[c]University College London, London, United Kingdom
[d]Aarhus University, Aarhus, Denmark
[e]Philipps University Marburg, Marburg, Germany
[f]Goethe University Frankfurt, Frankfurt am Main, Germany
[g]University Medical Center Utrecht, Utrecht, Netherlands

Background: MicroRNAs are short noncoding RNAs that shape the gene expression landscape, including during the pathogenesis of temporal lobe epilepsy. *In vivo* deployment of oligonucleotide inhibitors, termed antagomirs, has been successful in demonstrating functional roles for several microRNAs in epilepsy models. It is unknown, however, what portion of brain-expressed microRNAs are functionally engaged or whether additional microRNAs may be targets for seizure control.

Methods: Here we sequenced Argonaute 2-loaded microRNAs in the hippocampus from three different animal models, in two species and across multiple time-points, to identify unique and shared functional microRNA changes in experimental status epilepticus. We used this to rationally inform target microRNAs for seizure suppression and tested them using antisense oligonucleotides (antagomirs) in the mouse intra-amygdala kainate model. Finally, we used electrophysiological techniques to probe the mechanistic effects of these antagomirs in naïve rodent brain.

Results: We identified over 400 Argonaute 2-loaded microRNAs in each model and found levels of almost half changed in epilepsy. We selected microRNAs that were commonly upregulated in all three animal models and performed a systematic antagomir screen which identified anti-seizure phenotypes upon inhibition of miR-10a-5p, miR-21-5p and miR-142-5p. We assessed effects of these antagomirs on network, synaptic and biophysical properties of rodent hippocampi and identified mechanisms using a target capture sequencing assay.

Conclusions: Together, these studies provide a comprehensive cataloguing of the functional microRNA in the hippocampus and a pipeline of new targets for seizure control in experimental epilepsy. Antagomir based therapies represent a highly promising new disease-modifying therapy for epilepsy, which can suppress seizures with seemingly limited off-target effects.

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Efficacy of Intranasal Allopregnanolone in a Mouse Seizure Model

Dorota Zolkowska, Michael A. Rogawski
University of California, Davis, School Of Medicine, Sacramento, United States

Intranasal delivery (IN) is a noninvasive, efficient and safe route for drug administration that may circumvent poor gastrointestinal bioavailability. The IN route is increasingly being investigated for drugs intended to treat neurological disorders because of the potential that drugs deposited into the nasal cavity may be transported directly to the brain along the olfactory and trigeminal nerves. Allopregnanolone (5α,3α-P), an endogenous neurosteroid that acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors, is currently under evaluation as a treatment for status epilepticus. 5α,3α-P exerts antiseizure activity in various animal seizure models, including models of status epilepticus. 5α,3α-P protects against seizures when administered intravenously or intramuscularly, but it is not active orally. The objective of this study was to determine if 5α,3α-P has antiseizure activity when administered by the IN route.

Solutions of 5α,3α-P (15 mg/ml) were prepared in 40% sulfobutylether-β-cyclodextrin sodium salt in 0.9% saline. Seizures were induced in mice with pentylenetetrazol (PTZ; 80 g/kg IP). 5α,3α-P solution (6 & 10 mg/kg) or vehicle was administered IN 5, 10 and 15 min prior to administration of the PTZ. Animals were observed for 30 min following PTZ. The times to onset of myoclonic body twitches and clonic and tonic seizures were recorded. 5α,3α-P was considered to have antiseizure activity if it delayed the onset of seizure signs in comparison with the time of their occurrence in vehicle-treated animals.

5α,3α-P 6 mg/kg administered IN delayed the time to onset of all seizure signs with a pronounced effect on tonic hindlimb extension. At 10 mg/kg in addition to a delay in seizure signs, some animals were protected from tonic hindlimb extension and mortality. Delay in seizure signs was evidenced when 5α,3α-P was administered 5 min before PTZ but at 15 min it was less active, indicating a short acting effect.

Our results for the first time demonstrate that 5α,3α-P solubilized with a cyclodextrin excipient exhibits antiseizure activity when administered into the nose. In the model test system we used, 5α,3α-P acted rapidly to delay seizure onset and improve survival. Delivery by the IN route may allow 5α,3α-P to be conveniently and atraumatically administered by a non-medically-trained caregiver to abort ongoing seizures.

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Anticonvulsant and Neuroprotective Effects of Delayed Treatment with Midazolam in a Rodent Model of Organophosphate Exposure

Jay Spampanato, Wendy Pouliot, Bonnie Roach, Melissa Smolik, F. Edward Dudek
University Of Utah, Salt Lake City, United States

Background: Exposure to organophosphates (OP) can cause status epilepticus (SE) and irreversible neural injury. Rapid control of seizure activity is important to minimize central nervous system injury and the subsequent development of neurological and behavioral disorders. Although the standard-of-care for OP-induced SE is administration of benzodiazepines, the anticonvulsant effect of these agents has been reported to decrease as the duration of SE is prolonged. However, the effect of delayed treatment with midazolam (MDZ) on electrographically recorded seizures and subsequent neuronal death resulting from OP-induced SE has not been studied quantitatively as a function of time.

Methods: Male, Sprague Dawley rats (150-200 g) were implanted with electrodes for recording of the electroencephalogram (EEG) 1 week prior to the testing. On the day of treatment, SE was induced by administration of diisopropyl fluorophosphate (DFP). At 30, 60 or 120 min after the start of SE, rats were administered MDZ (2 mg/kg). EEG was recorded for 24 hr, at which time the rats were perfused, and the brains were sectioned and labeled with Fluoro-Jade B (FJB).