Experimental models of epileptogenesis

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A Babylonian tablet in London's British Museum dating from approximately 1060 BC refers to epilepsy as "the falling disease," with the subjective aura and the subsequent seizures themselves ascribed to the work of childless demons who view humans with envy and spite.

Support: NIH / NINDS

Seizure models are predictive for anticonvulsant development

Drug	Antiseizure effect in rats or mice on: MES, generalized tonic seizures	PTZ, generalized clonic seizures	Amygdala kindled focal and/or secondarily generalized tonic-clonic seizures	Spontaneous focal and/or secondarily generalized seizures in post-SE models	Effect on focal epilepsy in patients
Benzodiazepines	+	+	+ (but tolerance)	+	+ (but tolerance)
Brivaracetam	+	+	+		+
Carbamazepine	+	NE	+[a]	+	+
Eslicarbazepine acetate	+	NE	+		+
Ethosuximide	NE	+	NE	NE	NE
Felbamate	+	+	+[a]		+
Gabapentin	+	+	+[a]		+
Lacosamide	+	NE	+[b]		+
Lamotrigine	+	NE	+[a]	+[a]	+
Levetiracetam	NE	NE	+	+[a]	+
Oxcarbazepine	+	NE	+		+
Perampanel	+	+	+		+
Phenobarbital	+	+	+[a]	+[a]	+
Phenytoin	+	NE	+[a]	+[a]	+
Pregabalin	+	+	+[b]	+	+
Primidone	+	+	+		+
Retigabine/ezogabine	+	+	+		+
Tiagabine	NE	+	+	+	+
Topiramate	+	NE	+[a]	+	+
Valproate	+	+	+[a]	+	+
Vigabatrin	NE	+	+[a]	+	+
Zonisamide	+	NE	+		+

Klein et al. 2018

Disclosures

None

But are NOT predictive for antiepileptogenesis development

First 47 attempts to prevent epileptogenesis

Rationale
- "Seizures beget seizures"
- Repeated seizures cause brain injury
- Therefore, anticonvulsants might prevent epilepsy in those at risk.

47 clinical trials to determine whether early treatment with diazepam, phenobarbital, valproate or phenytoin prevents the development of epilepsy after prolonged febrile seizures, brain tumor, craniotomy or traumatic head injury.

All 47 trials failed.

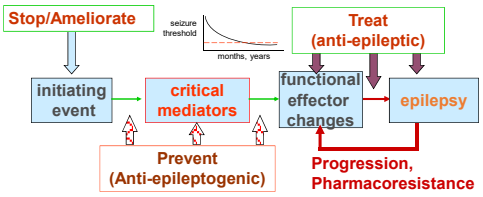
Preventive or disease-modifying Rx of common CNS disorders

Successes
- Infectious diseases, stroke, migraine

Failures (symptomatic treatments only)
- AD, bipolar, PD, schizophrenia, epilepsy, etc

Conclusions from the first 47 attempts

- Anticonvulsants suppress acute seizures but not epileptogenesis.
- The biology of epileptogenesis is likely to be quite different from the biology of the epileptic brain.
- New directions, and new animal models, are needed



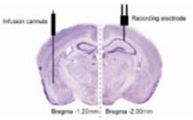
Framework for thinking about interrupting epileptogenesis

- Based largely on study of the Mendelian epilepsies and the common molecular targets of anticonvulsants, this disorder is often considered to be primarily a channelopathy, a disease caused by dysfunction of ion channels that control seizure threshold.
- However, for the much more numerous patients with *acquired* epilepsies, we must search for mechanisms that *create* ion channel dysfunction.

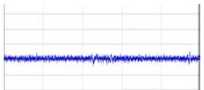
Key ideas

- Epilepsy is a disorder of chronically reduced seizure threshold.
- Identification of those proteins that regulate the expression level or functional state of the ion channels that control seizure threshold is the key to interrupting or attenuating epileptogenesis.
- Processes that regulate seizure threshold
  - Inflammation (microgliosis, astrogliosis)
  - Breakdown of blood-brain barrier
  - Synaptic plasticity

Mouse status epilepticus models of epilepsy



Intra-amygdala kainate
(1 nmole in 0.5 μl)



Mouse intrahippocampal EEG (starting 9 min after kainate injection)

Animal models of epilepsy

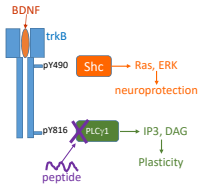
Chemically-triggered models
- Focal injections of tetanus toxin or aluminum gels
- De novo bout of status epilepticus
  - Systemic pilocarpine, kainate or organophosphates (eg DFP, soman)
  - Mouse intra-amygdala or intra-hippocampal kainic acid

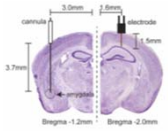
Etiologic models
- Head injury: fluid percussion, undercut cortex, focal Fe salts
- Infection: cerebral malaria, neurocysticercosis, Theiler's murine encephalitis virus
- Fever in immature rodents: febrile SE

Genetic models
- monogenic: SCN1A for Dravet's, TSC1 for tuberous sclerosis, etc
- GEPR (genetically epilepsy-prone rats), GAER (genetically absence epilepsy rats), beagles & baboons

