Role of Interleukin-1 System in Alcohol Drinking and Preference

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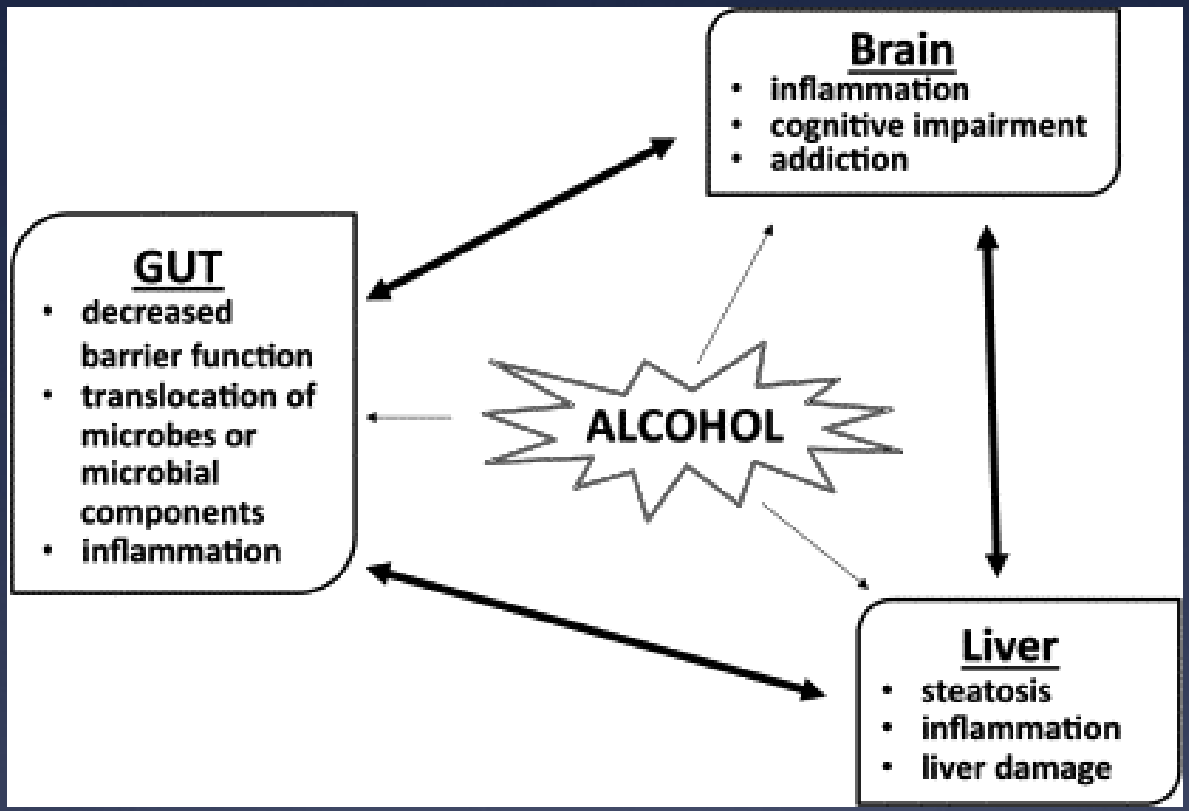
The Scripps Research Institute, La Jolla, USA

3rd International Conference and Exhibition on
Clinical & Cellular Immunology
September 29 - October 01, 2014 Baltimore, USA

Alcohol and Immunity



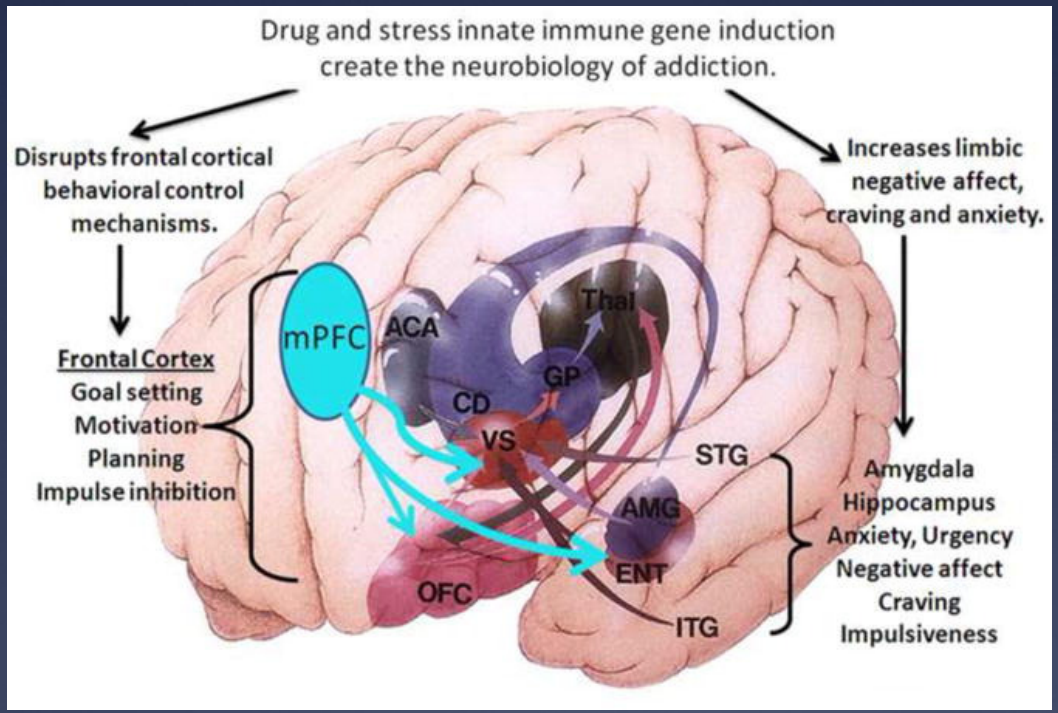
Szabo and Lippai, International Review of Neurobiology 2014; 118:359–380

IL-1 system in Alcohol Addiction

- ✓ IL-1β is increased in the brain after alcohol exposure in humans and animal models
- ✓ Polymorphisms in genes encoding IL-1ra and IL-1β have been associated with a susceptibility to alcoholism in Spanish men
- ✓ Several genes encoding IL-1R1 signaling pathways in brain with genetic predisposition to alcohol consumption in mice
- ✓ Reduction in alcohol drinking and/or preferences in *Il1rn* KO mice
- ✓ Central injection of IL-1 augmented withdrawal-associated anxiety
- ✓ Recombinant IL-1ra:
  - prevented and protected from advancement of alcohol-induced liver disease as well as alcohol-induced neuroinflammation
  - reduced sedation and motor impairment recovery time

Hypothesis

IL-1 system effects on alcohol related behaviors are mediated by modulation of key neurotransmitter and neuropeptide systems that play a role in alcohol drinking and development of alcohol dependence.



Crews et al., Brain, Behav., Immunity, 2011

Project #1

Question 1: What are effects of acute IL-1β on GABAergic transmission in Central Nucleus of the Amygdala (CeA)?

Question 2: Are there any interactions between acute ethanol and IL-1β effects on the CeA GABAergic transmission?

