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The Role of the P2X7 Receptor in Chronic Methamphetamine Abuse

Anisha Kadubandi
University of Nebraska Medical Center

Katherine E. Odegaard
University of Nebraska Medical Center

Sowmya V. Yelamanchili
University of Nebraska Medical Center

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Role of P2RX7 receptor in chronic methamphetamine abuse

Anisha Kadubandi

Summer Intern

Dr. Yelamanchili Laboratory

**Department of Pharmacology and Experimental
Neuroscience**

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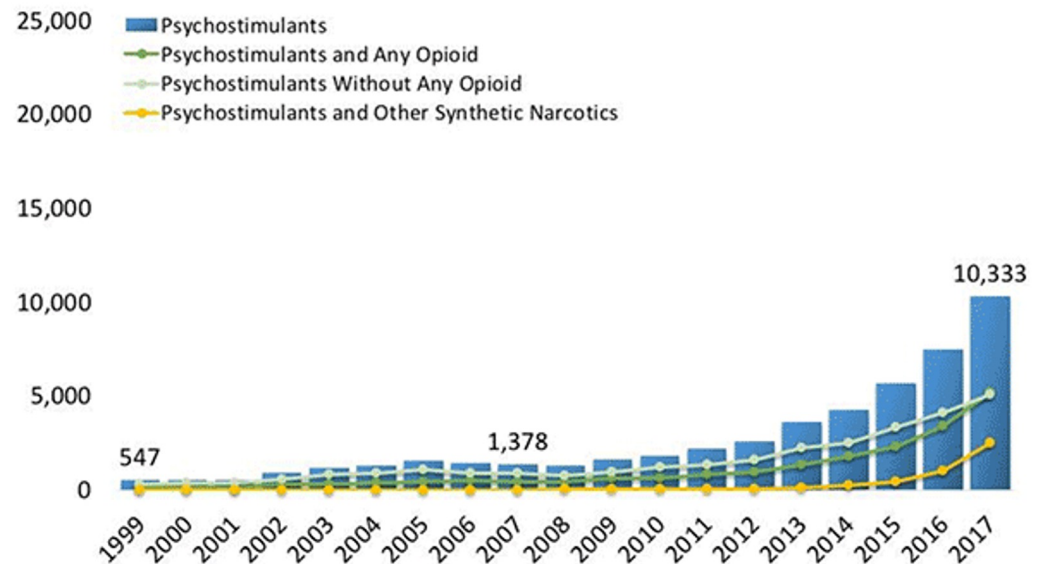


**University of Nebraska
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Methamphetamine (Meth) Addiction

- According to NIH, 15% of drug overdose deaths fall under methamphetamine
- Dramatic increase seen in recent years
 - Self-reported 684,000 individuals in 2016 → estimated 964,000 people in 2017

Figure 6. National Drug Overdose Deaths Involving Psychostimulants With Abuse Potential (Including Methamphetamine), by Opioid Involvement
Number Among All Ages, 1999-2017

