



National Institute
on Alcohol Abuse
and Alcoholism

Alcohol Use Disorders and Seizure/Epilepsy

Qi-Ying Liu, M.D., M.Sci.
Program Director
Division of Neuroscience and Behavior
NIAAA, NIH

ICARE
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National Institute
on Alcohol Abuse
and Alcoholism

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

Contacts: Qi-Ying Liu: liuqiy@mail.nih.gov
Antonio Noronha: anoronha@mail.nih.gov



NIAAA Workshop - Speakers

Glia in Seizure & Epileptogenesis

GABA_AR Subunit Plasticity

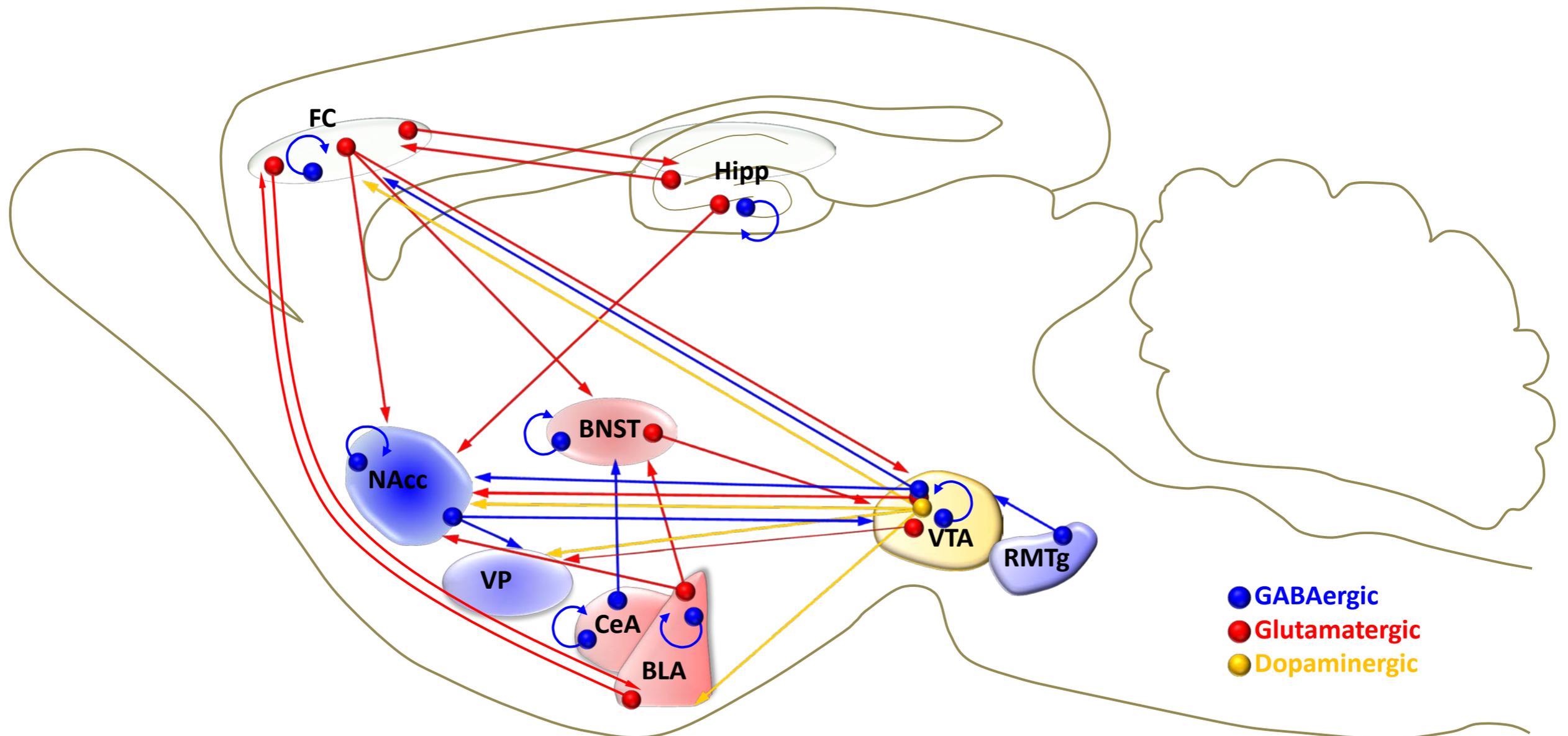
Morning

- 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

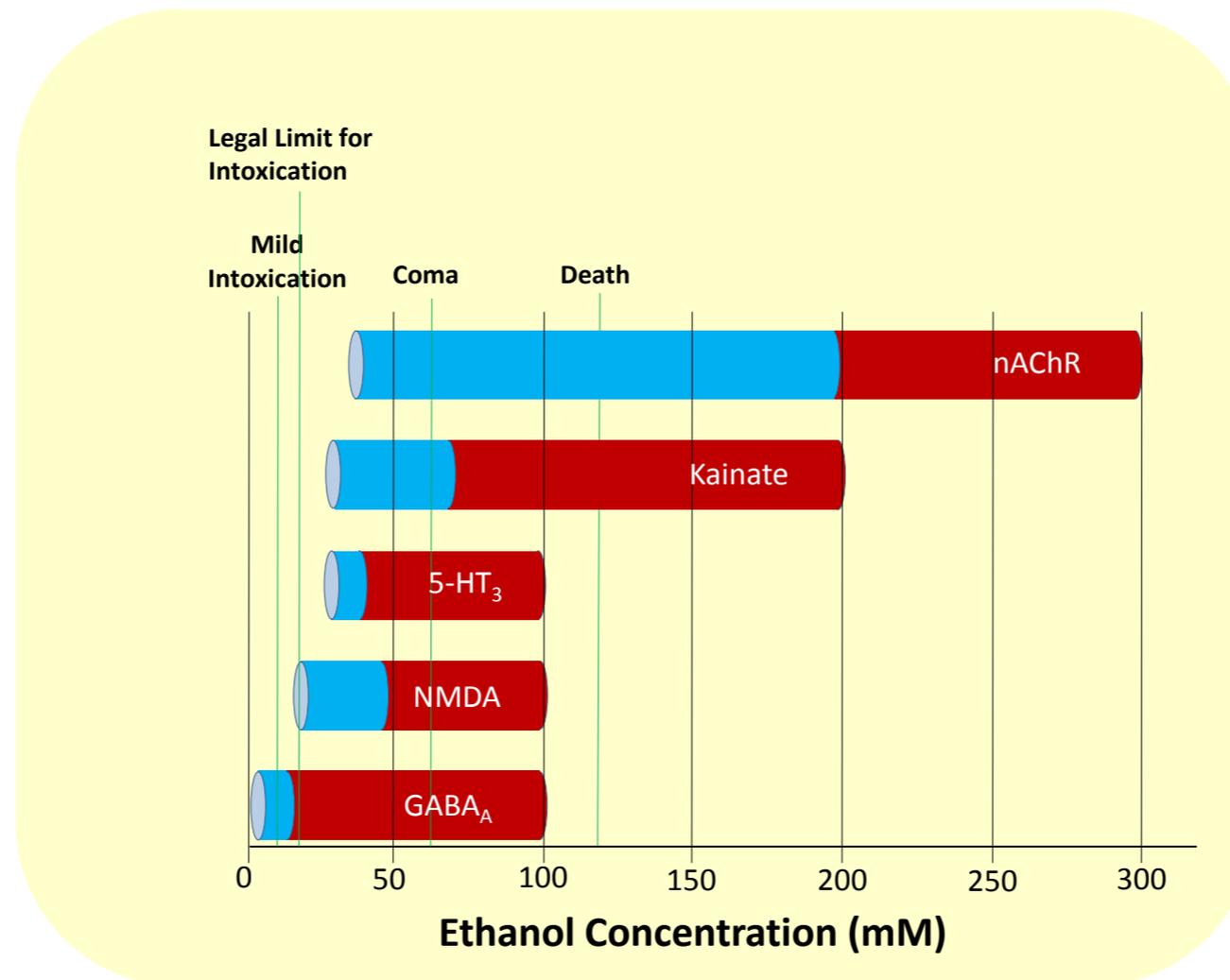
Afternoon

- 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**
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Alcohol Affects Virtually all Neurotransmission Systems