Methods

Brain slices containing CeA prepared from B6129SF2/J mice (# 101045; Jackson Laboratories)

Electrophysiological techniques:

whole-cell recordings

intracellular recording with sharp electrodes

GABAergic transmission

Phasic

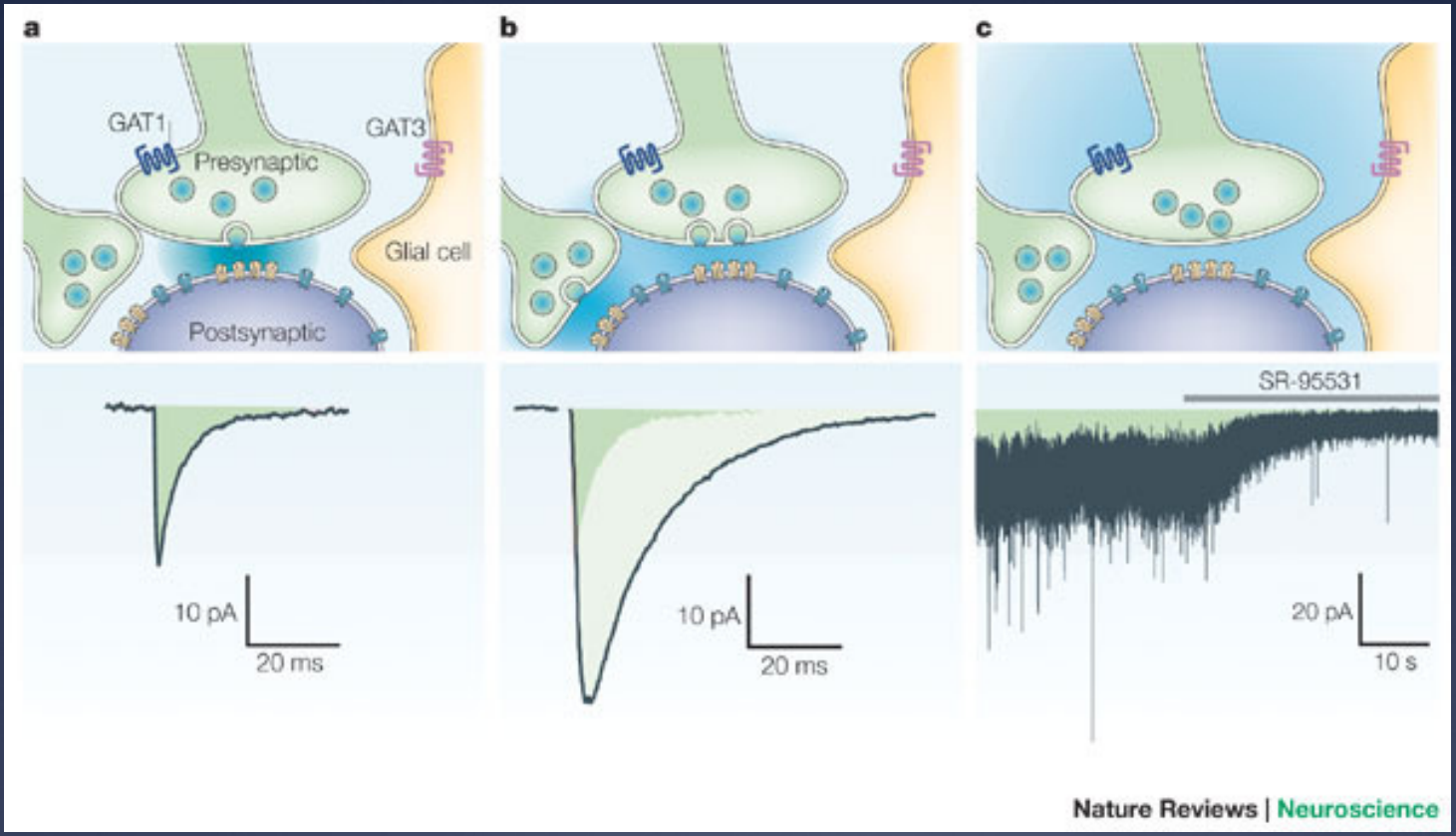
∗ Transient IPSCs

∗ Mediates ‘point to point’ synaptic transmission

Tonic

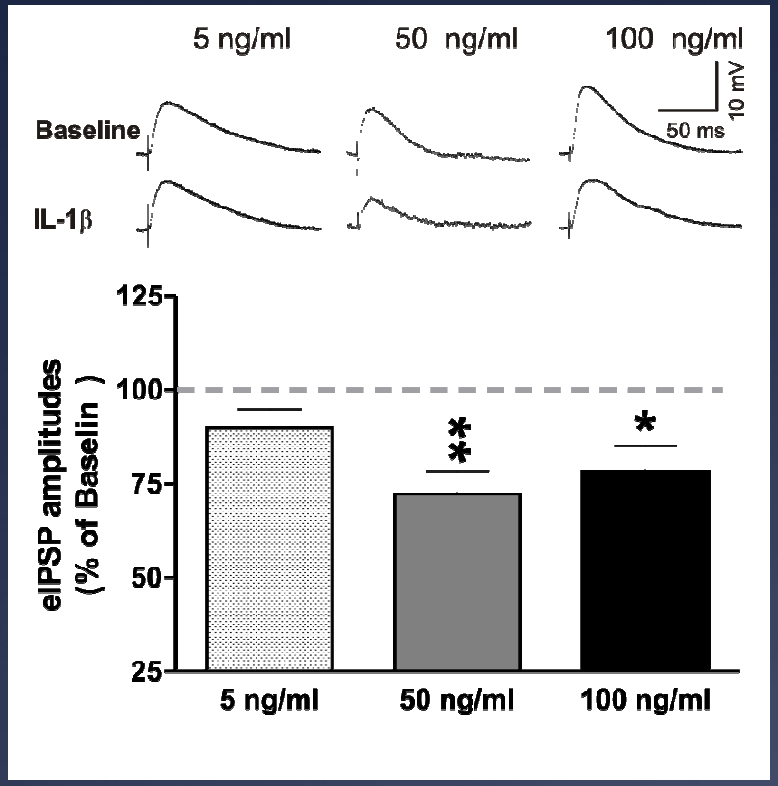
∗ Persistent inhibitory conductances

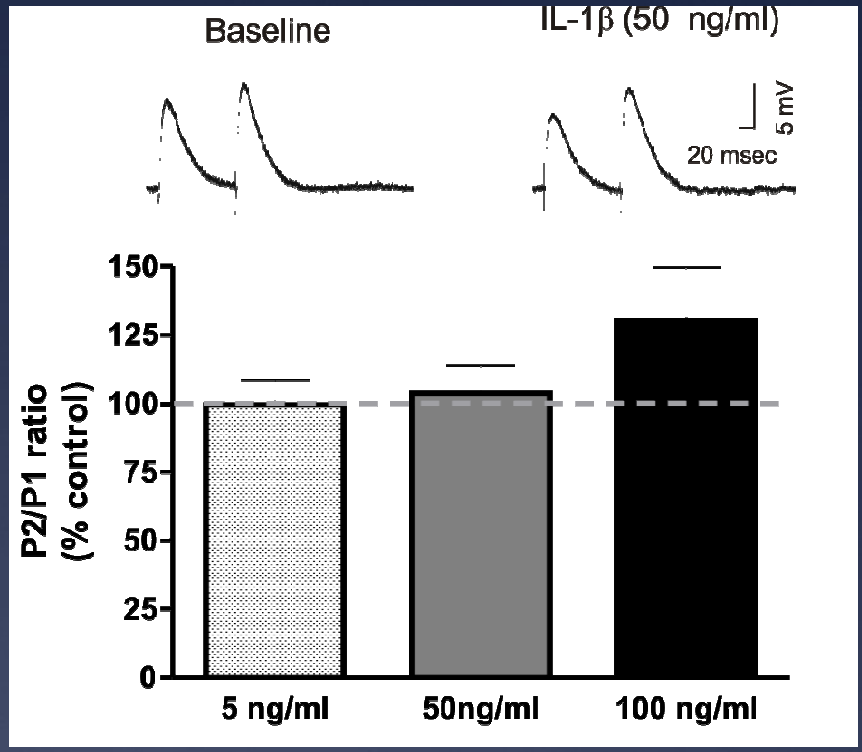
∗ Mediates overall cell/network excitability