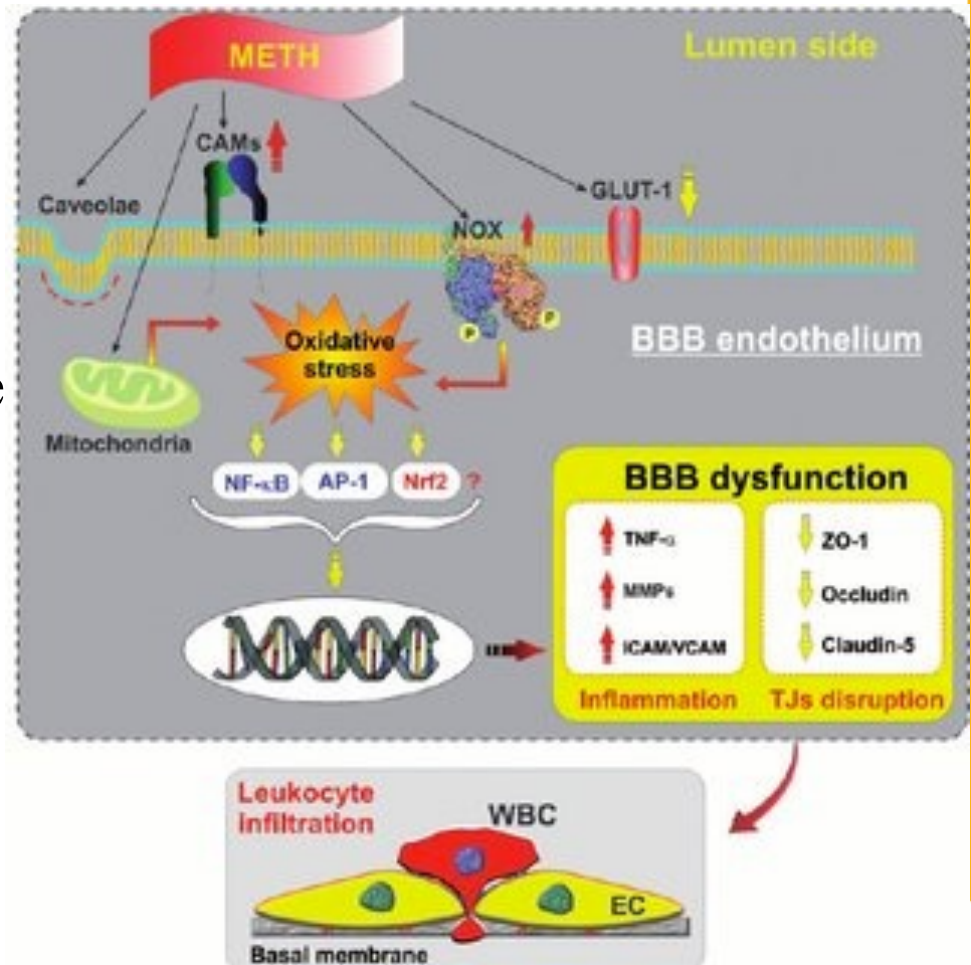


Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018



Crystal Methamphetamine

- A powerful, highly addictive stimulant affecting the CNS
- Increased levels of dopamine release and blocks dopamine reuptake
- Chronic use associated with increased inflammatory response
 - Activation of microglia
 - Oxidative stress



P2RX7 Receptor

P2X7 Family

- ATP gated P2X7 receptors (P2X7R) are non-selective cation channels found on cells of hematopoietic lineage as well as cells of other lineage such as nervous tissue (microglia, astrocytes, oligodendrocytes and neurons)

Functional Role

- Acts as a crucial ATP sensor
- P2X7R acts as a regulatory element in the cytokine response
- Synaptic transmission
- Regulating immune responses



Hypothesis

Rationale:

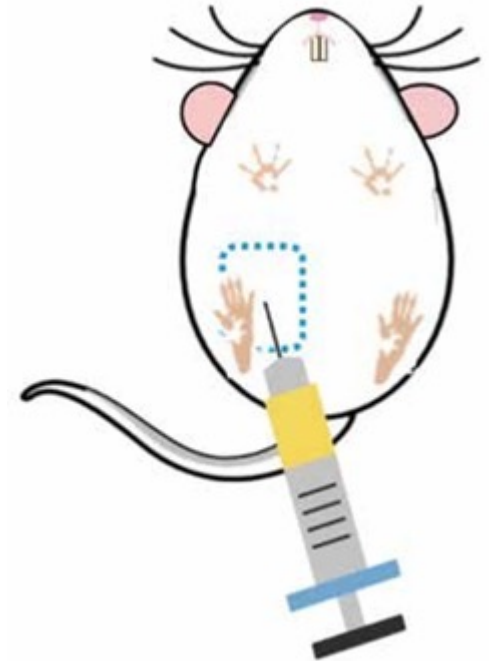
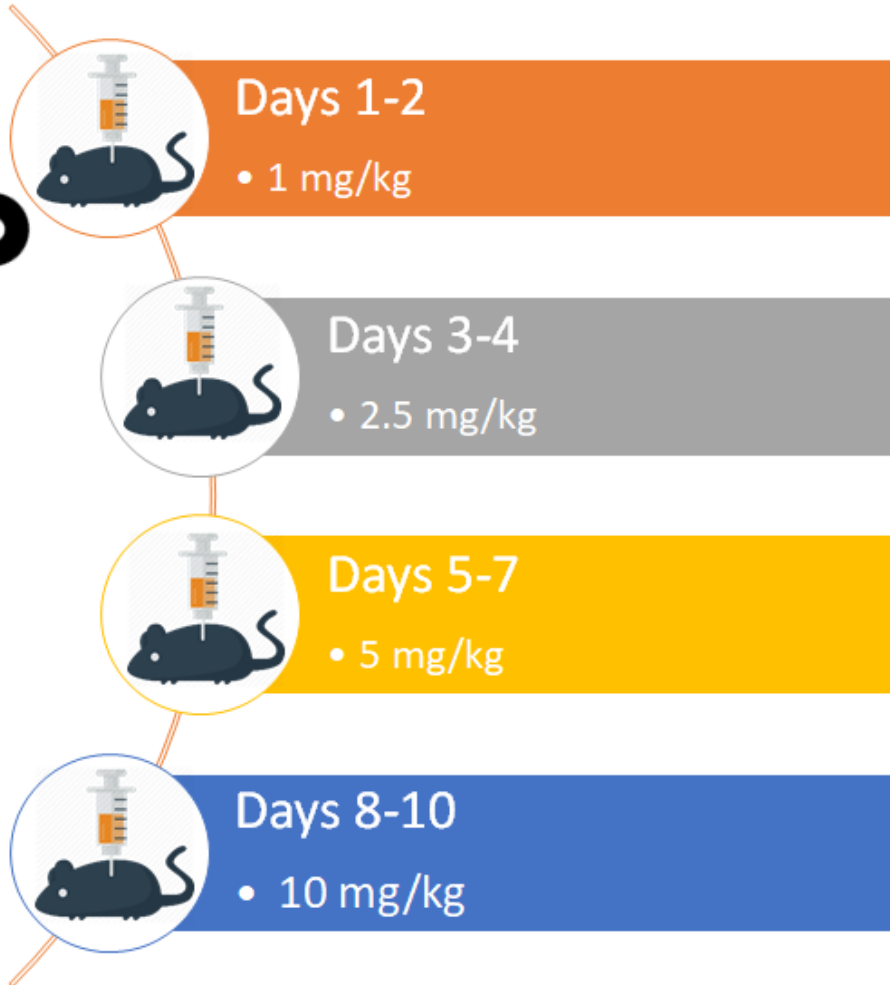
Meth is known to alter intracellular ATP levels thereby perturbing energy metabolism leading to neurotoxicity. However, it is unknown whether Meth influences P2X7 receptors and induce neurotoxicity.

Hypothesis:

We hypothesize that P2X7 receptor mediates Meth induced neurotoxicity by altering synaptodendritic changes in mice undergoing chronic meth treatment.