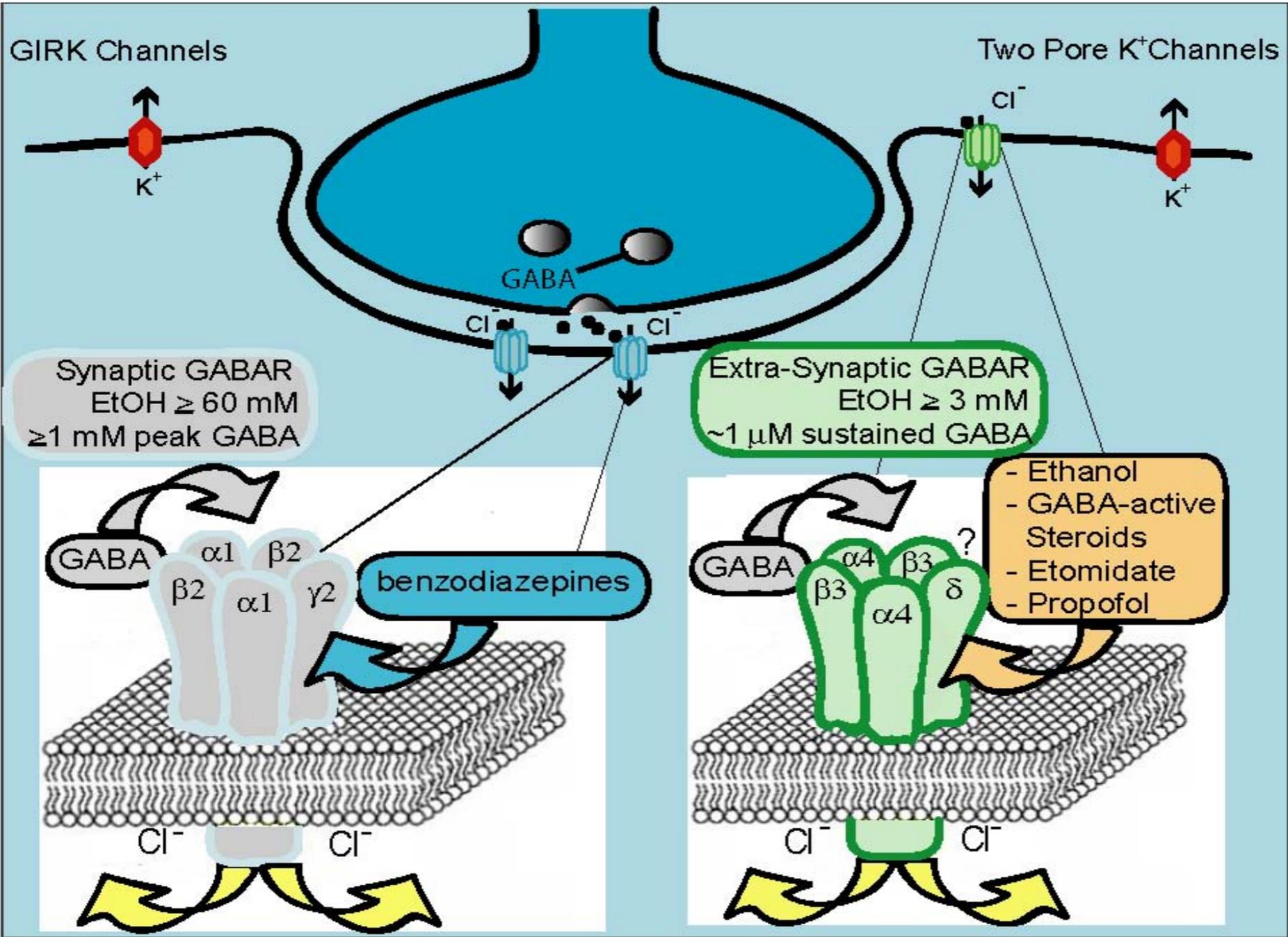


Concentration-Dependence of Alcohol Effects

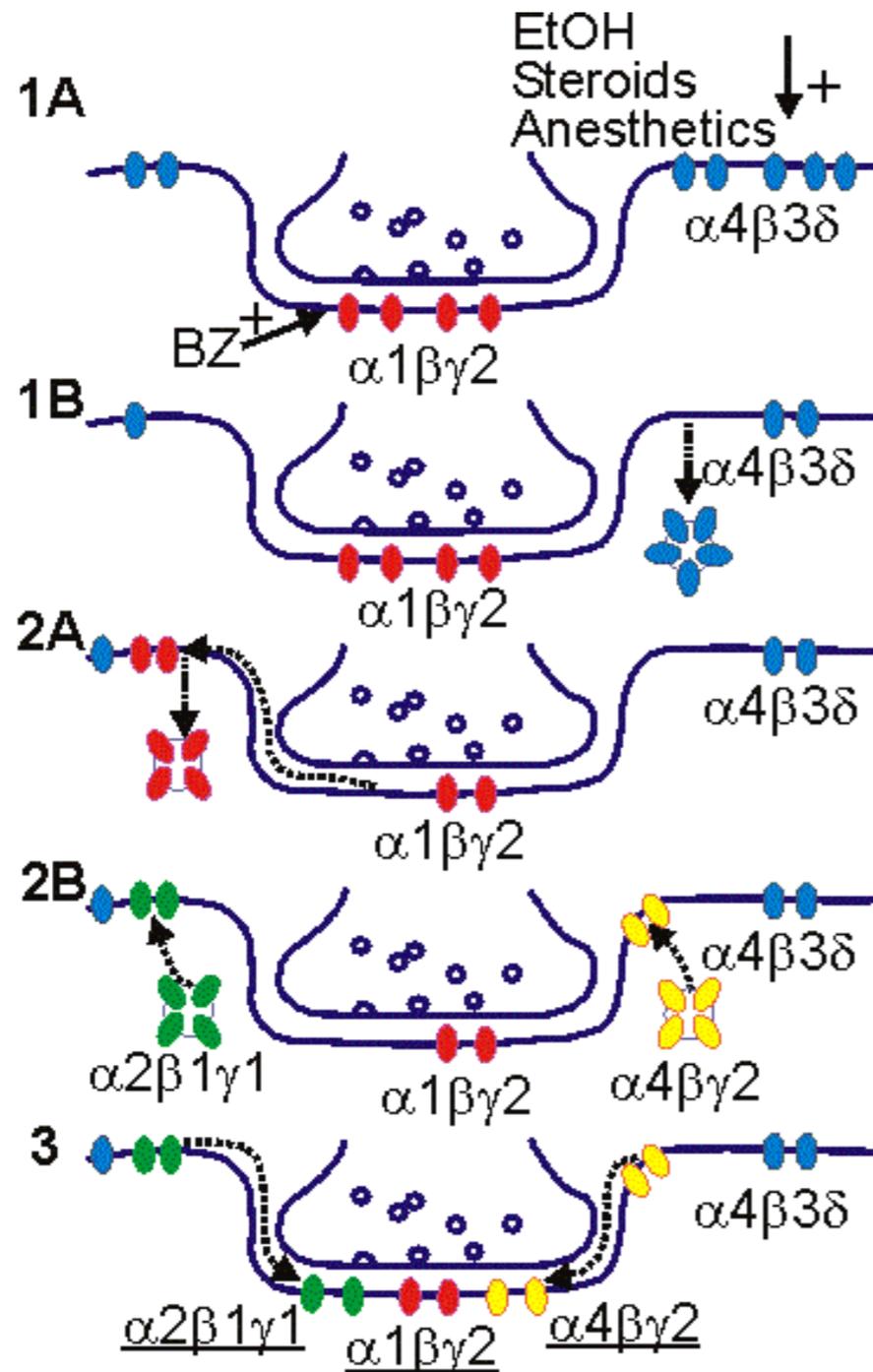


(Modified from Krystal *et al.*, 2006)

Alcohol and GABAergic Synapse



Wallner et al., PNAS (2003)



1A. Binding of positive modulators to GABA_ARs overstimulation.

