Targeting hippocampal GABA neurons to produce a model of cryptogenic temporal lobe epilepsy.

Epilepsy

Animal Model

Chun *et al. Epilepsia* (2019)

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Announcing a new animal model for temporal lobe epilepsy (TLE), the most common form of human epilepsy. Up to now, current models and derivatives of current models show manifold problems. These problems begin with the variety of models being used, such that results can become confounded and conflicting. There are data variations because existing models do not properly demonstrate the actual TLE present in humans. The vast majority of animals given pilocarpine or kainate systemically to induce prolonged status epilepticus (SE) exhibit extensive extrahippocampal damage, widespread brain damage, but inconsistent hippocampal damage. Animal death is prominent often at a high percentage.[1] Prolonged SE does not occur in human epilepsy. Use of optogenetic and Cre variations obfuscate the situation and are, of course, tremendously expensive.[2] See table for a comprehensive review of current models and their lack of similarity to human epilepsy.[3]

TLE can be caused genetically, but often is the result of an "initial precipitating injury" in the hippocampus that causes a loss of inhibitory mechanisms and an abnormal epileptic state. To state things simply, the loss of inhibitory neurons can result in an epileptic state in which non-inhibited excitatory neurons can give rise to seizures. Up to this time, the markings of human epilepsy have not been present in animal models.

We now introduce an animal model that:

- *Has close histological and behavioral similarities to human epilepsy*
- *Does not show continued SE, as is the case in humans*
- *Results in spontaneous seizures, just as occurs in humans*

The model is incredibly fast, easily reproduced, non-lethal, and results in rats that exhibit normal behavior patterns with the exception of their seizures. Injections of SSP-SAP into the hippocampus of a rat causes acute hippocampal injury, permanent dentate granule cell-onset epilepsy, and hippocampal sclerosis that closely resembles the selective hippocampal pathology exhibited by patients diagnosed with TLE. The rats are chronically epileptic.[4]

ADVANCED TARGETING SYSTEMS

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References

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Summary of TLE Models*

Model	Induction	Manifestations	Human relevance	Use	Limitations
TARGETED TOXINS					
SSP-SAP (Substance P – Saporin) ***Epilepsy@atsbio.com***	Intrahippocampal micro-injections	No SE. No deaths. Chronic focal motor seizures established in 2 weeks; lasting at least 240 days.	TLE with hippocampal sclerosis	AeD screening, mechanisms of epileptogenesis	Subtle behavioral seizures. Electrode implantation with digital depth recording data and video files recommended.
CHEMOCONVULSANTS					
KA-Se	Systemic or intrahippocampal injection	Limbic Se and chronic seizures	TLE with hippocampal sclerosis	AeD screening, mechanisms of epileptogenesis	High mortality; variable frequency and severity of spontaneous seizures; not all neural damage comes from seizures
Pilo-Se	Systemic or intrahippocampal injection	Limbic Se and chronic seizures	TLE with hippocampal sclerosis	AeD screening, mechanisms of epileptogenesis, and cognitive/psychiatric comorbidities	High mortality; variable frequency and severity of spontaneous seizures; neocortical lesions
BRAIN PATHOLOGY					
Hyperthermic seizures	increase of body temperature in immature rodents through stream of heated air	immobility, facial automatism, myoclonic jerks	Febrile seizure	epileptogenesis mechanisms and cognitive consequences	Subtle behavioral seizures, necessity of eeG recording, possible morbidity from heat exposure
Hypoxia model	exposure to air with low O2 concentration in immature rodents	Brief and repetitive tonic-clonic seizures	Neonatal hypoxic encephalopathy	AeD screening, long- term consequences, and epileptogenesis mechanisms	Susceptibility for seizures varies with the strain and age of rodents
Posttraumatic epilepsy	Rostral parasagittal fluid percussion injury	Generalized tonic-clonic seizures in the long term, with low frequency	Posttraumatic epilepsy	AeD screening, mechanisms of epileptogenesis, and hippocampal sclerosis with dual pathology	Laborious induction, long latency periods, mild seizures during the first 4 months posttrauma
GENETIC MODELS					
Audiogenic models	Acoustic stimulation in genetically prone rats	wild running and tonic-clonic seizures	Reflex epilepsy and TLE studies	epileptogenesis mechanisms and comorbidities associated with epilepsies	Necessity of a trigger to evoke seizures; lack of spontaneous recurrent seizures
GAeRS, wAG/Rij, and mouse models of absence seizures	Spontaneous seizures	SwD generalization, behavioral arrest	Generalized idiopathic epilepsies	electrographic and behavioral similarity to human absence seizures, response to AeDs	Diverse (and not fully known) genetic alterations
Abbreviations: KA, kainic acid; Se, status epilepticus; TLE, temporal lobe epilepsy; AeD, antiepileptic drugs; Pilo, pilocarpine; PTZ, pentylenetetrazol; eeG, electroencephalography; GAeRS, Genetic Absence epilepsy in Rats from Strasbourg; wAG/Rij, wistar Albino Glaxo/Rijswijk rats; SwD, spike-and-wave discharges.					

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