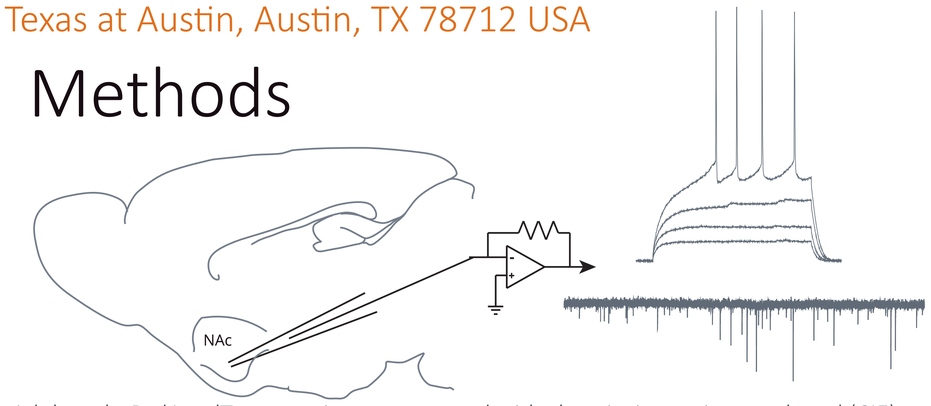
REGULATION OF NEURONAL EXCITABILITY BY INTERLEUKIN-33 (IL-33)

Heather C. Aziz, Regina A. Mangieri| reginamangieri@utexas.edu
College of Pharmacy, Division of Pharmacology & Toxicology, The University of Texas at Austin, Austin, TX 78712 USA

Background and Aims

- IL-33 is a cytokine that regulates synaptic structure and function via glia-neuron crosstalk[1-3].
- IL-33 is involved in peripheral tissue responses to alcohol; nucleus accumbens (NAc) *Il33* expression is associated with risk for heavy drinking[4]; and brain *Il33* is regulated by ethanol treatment[5,6].
- Our lab has linked glutamatergic signaling and membrane excitability in NAc D1 receptor-expressing medium spiny neuron (D1MSNs) to excessive alcohol consumption[7,8].
- The overarching, long-term goal of this project is to determine whether IL-33 is a mediator of glia-neuron crosstalk in the NAc that contributes to excessive alcohol consumption. Here we asked whether IL-33 and ethanol experience interact to alter NAc D1MSN physiology.

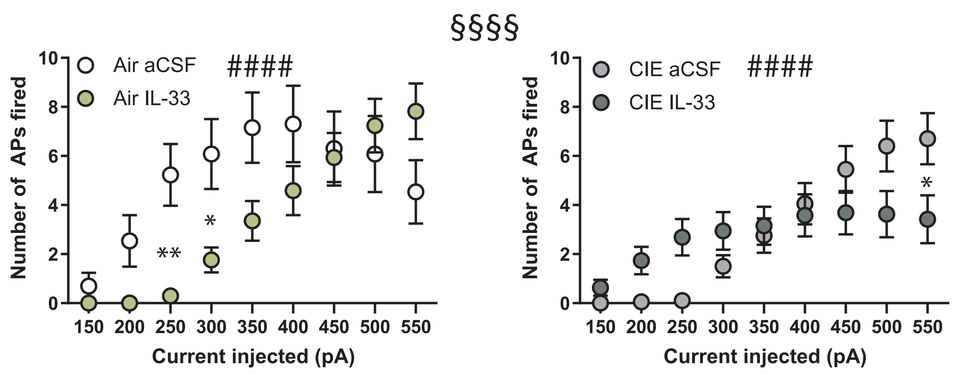
Methods



Adult male *Drd1a*-tdTomato mice were treated with chronic, intermittent ethanol (CIE) vapor or air for 16 hours/day for 4 days. Brain slices were prepared 24 hours into withdrawal. Slices recovered in, and recordings were performed in, either aCSF + IL-33 (50 ng/mL) or control aCSF. Whole-cell patch clamp recordings were collected from tdTomato+ neurons (D1MSNs) in the medial NAc shell.