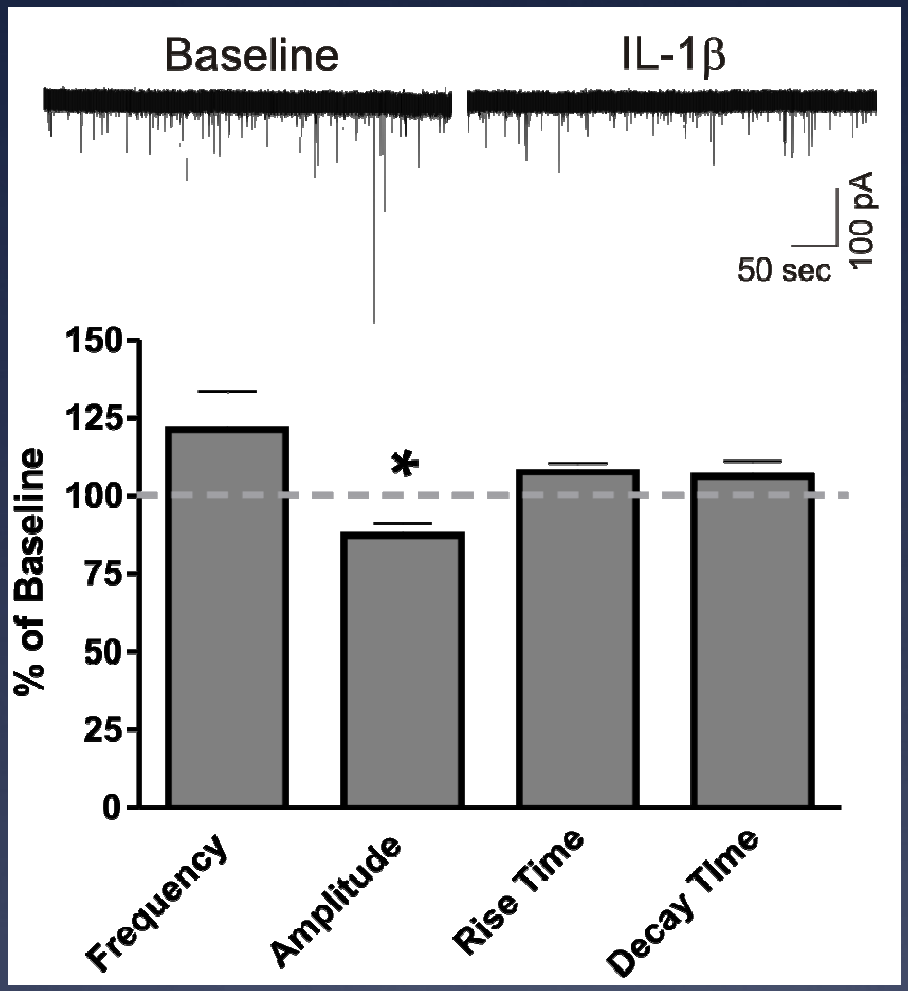
Farrant and Nusser, Nat. Rev. Neurosci, 2005