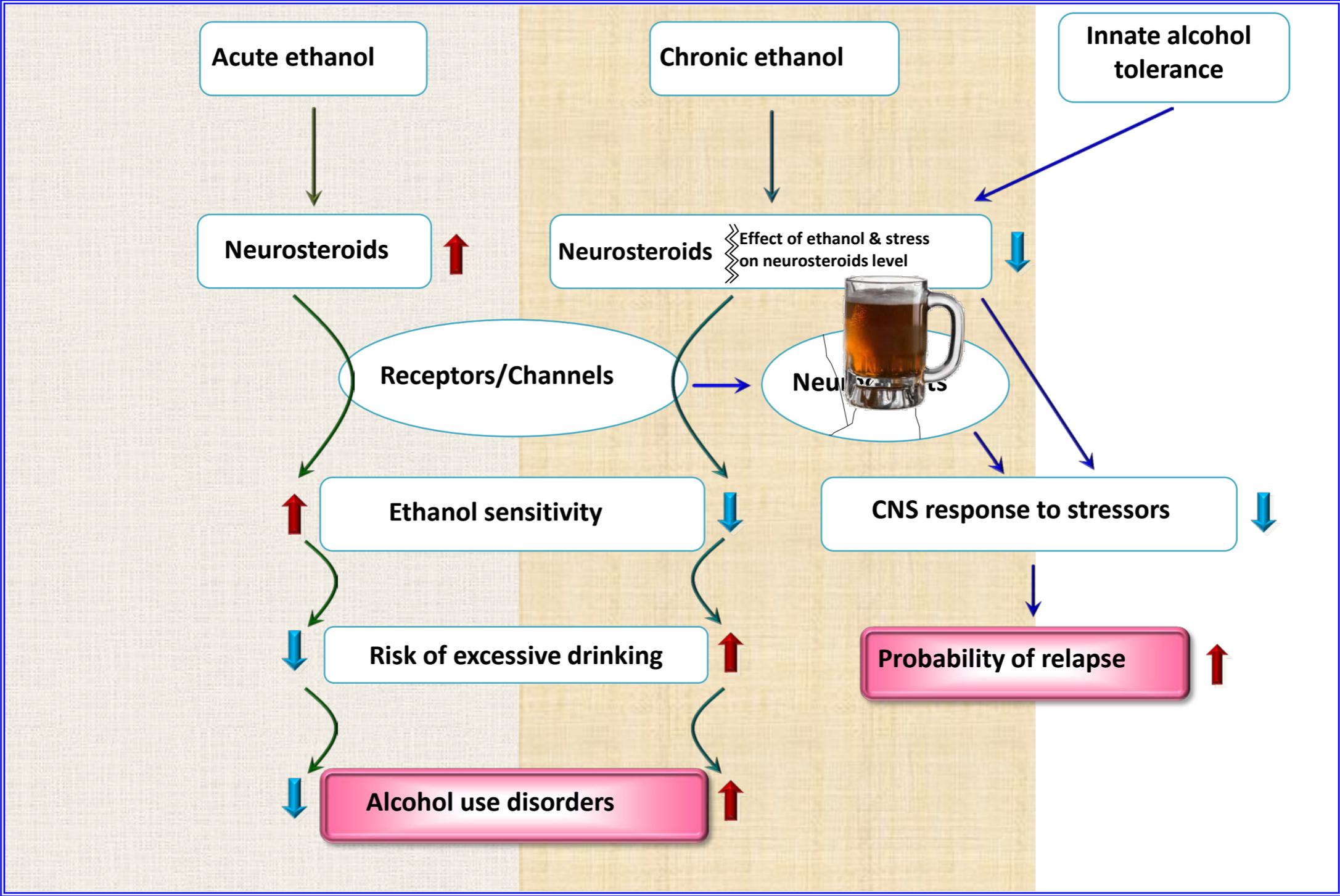
1B. Within 1hr, internalization of δ -containing GABA_ARs that bind to positive modulators (e.g., EtOH, $\alpha 4\beta\delta$), leading to reduced tonic inhibition, hyperexcitability, acute tolerance.

