludes Merab Kokaia.

ABOUT THIS NEUROSCIENCE RESEARCH ARTICLE

Source:
Lund University
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Original Research: Open access
"Disease Modification by Combinatorial Single Vector Gene Therapy: A Preclinical Translational Study in Epilepsy". Merab Kokaia et al.
Molecular Therapy Methods & Clinical Development doi:10.1016/j.omtm.2019.09.004.

Abstract

Disease Modification by Combinatorial Single Vector Gene Therapy: A Preclinical Translational Study in Epilepsy

Gene therapy has been suggested as a plausible novel approach to achieve seizure control in patients with focal epilepsy that do not adequately respond to pharmacological treatment. We investigated the seizure-suppressant potential of combinatorial neuropeptide Y and Y2 receptor single vector gene therapy based on adeno-associated virus serotype 1 (AAV1) in rats. First, a dose-response study in the systemic kainate-induced acute seizure model was performed, whereby the 1012 genomic particles (gp)/mL titer of the vector was selected as an optimal concentration. Second, an efficacy study was performed in the intrahippocampal **kainate chronic model** of spontaneous recurrent seizures (SRSs), designed to reflect a likely clinical scenario, with magnetic resonance image (MRI)-guided focal unilateral administration of the vector in the hippocampus during the chronic stage of the disease. The efficacy study demonstrated a favorable outcome of the gene therapy, with a 31% responder rate (more than 50% reduction in SRS frequency) and 13% seizure-freedom rate, whereas no such effects were observed in the control animals. The inter-SRS and SRS cluster intervals were also significantly prolonged in the treated group compared to controls. In addition, the SRS duration was significantly reduced in the treated group but not in the controls. This study establishes the SRS-suppressant ability of the single vector combinatorial neuropeptide Y/Y2 receptor gene therapy in a clinically relevant chronic model of epilepsy.

Note: The document affixed to this article was prepared using quantum biology to discuss kainate as the near certain primary factor for epilepsy when its epigenetic is "fused" into a kinase.

This thread of documents has been prepared for discussion with qualified computational biologists to enable then to perform a DIY exercise from which the causal path of epilepsy outlined in this document can be modified/enhanced to resolve the heretofore mysteries of epilepsy beyond merely focusing on NPY.

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It is essential to note that existing research establishes irrefutable links between neuropeptide Y and epilepsy.

Mention of valproate as a drug treatment option for epilepsy as noteworthy because it supports our quantum biology model that identified NPY abnormalities as a factor for epilepsy.

The following is provided for discussion with qualified computational biologists.

Valproic Acid (aka NPY)

Quantum Biology has identified valproic acid as heretofore having been identified as NPY (the neuropeptide derived from the neurosteroid cortisol).

Subjected to autophagy, the following constituents of brain derived neurotrophic factor BDNF) have been verified as byproducts of valproic acid:

- Valparin - serotonin
- Valproate - oxytocin
- Valeric Acid (aka pentanoic acid) - prolactin

Valproic acid has been identified as a source for auto-brewery syndrome.

For discussion;

The BDNFs are byproducts of the neuropeptide pancreatic polypeptide (PP). The following must be addresses are factors for the underlying causes of auto-brewery syndrome:

- ✓ It the cause the mutation of PYY and the inability to disassemble NPY and PP

- ✓ Is the transposition of the NUP98 DNA binding into catabolic activity being prevented by mutation of allopregnanolone
- ✓ A TBD cause of the aggregation of BDNF to form kinase-like iteration with auto-brewery syndrome being an outcome.

Note: The constituents of valproic acid should be used as pharmaceutic strategies in behavioral health.

https://medicalxpress.com/news/2019-11-anti-seizure-drugs-equally-effective-severe.html

NOVEMBER 27, 2019

Study finds three anti-seizure drugs equally effective for severe form of epilepsy

by National Institutes of Health

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There are three treatment options commonly used by doctors in the emergency room to treat patients with refractory status epilepticus, severe seizures that continue even after benzodiazepine medications, which are effective in controlling seizures in more than two-thirds of patients. New findings published in the *New England Journal of Medicine* reveal that the three drugs, levetiracetam, fosphenytoin, and **valproate,** are equally safe and effective in treating patients with this condition. The study was supported by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

"Doctors can be confident that the particular treatment they choose for their patients with status epilepticus is safe and effective and may help them avoid the need to intubate the patient as well as stays in the intensive care unit," said Robin Conwit, M.D., NINDS program director and an author of the study. "This was a truly collaborative, multidisciplinary study that involved pediatricians, emergency medicine doctors, neurologists, pharmacologists, and biostatisticians all contributing their expertise."

In the Established Status Epilepticus Treatment Trial (ESETT), led by Robert Silbergleit, M.D., professor at the University of Michigan, Ann Arbor; Jordan Elm, Ph.D., professor at Medical University of South Carolina; James Chamberlain, M.D., professor at George Washington University; and Jaideep Kapur, M.B., B.S., Ph.D., professor at the University of Virginia, more than 380 children and adults were randomized to receive

levetiracetam, fosphenytoin, or valproate when they came to the emergency room experiencing a seizure. The researchers were trying to determine which of the anticonvulsant drugs was most effective in stopping seizures and improving a patient's level of responsiveness within 60 minutes of administering treatment.

The results showed that the three drugs stopped seizures and improved responsiveness in approximately half of the study participants. Specifically, these benefits were seen in 47% of subjects in the levetiracetam group, in 45% of participants in the fosphenytoin group and in 46% of subjects in the valproate group. These differences were not statistically significant.

There were no differences in serious side effects among the drugs.

"Our study suggests that clinical outcomes are driven by factors other than drugs. Differences in how doctors decide to treat status epilepticus, such as when they give more drugs or when to anesthetize patients and put them on a mechanical ventilator, may be more important than the specific treatments used to control seizures in patients," said Dr. Silbergleit.

The study was stopped early when a planned interim analysis found that the drugs were equally safe and effective.

ESETT researchers utilized a clinical trial design known as response adaptive randomization to improve the study's efficiency and maximize the chances of identifying the best treatment. The study used an algorithm to determine which drugs patients would receive based on accumulating trial data.

"Using an innovative design for this clinical trial, we were able to answer this important question in a timely and cost-effective manner," said Dr. Kapur. "In addition, this design lowered risk by reducing the chances that participants could have received what might have been determined to be the least effective treatment."

Status epilepticus is characterized by individual seizures or multiple seizures close together lasting more than five minutes, with a loss of consciousness. If not treated, it can lead to severe brain damage or death. Benzodiazepines are the first line of treatment for status epilepticus and are effective in two-thirds of patients. Refractory status epilepticus occurs in those patients in whom benzodiazepines do not stop their seizures.

Additional research is needed to prevent refractory status epilepticus and to find treatment options for the patients whose seizures do not respond to the three drugs investigated in this study.

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Kainate Activity

Using quantum biology as a foundation, the following near certain variables have been compiled for discussion/consideration with qualified computational biologists.

- SMN1 - SMN2 and SNRPC constitute the kainate trefoil with SNRPC being the modulator (enzymatic activity)
- Numerous alterative designative designations have evolved but iterations of Kv2.1, Kv2.2 and Kv2.3 should suffice.
- Mutation of kainate (fusion) into a kinase is the near certain primary cause for epilepsy with the activity exists within the glial cells of the hippocampus.

Note: Discussions relative to the MCIP theories to mitigating such kinase configurations without drugs can be help with quantum biology partners.