IL-1β Decreases evoked GABA IPSPs in CeA Neurons



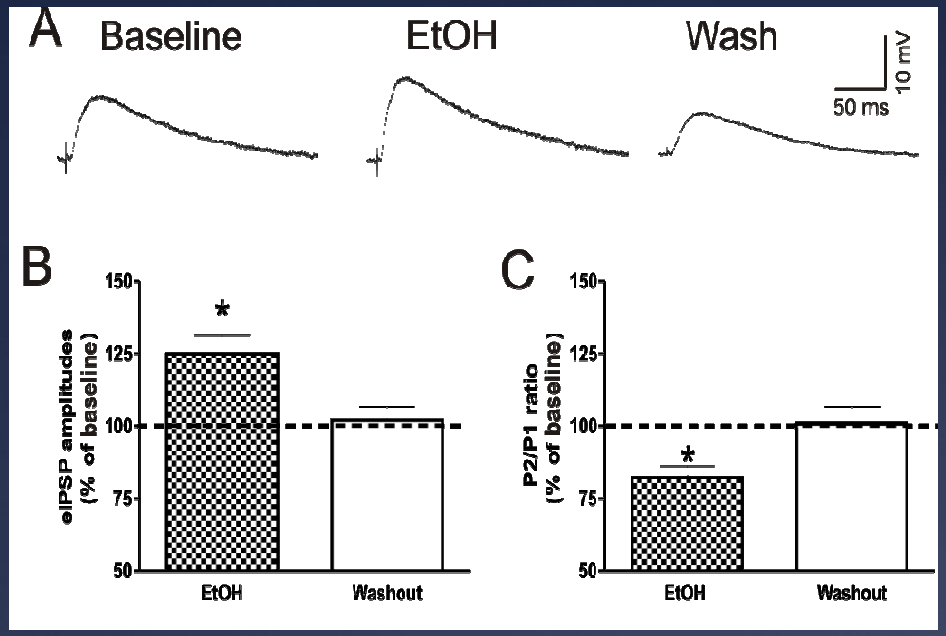


IL-1β Decreases mIPSCs Amplitudes in CeA Neurons

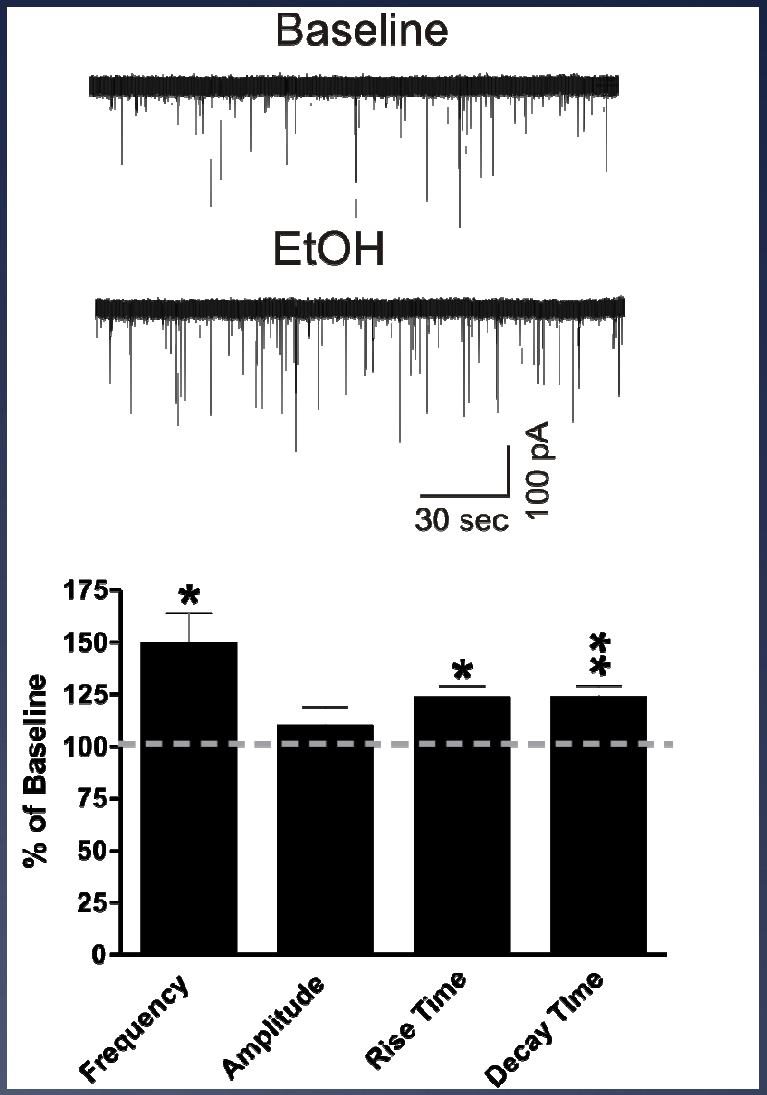


50 ng/ml IL-1β

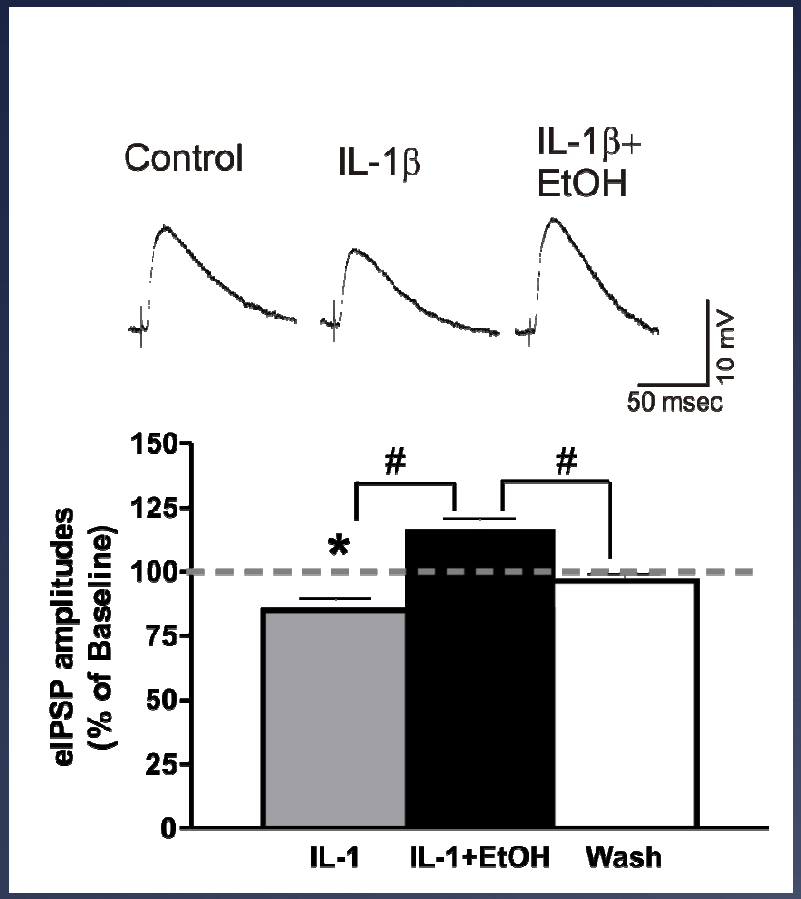
Ethanol Increases both Evoked and Spontaneous GABA Transmission in CeA