2A. Within a few hrs, internalization of synaptic GABA_ARs (e.g., $\alpha 1\beta\gamma 2$), leading to reduced synaptic inhibition, hyperexcitability, cross-tolerance to BZs.

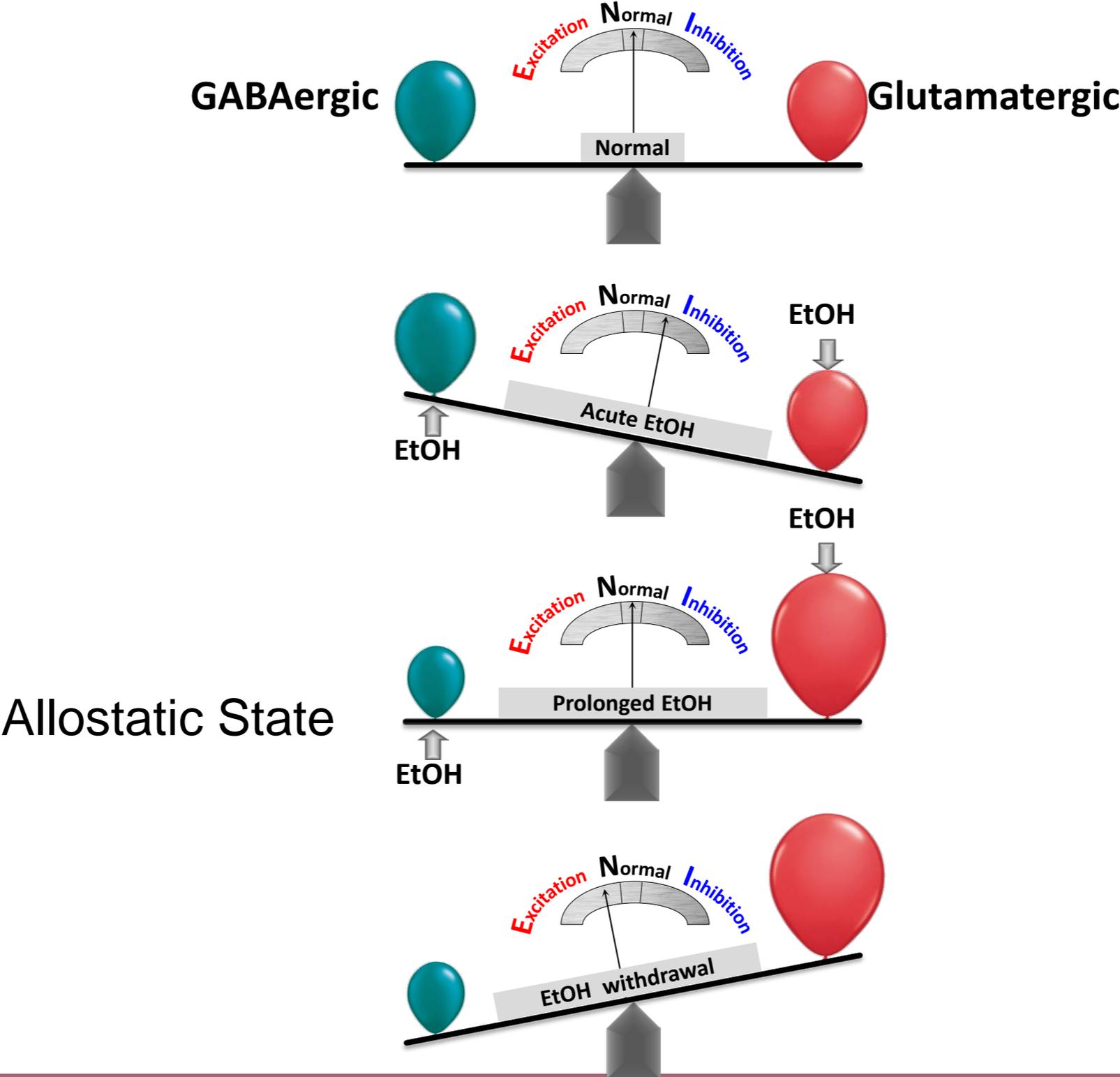
2B. At the same time, increased biosynthesis of $\alpha 4$ and $\gamma 2$, as well as $\alpha 2$, $\beta 1$, and $\gamma 1$; assembly; trafficking to surface membrane.

