Alcohol Use Disorders and Seizure/Epilepsy

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ICARE
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NIAAA Workshop

Alcohol Consumption, Seizure and Epilepsy: Molecular, Cellular & Neural Circuit Mechanisms

RSA Satellite Meeting
Division of Neuroscience and Behavior, NIAAA, NIH

Saturday June 22, 2013
8:30 am – 4:30 pm

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NIAAA Workshop - Agenda

Morning
8:40 – 8:50  Dr. Qi-Ying Liu  Introduction
8:50 – 9:35  Dr. Helen E. Scharfman  The Neurobiology of Seizure and Epilepsy
9:35 – 10:15 Dr. David M. Lovinger  Synaptic Substrates of Alcohol Use- and Withdrawal-Induced Seizure and Epilepsy
10:30 – 11:15 Dr. Kari J. Buck  Genes & Neural Networks Underlying Seizure Susceptibility and Alcohol Withdrawal Seizure
11:15 – 11:55 Dr. Daniel D. Savage  Prenatal Alcohol Exposure and Seizure/Epilepsy Susceptibility

Afternoon
1:00 – 1:40  Dr. Prosper N'Gouemo  Ion Channels and Alcohol-Related Seizure and Epileptogenesis
1:40 – 2:20  Dr. Sally McIver  Glia in Seizure and Epileptogenesis
2:35 – 3:15  Dr. Richard W. Olsen  GABA_A Receptor Subunit Plasticity in Alcohol Use- and Withdrawal-Induced Seizure/Epilepsy
3:15 – 3:55  Dr. A. Leslie Morrow  Molecular Mechanisms of Alcohol Withdrawal-Induced CNS Hyperexcitability: the Role of Neuromodulatory Systems
3:55 – 4:30  Discussion and Summary
Alcohol Affects Virtually all Neurotransmission Systems
Concentration-Dependence of Alcohol Effects

(Ethanol Concentration (mM))

- Legal Limit for Intoxication
- Mild Intoxication
- Coma
- Death

(Modeled from Krystal et al., 2006)
Alcohol and GABAergic Synapse

1A. Binding of positive modulators to GABA\(_{\text{A}}\)Rs overstimulation.

1B. Within 1 hr, internalization of \(\delta\)-containing GABA\(_{\text{A}}\)Rs that bind to positive modulators (e.g., EtOH, \(\alpha4\beta\delta\)), leading to reduced tonic inhibition, hyperexcitability, acute tolerance.

2A. Within a few hrs, internalization of synaptic GABA\(_{\text{A}}\)Rs (e.g., \(\alpha1\beta\gamma2\)), leading to reduced synaptic inhibition, hyperexcitability, cross-tolerance to BZs.

2B. At the same time, increased biosynthesis of \(\alpha4\) and \(\gamma2\), as well as \(\alpha2\), \(\beta1\), and \(\gamma1\); assembly; trafficking to surface membrane.

3. Major increase in surface \(\alpha4\beta\gamma2\), including some synaptic localization, and \(\alpha2\beta1\gamma1\) (synaptic). Altered kinetics and pharmacology of mIPSCs, including EtOH sensitivity (due to \(\alpha2\beta1\gamma1\) and/or \(\alpha4\beta\gamma2\)).
Neurosteroids and Risk for Alcoholism

- Acute ethanol
- Chronic ethanol
- Innate alcohol tolerance

Neurosteroids

- Receptors/Channels
- Ethanol sensitivity
- Risk of excessive drinking
- Alcohol use disorders

- CNS response to stressors
- Probability of relapse

Effect of ethanol & stress on neurosteroids level
Inhibitory/Excitatory Balancing and Imbalance

GABAergic

Glutamatergic

Acute EtOH

Prolonged EtOH

EtOH withdrawal

Allostastic State

EtOH

Normal

Inhibition

Excitation

Normal

EtOH
Persistent Decrease in Seizure Threshold in CIE Rats after Cessation of Ethanol Treatment

Kokka, N. et al., A.C.E.R. 17: 525-531, 1993
Alcohol Withdrawal Seizures

- Partial seizures
- Generalized tonic-clonic seizures
- Status epilepticus

*There are still significant gaps in the mechanisms underlying neuronal hyperexcitability that leads to alcohol withdrawal seizures.*
Cellular Mechanisms of Seizure Generation