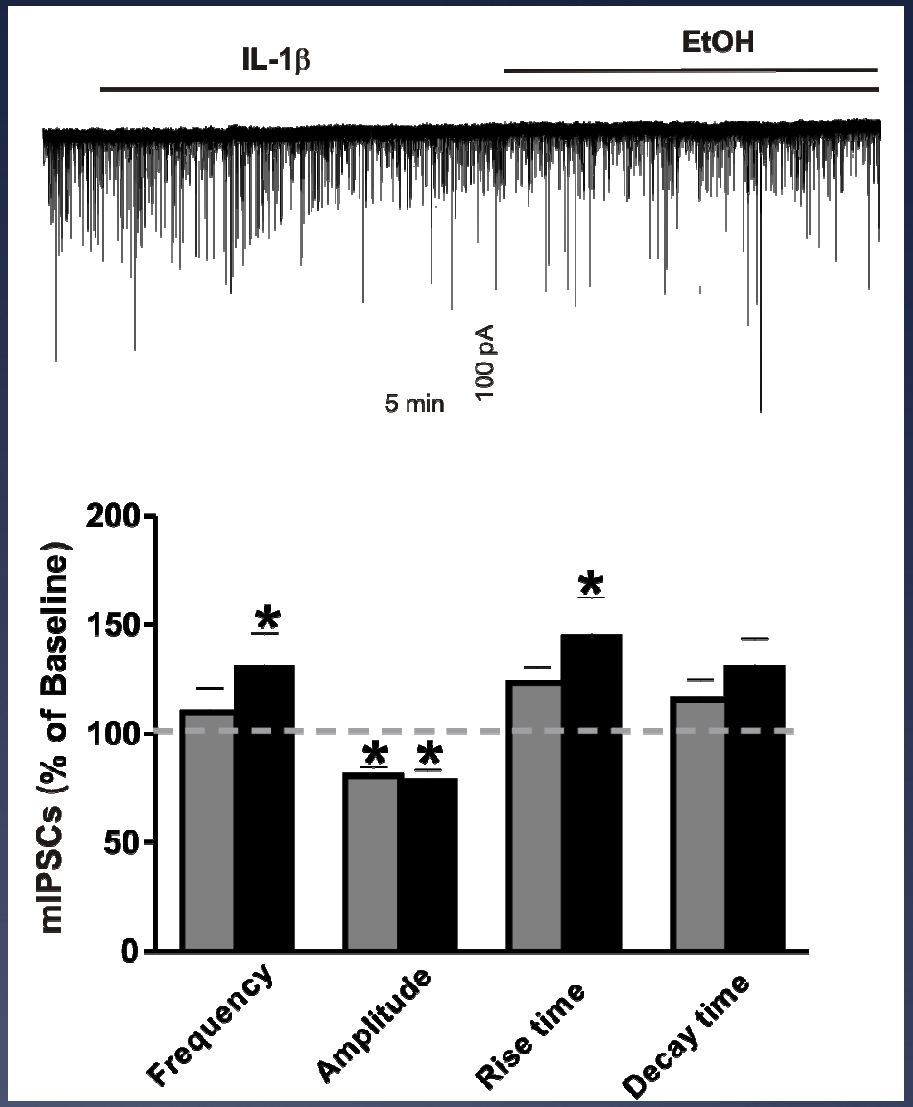


44 mM EtOH=Maximal ethanol concentration



IL-1β Does not Affect the Ethanol-induced Increase in GABA Transmission

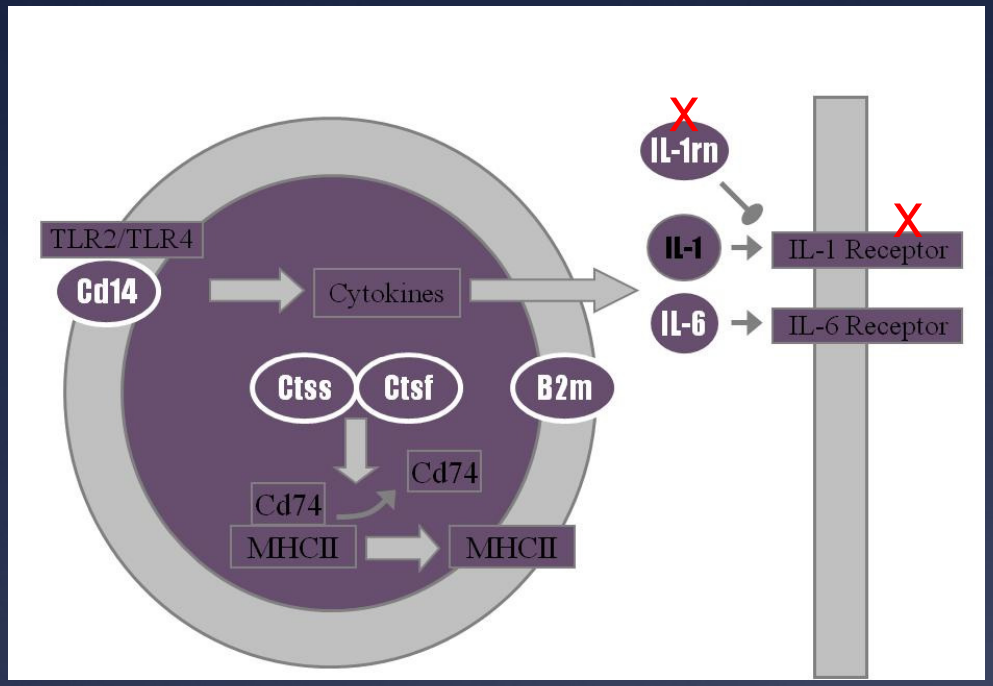




Summary

I. IL1β decreases GABAergic transmission via postsynaptic mechanisms, but in some neurons, it acts also via presynaptic mechanisms

I. Acute IL-1β modulation of ethanol effects on CeA GABAergic transmission via different mechanisms



Deletion of *Il1rn*:

- reduces alcohol intake in several behavior tests
- increases sensitivity to the sedative/hypnotic effects of ethanol and a GABA-receptor allosteric modulator flurazepam
- reduces the severity of acute ethanol withdrawal
- recombinant IL-1ra rescues some of the alcohol related behaviors

Wu et al., Brain Behav Immun 2011; Blednov et al., Addict Biol, 2012; Blednov et al., Brain Behav Immun, in submission 2014

Project #2

Question 1: Are changes in alcohol related behaviors found in mice with perturbations in IL-1 system associated with alterations of GABAergic system?

Question 2: Does perturbation of IL-1 system alters ethanol effects on GABAergic transmission?

Methods

Brain slices containing CeA prepared from *Il1rn KO (B6.129S-Il1rntm1Dih/J;* #004754; Jackson Laboratories) and WT mice

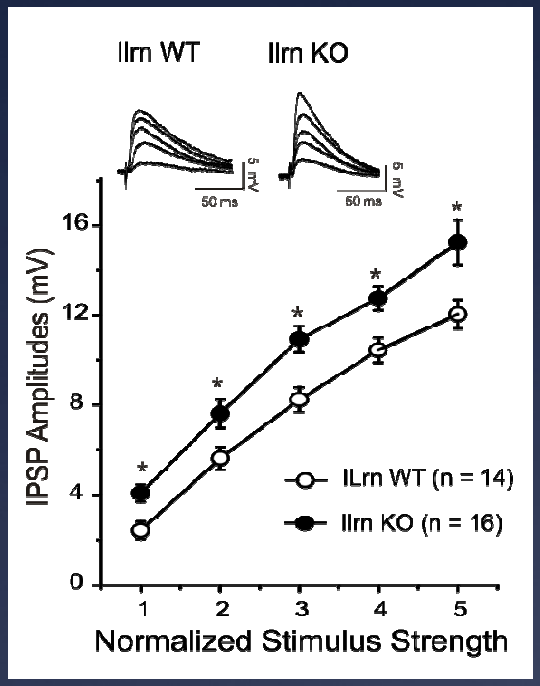
Electrophysiological techniques:

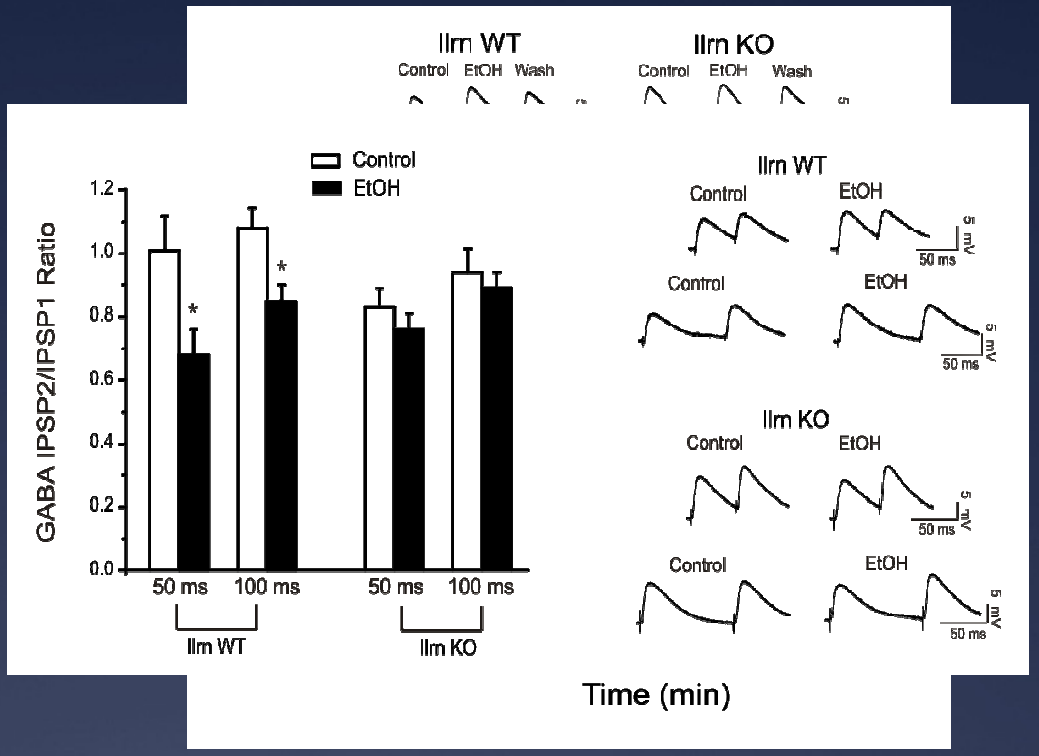
whole-cell recordings

intracellular recording with sharp electrodes

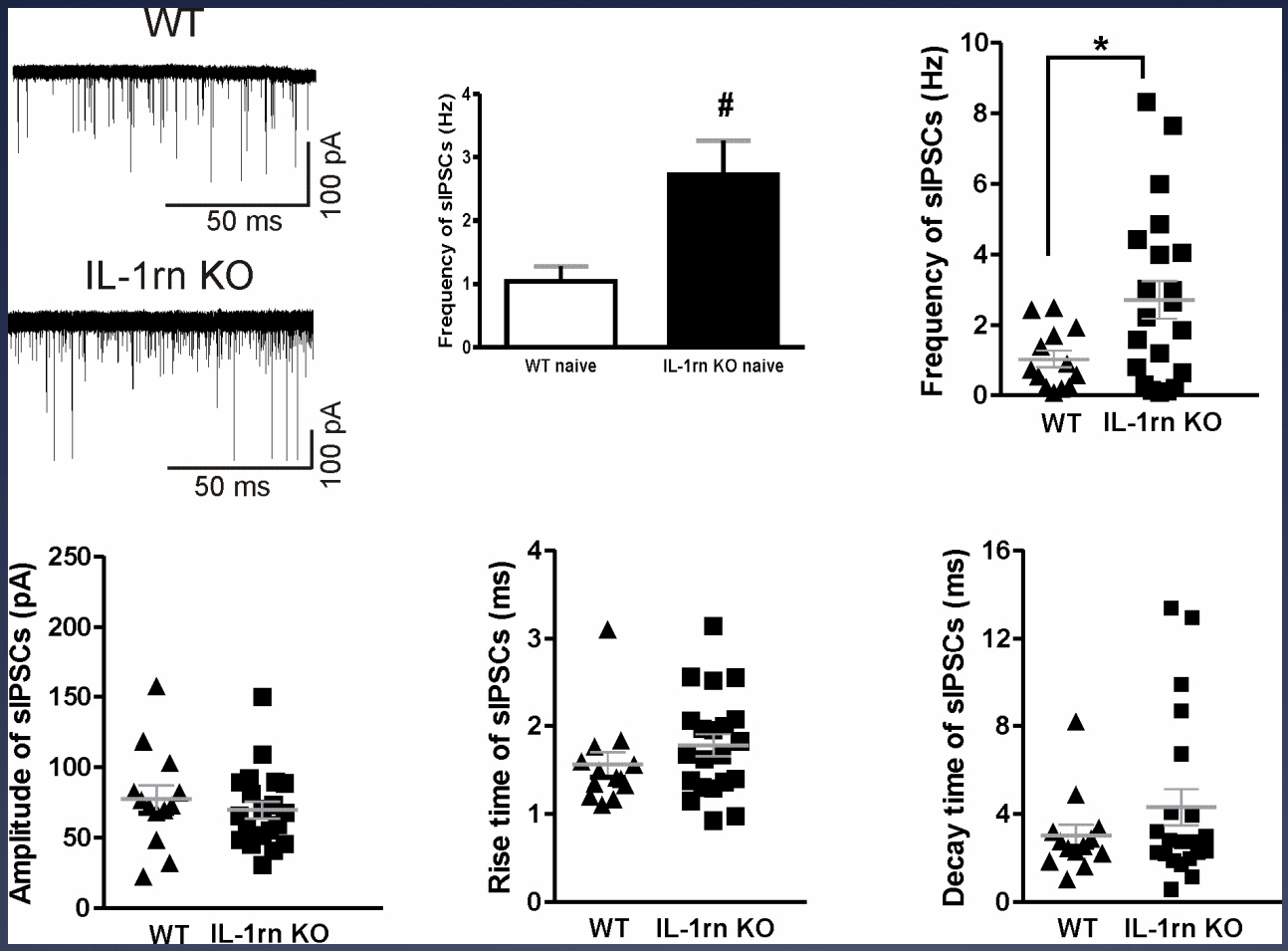
Bajo et al, *in submission*; Blednov et al., *in submission*

Basal Evoked GABA Transmission is Elevated in CeA of *Il1rn* KO compared to WT Mice

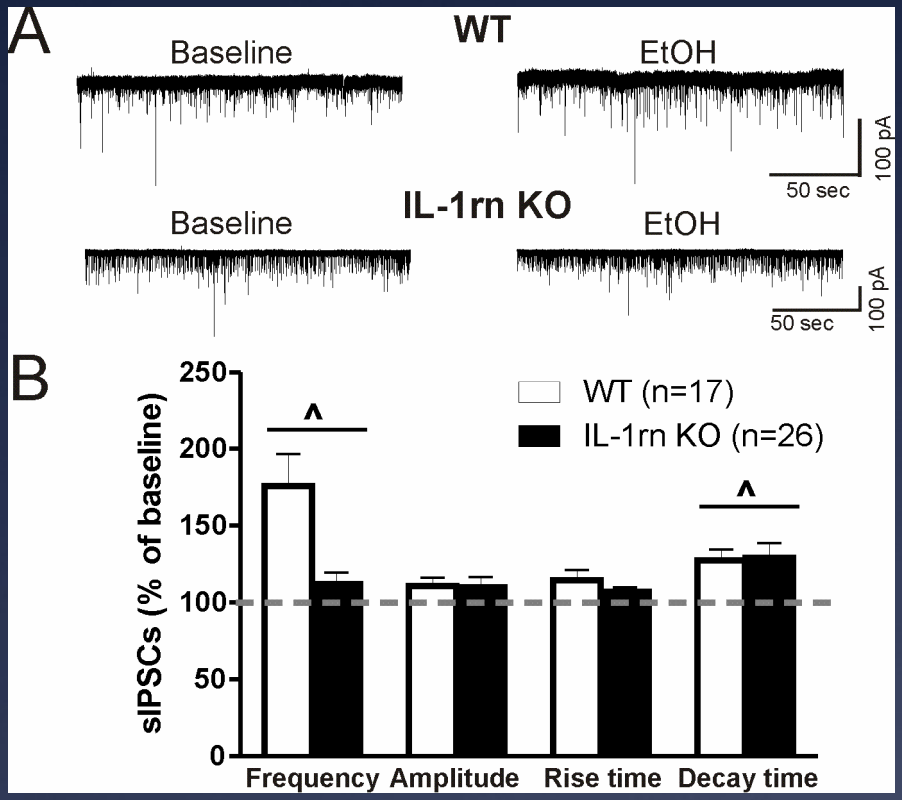


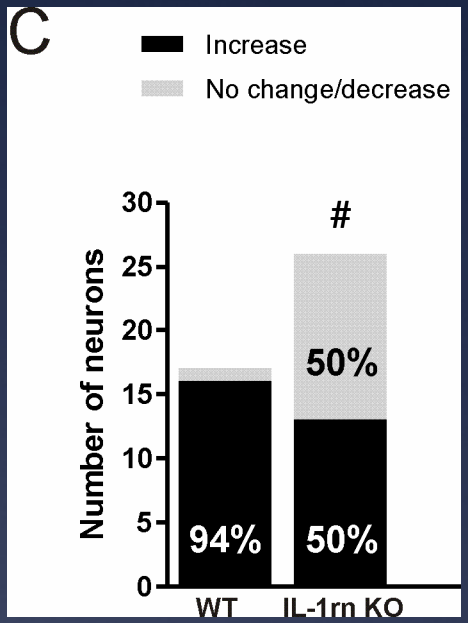


The Frequency of sIPSCs is Significantly Higher in IL1rn KO Compared to WT Mice



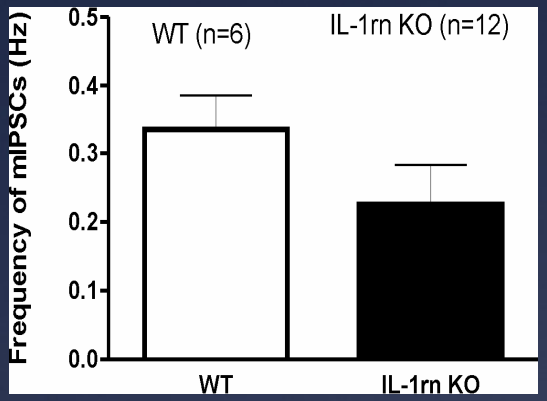
The Number of CeA Neurons Responding to Acute EtOH is Decreased in *Il1rn* KO Mice