3. Major increase in surface $\alpha 4\beta\gamma 2$, including some synaptic localization, and $\alpha 2\beta 1\gamma 1$ (synaptic). Altered kinetics and pharmacology of mIPSCs, including EtOH sensitivity (due to $\alpha 2\beta 1\gamma 1$ and/or $\alpha 4\beta\gamma 2$).

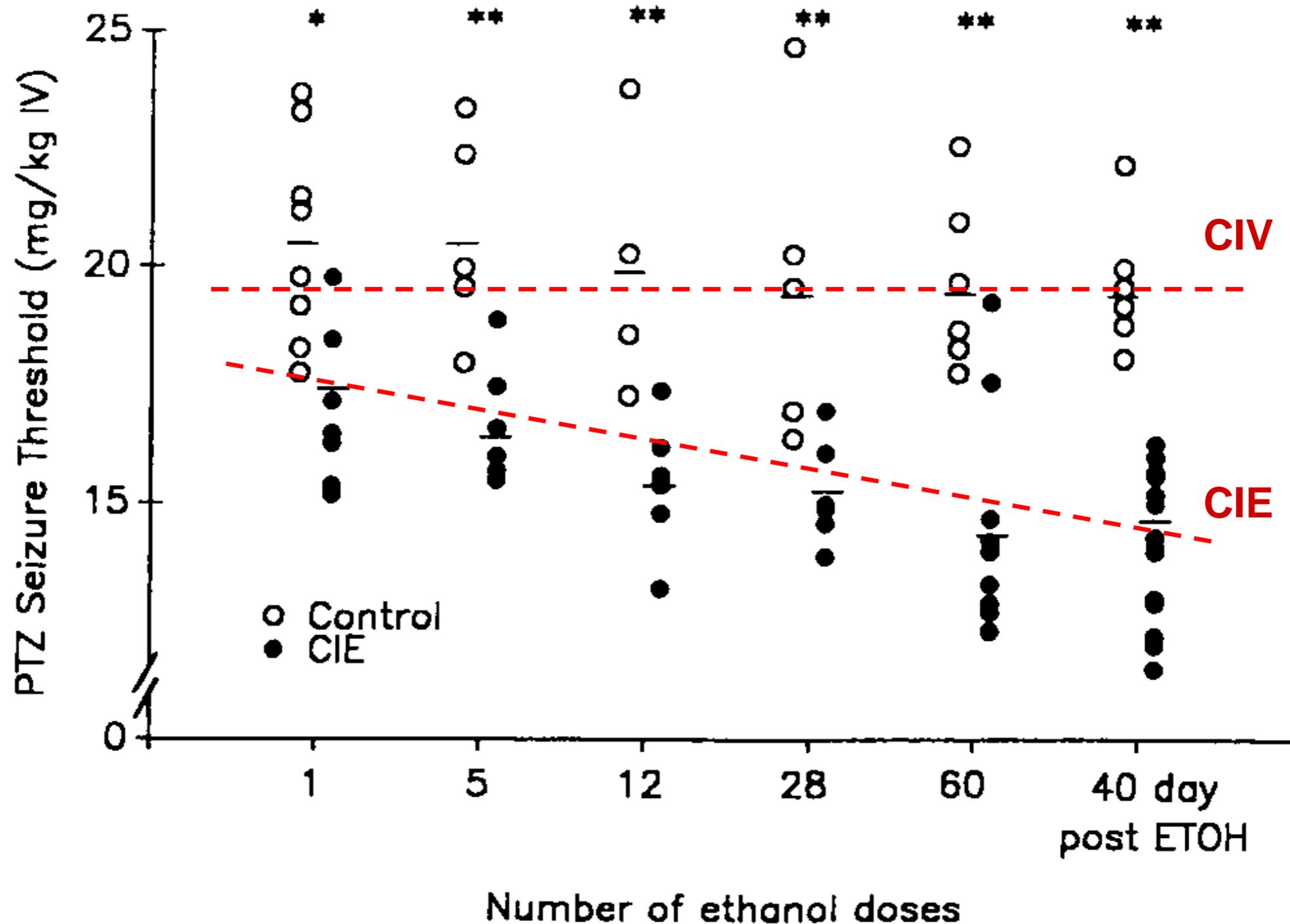
Neurosteroids and Risk for Alcoholism



Inhibitory/Excitatory Balancing and Imbalance