- **Excitation (too much)**
  - Ionic—inward Na⁺, Ca++ currents
  - Neurotransmitter—glutamate,

- **Inhibition (too little)**
  - Ionic—inward Cl⁻, outward K⁺ currents
  - Neurotransmitter—GABA
Inhibitory/Excitatory Imbalance as a Cause of Epilepsy

- Reduced numbers of GABAergic interneurons
- Increased recurrent excitatory circuitry
- Many other changes in GABA and glutamate
- Neurotransmission
- Gliosis
- Angiogenesis
- Proliferation of neurons that are abnormal
Three Stage Hypothesis for Acquired Epilepsy

Initial event          Latent period           Chronic period

Insult        Plasticity               Epilepsy

Genes, Development
Fetal Alcohol Syndrome

Stress
Alcohol withdrawal

Scharfman, Pedley (2006): The Neurobiology of Disease
Does prenatal ethanol exposure increase:

- Risk of developing epilepsy?

or

- Enhance seizure susceptibility?
Prenatal Ethanol Exposure & Risk of Epilepsy

| Prevalence in general population (all ages) | <1% |
| Prevalence in FAS or prenatal ethanol-exposed children: | |
| Olegaard et al., 1979 | 10% |
| Iosub et al., 1981 | 3% |
| Majewski & Goecke, 1982 | 12% |
| Spohr & Steinhausen, 1987 | 10% |
| O’Malley & Barr, 1998 | 21% |

Impression:
“Seizures are often found in children with FAS”
Early studies consisted mainly of case reports or small numbers of individuals, frequently the most severely affected patients

Abel, 1998 (Meta-analysis of 550 subjects) 3%
Bell et al., 2010 (Canadian Study – 425 subjects) 5.9%
Sun et al., 2009 (Danish Cohort – 80,526 subjects) 1.8 fold ↑

BUT, the perception among pediatric neurologists and clinical psychologists: “Epilepsy is not that common among patients with FASD”
Most severely affected children with FASD at greater risk of epilepsy

Link between fetal EtOH exposure & epilepsy may be EtOH dose-dependent
- No evidence suggesting low to moderate drinking linked to epilepsy
- Higher levels of consumption may lead to:
  - Neonatal withdrawal seizures
  - Febrile Seizures
  - Seizure episodes and/or Epilepsy

No clear indication of whether prenatal ethanol exposure is associated with specific seizure types.
Perinatal ethanol exposure may differentially affect seizure susceptibility in different animal models of epilepsy.

Interpretation of preclinical data across studies using similar models of epilepsy difficult, primarily due to:
- Variations in perinatal ethanol exposure paradigms (species, ethanol dose, timing of exposure)
- But also prospect of experimental confounds (malnutrition, maternal stress).

More moderate ethanol exposure does not appear to increase seizure susceptibility and may lower susceptibility in some cases.

Higher ethanol doses, delivered during critical periods of greatest neural susceptibility to ethanol’s cytotoxic effects appear more likely to lower seizure threshold.

Lack of systematic follow-up of initial observations to determine mechanisms underlying altered seizure susceptibility.
Alcohol use disorders (AUD) and epilepsy affect large numbers of Americans.
- AUD affects 18 million and costs an estimated $185 billion/year
- Epilepsy affects ~ 3 million Americans.

Chronic alcohol exposure induces complex adaptive changes in the CNS, allowing the brain to function in an allostatic state in the presence of alcohol.

Alcohol withdrawal reveals the hyper-excitable state and causes symptoms, including severe and life-threatening seizures, that often make quitting drinking difficult.

Alcohol abuse and withdrawal may decrease seizure threshold and increase frequency/severity of seizure in epilepsy patients (moderate and occasional drinking might be okay).

Meta-analysis found an association between alcohol consumption and epilepsy/unprovoked seizures.
High prevalence of epilepsy and seizure in patients with fetal alcohol spectrum disorders.

Risk factors:
- Genetic susceptibility
- Metabolic perturbations
- Cumulative effects and possible multiple organ damage including brain
- High total alcohol consumption, including binge drinking
- Repeated severe intoxication and withdrawal.
Thank You