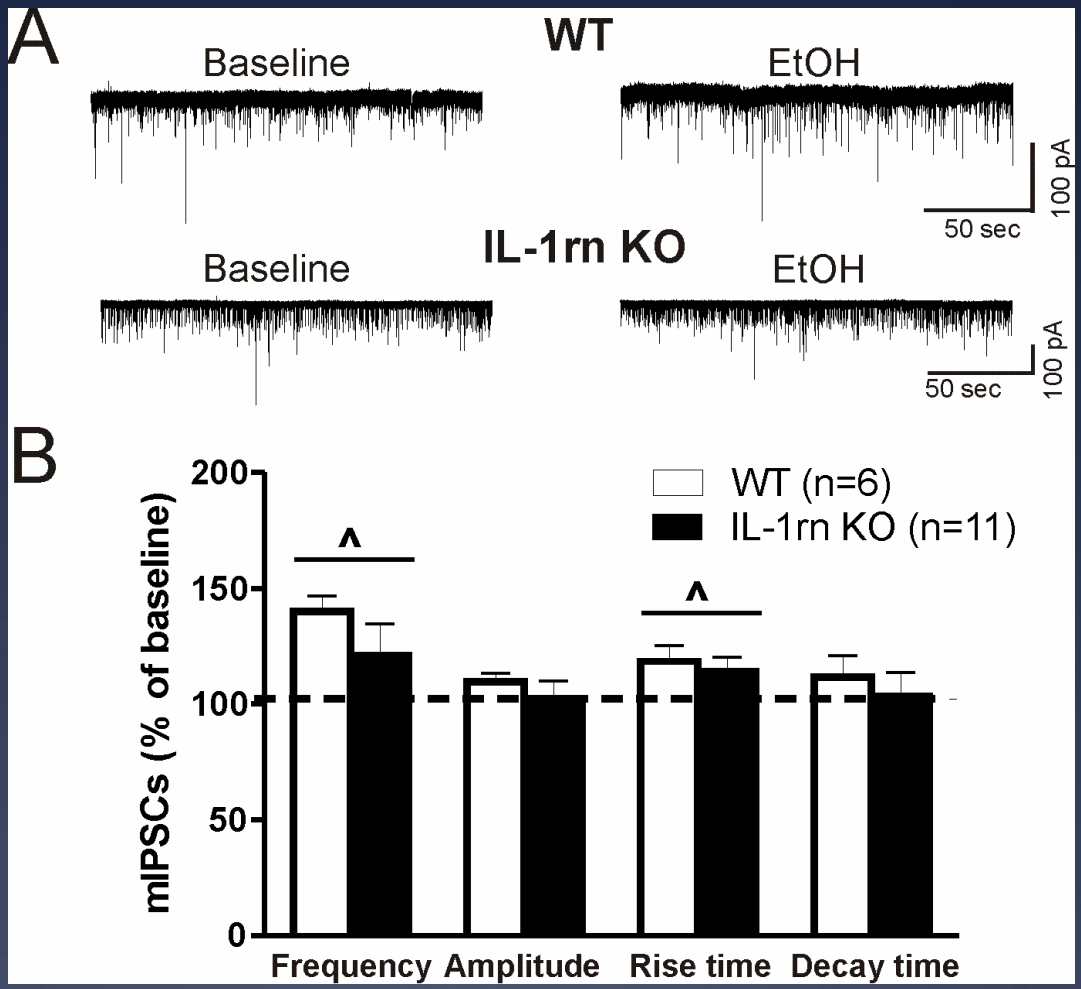




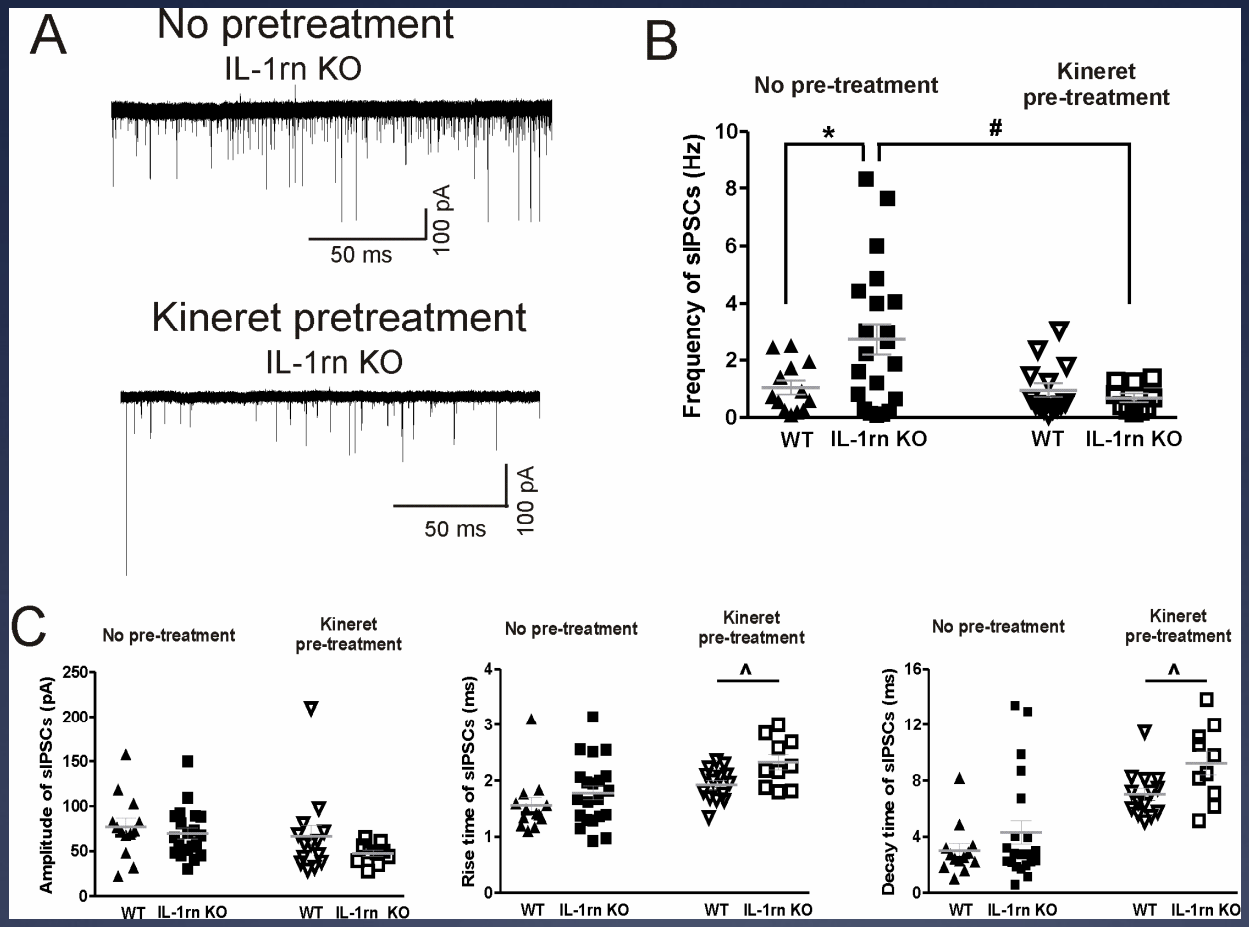
Chi-square test

The Basal Frequency and the EtOH-induced Increase of mIPSCs are Similar in *Il1rn* KO and WT