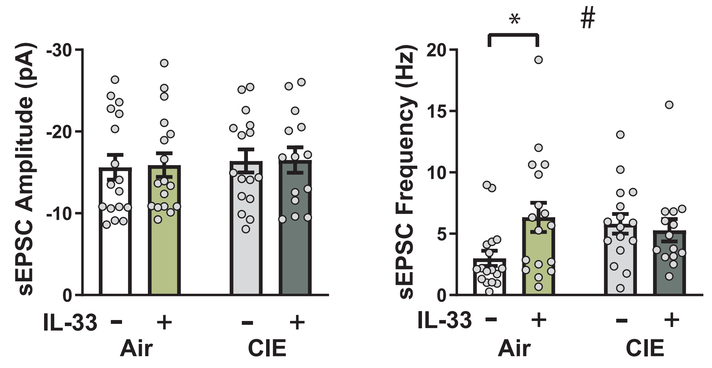
Results

IL-33 and CIE interact to alter NAc D1MSN action potential (AP) firing



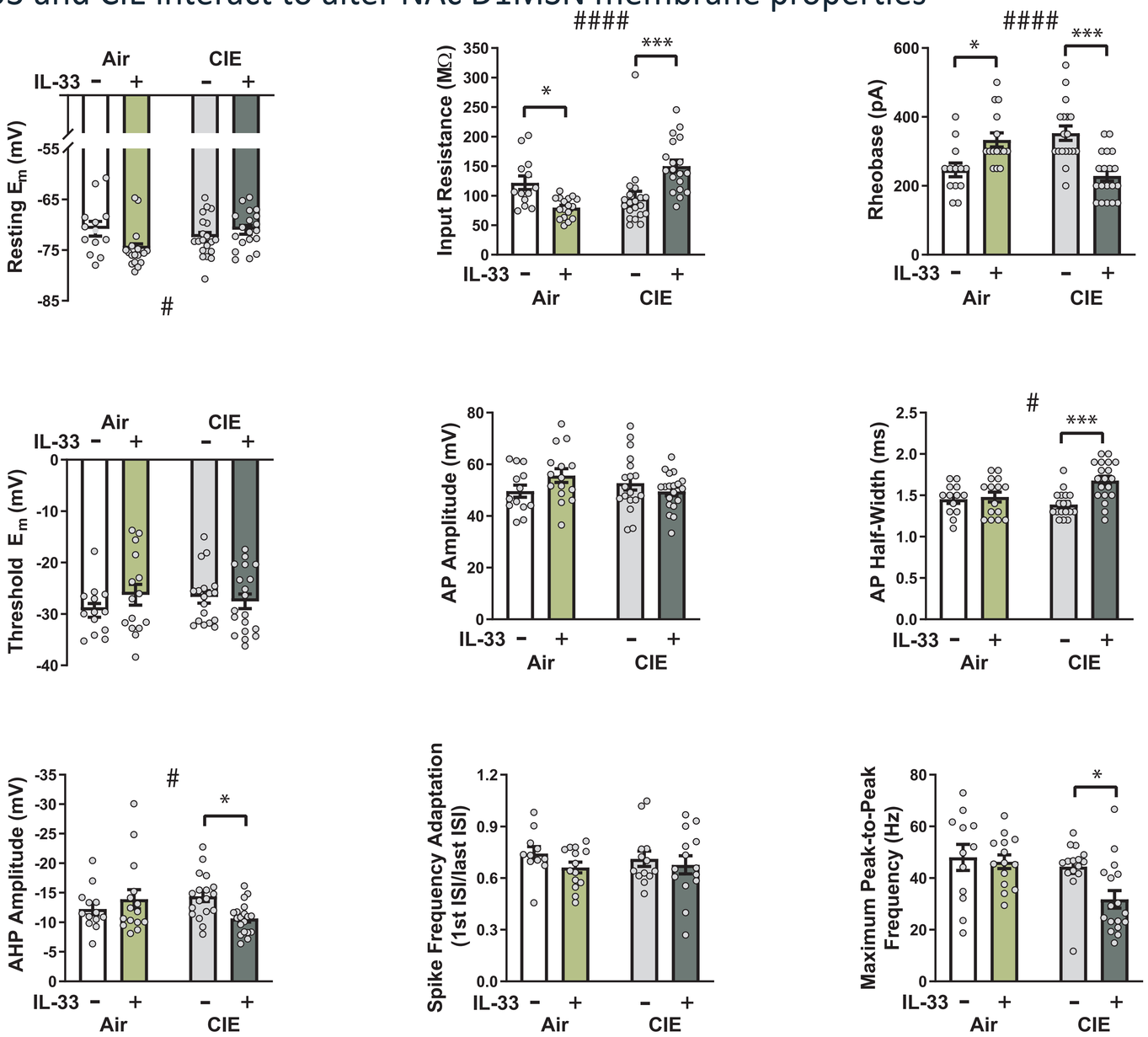
§§§§, p < 0.0001, 3-way ANOVA, Condition X Treatment X Current amplitude interaction
####, p < 0.0001, Treatment X Current amplitude interaction
*, **, p < 0.05, 0.01, Sidak's multiple comparisons

IL-33 mimics effect of chronic ethanol on NAc D1MSN excitatory synapses



#, p < 0.05, 2-way ANOVA, Condition X Treatment interaction
*, p < 0.05, Tukey's multiple comparisons

IL-33 and CIE interact to alter NAc D1MSN membrane properties



#, ####, p < 0.05, 0.0001, 2-way ANOVA, Condition X Treatment interaction
*, **, ***, p < 0.05, 0.01, 0.001, Tukey's multiple comparisons

Summary

- In ethanol-naive, but not ethanol-treated, brain slices, IL-33 promoted excitatory synaptic transmission, but suppressed membrane excitability in shNAc D1MSNs.
- IL-33 tended to suppress excitability of ethanol naive D1MSNs, and to promote excitability of CIE-treated D1MSNs, by altering membrane properties relating to inwardly rectifying K^+ channels.
- In CIE-treated D1MSNs only, sustained action potential firing, AHP amplitude, and maximum firing frequency were suppressed by IL-33, suggesting an ethanol experience-dependent effect on Ca^{++}-activated and voltage-gated K^+ channels.

Acknowledgements

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