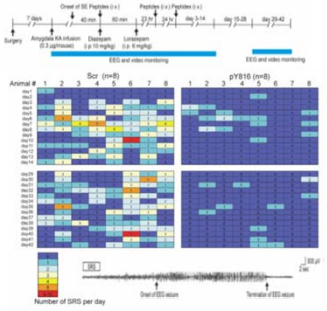
Predisposition to epilepsy (multi-hit models)
- Neonatal hypoxia followed by fluorothyl, PTZ, etc
- Prolonged febrile seizures in neonates

TrkB-PLCγ inhibitor is disease-modifying in mIAK model of SE



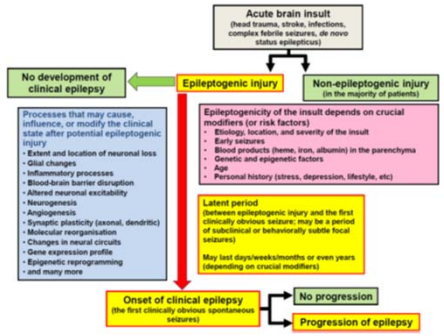


mIAK model



Gu,... McNamara Neuron 2015

Commonalities in development of epilepsy after brain insults

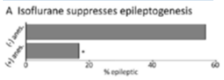


Klein et al. 2018

Isoflurane prevents epilepsy in rat SE models

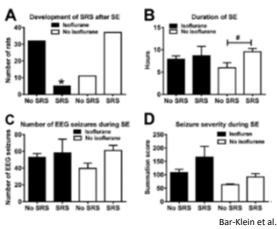
Paraoxon rat SE model

Paraoxon
↓
Midazolam
↓
Vehicle or
Isoflurane
(1% for 1 hr at
1,6,12hr; 1,2,3,7 days, 1 month)
↓
EEG 5-7 weeks later



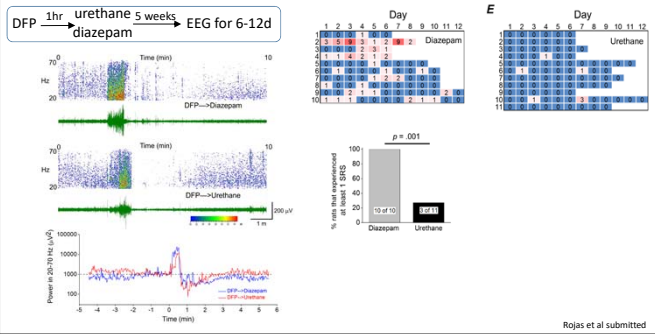
Rat intra-hippocampal kainate SE model

Isoflurane (1.5-2%) or vehicle for 2 hr
Intrahippocampal kainate injection
↓
EEG 5-12 weeks later



Bar-Klein et al., Ann Neurol. 2016

Preventive & disease-modifying effects of urethane in rat DFP SE model



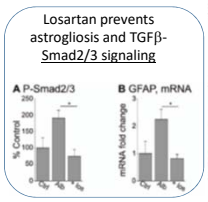
Rojas et al submitted

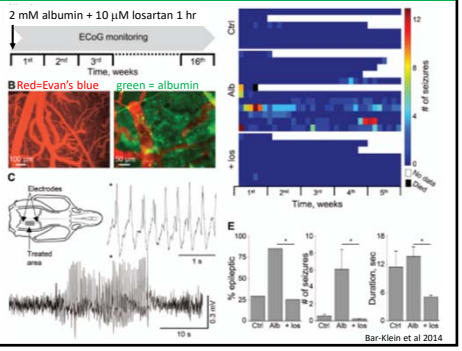
Summary and conclusions

- The biology of epileptogenesis is likely to be quite different from the biology of the epileptic brain.
- Acquired human epilepsies with different etiologies share some features with animal models: e.g., disrupted BBB, neuroinflammation.
- Several strategies have been shown to be effective in rodent SE models
  - Preventing overnight return of SE with isoflurane or urethane;
  - Interrupting trkB signaling through its PLCγ effector pathway;
  - Blunting inflammatory pathways mediated by IL-1β and TLR4;
  - Blocking TGF-β signaling to astrocytes with losartan (note: vascular injury model).
- These strategies should now be tested in models of head injury and infection.
- The diversity of molecular targets identified preclinically, and the likely multidimensional nature of epileptogenesis, together argue for a combinatorial strategy in prevention or disease-modification therapy.

Losartan prevents epilepsy in vascular injury rat model

Losartan prevents astrogliosis and TGFβ-Smad2/3 signaling

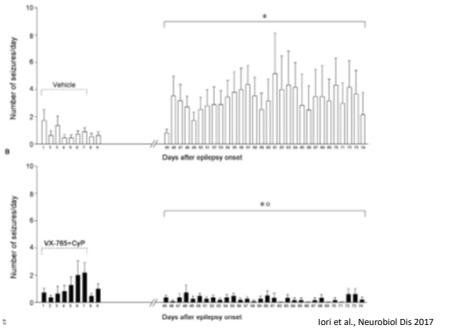




Bar-Klein et al 2014

Disease-modifying effects of inhibitors of caspase-1 and TLR4 inhibitors

Mouse
intra-amygdala kainate
↓
5.5 days
↓
Epilepsy onset
↓
Vehicle/drugs
For 7 days
↓
EEG throughout



Iori et al., Neurobiol Dis 2017