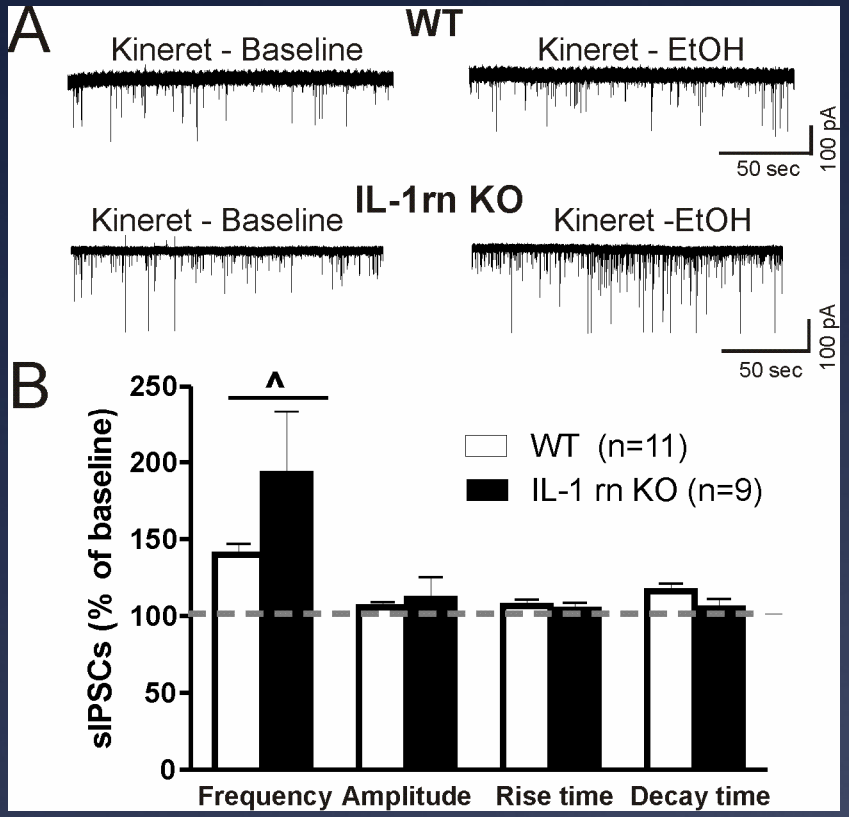


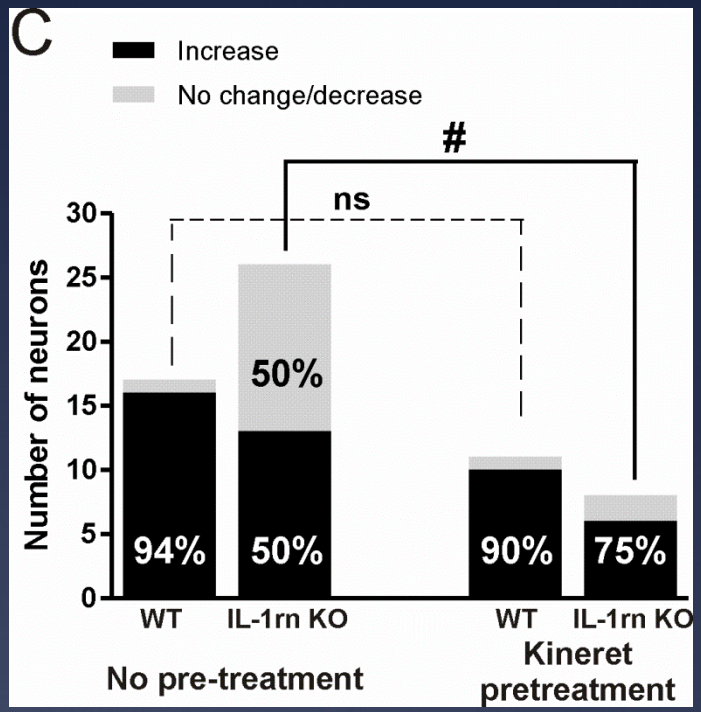


Kineret (exogenous IL-1R antagonist) "Normalized" the Baseline sIPSC Frequency in *Il1rn* KO Mice



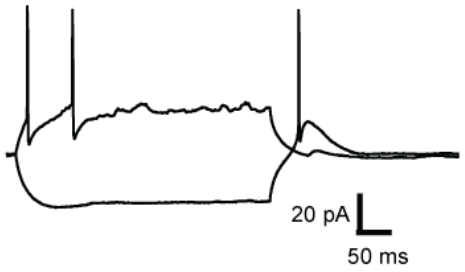
Kineret "increases" the Number of CeA Neurons Responding to Acute EtOH in *Il1rn* KO Mice

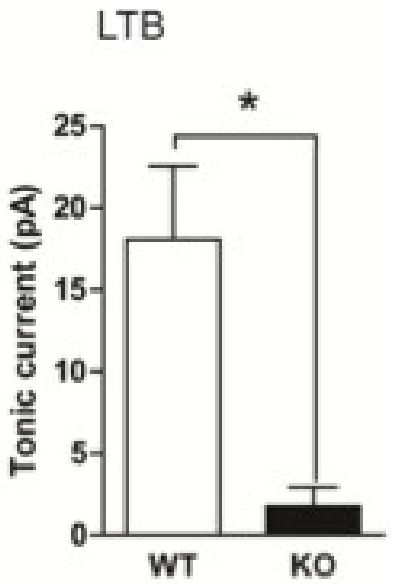




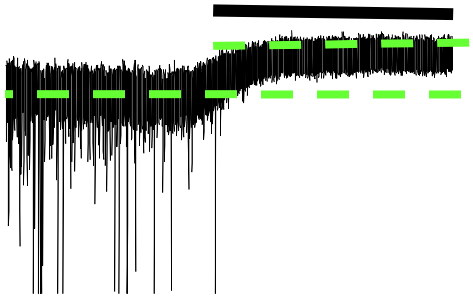
Shift in Ongoing Tonic Conductance in CeA Neurons from *Il1rn* KO mice Compared to WT Mice

Low Threshold Bursting (LTB)

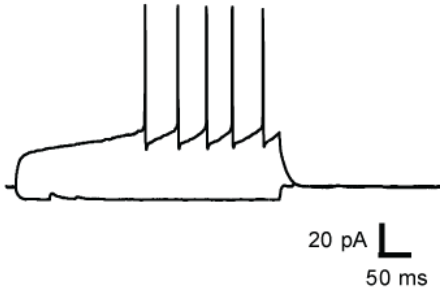


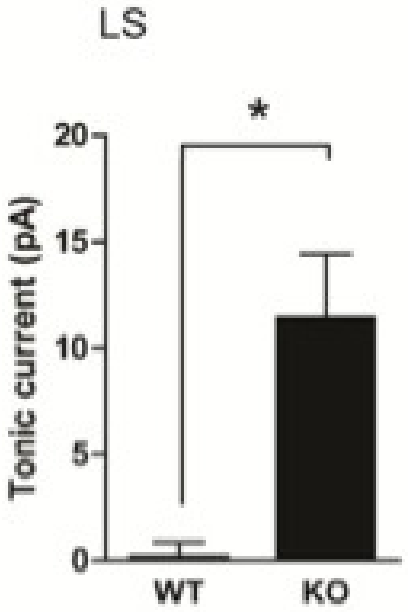


Persistent Tonic Conductance



Late Spiking (LS)





Summary and Conclusion

I. The baseline GABAergic transmission is significantly higher in *Il1rn* KO compared to WT

II. There is a shift in ongoing tonic conductance in CeA neurons from *Il1rn* KO mice compared to WT

III. The number of CeA neurons responding to acute ethanol is decreased in *Il1rn* KO mice

IV. Kineret "normalized" the GABAergic transmission in *Il1rn* KO and "increases" the number of CeA neurons responding to acute ethanol in *Il1rn* KO

Based on behavioral studies of Blednov et al., IL-1R1 is not involved in alcohol drinking and preference, but it plays an important role in alcohol sedative effects and alcohol withdrawal.

Acknolwedgement

Marisa Roberto:

Sam Madamba

Melissa Herman

Florence Varodayan

Christopher Oleata

Dean Kirson

Marian Logrip

Former members

Maureen Cruz

George Luu

Collaborators:

TSRI

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University of Texas

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Yuri A. Blednov

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NIAAA National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health