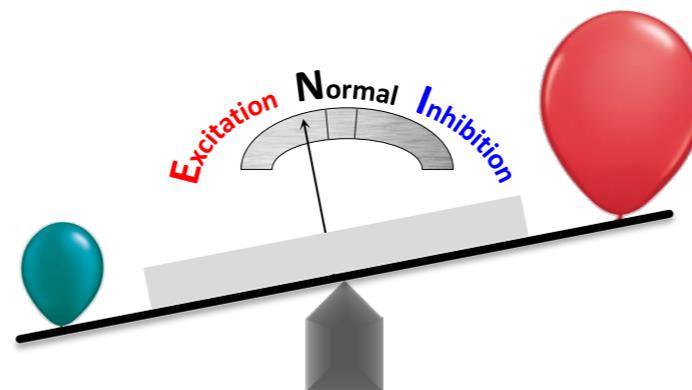
Persistent Decrease in Seizure Threshold in CIE Rats after Cessation of Ethanol Treatment



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

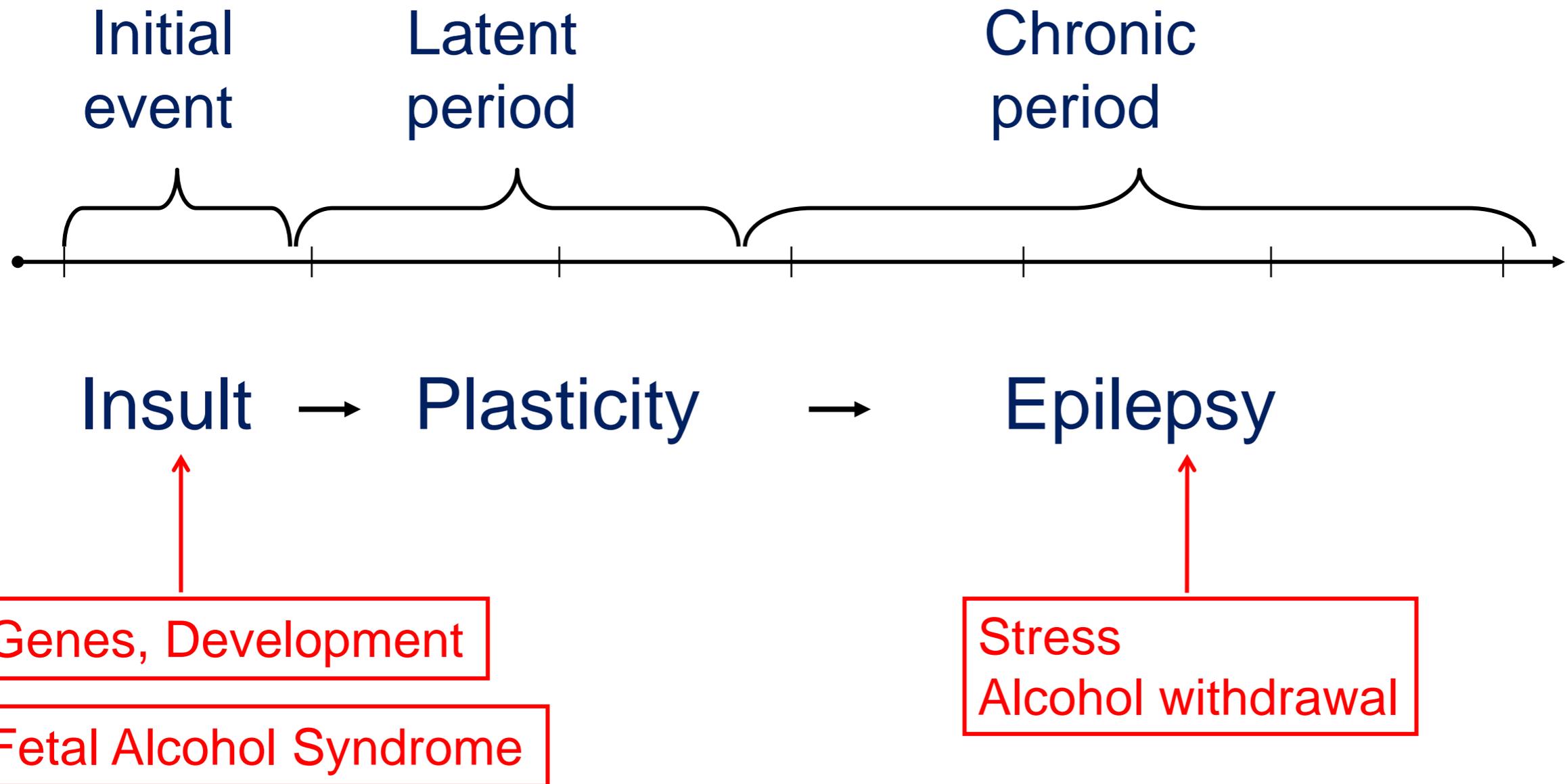
There are still significant gaps in the mechanisms underlying neuronal hyperexcitability that leads to alcohol withdrawal seizures.

- Excitation (too much)
 - Ionic—inward Na^+ , Ca^{++} currents
 - Neurotransmitter—glutamate,
- Inhibition (too little)
 - Ionic—inward Cl^- , outward K^+ c
 - Neurotransmitter—GABA



- 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



Scharfman, Pedley (2006): The Neurobiology of Disease

Does prenatal ethanol exposure increase:

- Risk of developing epilepsy ?

or

- Enhance seizure susceptibility ?

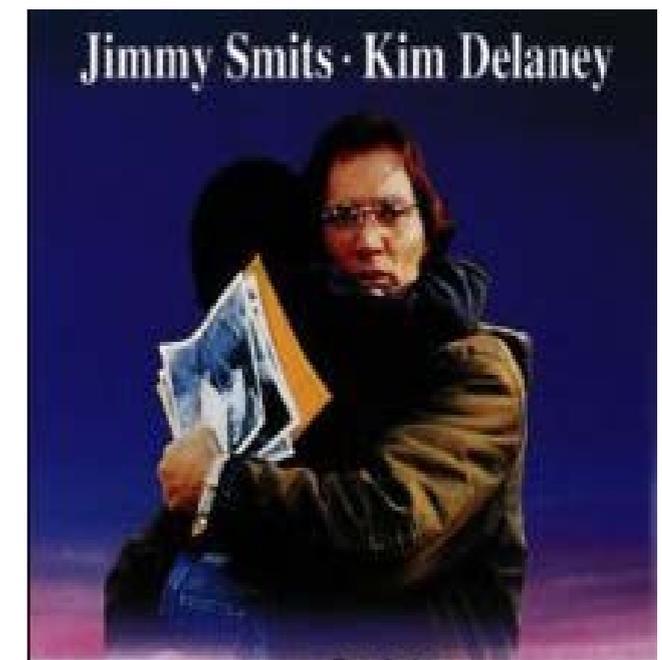
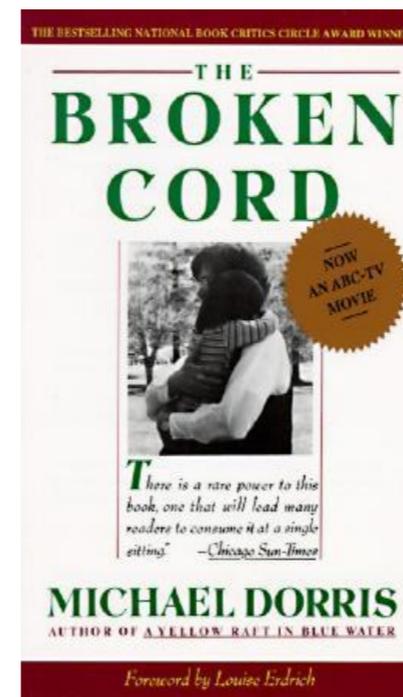
Prenatal Ethanol Exposure & Risk of Epilepsy

Prevalence in general population (all ages) **<1%**
(higher in young children and elderly patients)

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.**
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- **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**
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- 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-excitability 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.



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Thank You