Chronic Meth Regimen

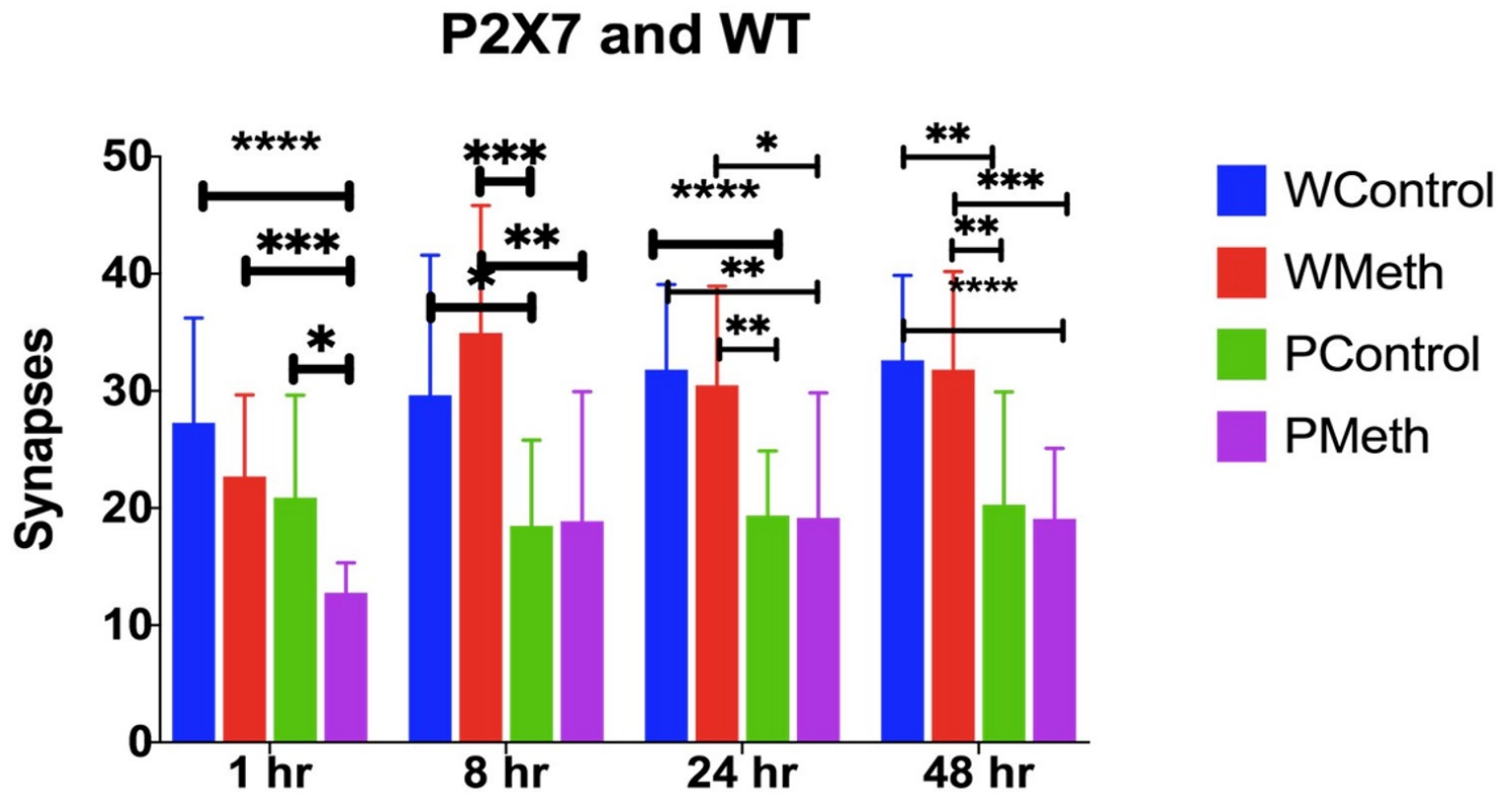


Methodology

- Synapse Data (in vitro)
- Western Blots (in vivo)
 - Synaptosome Preparation



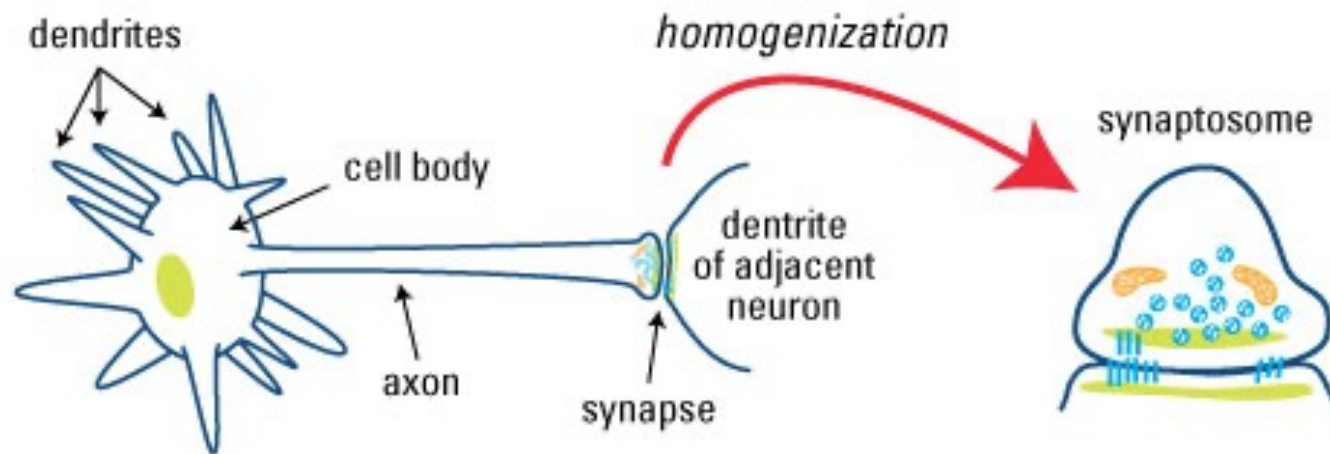
Synapse Data



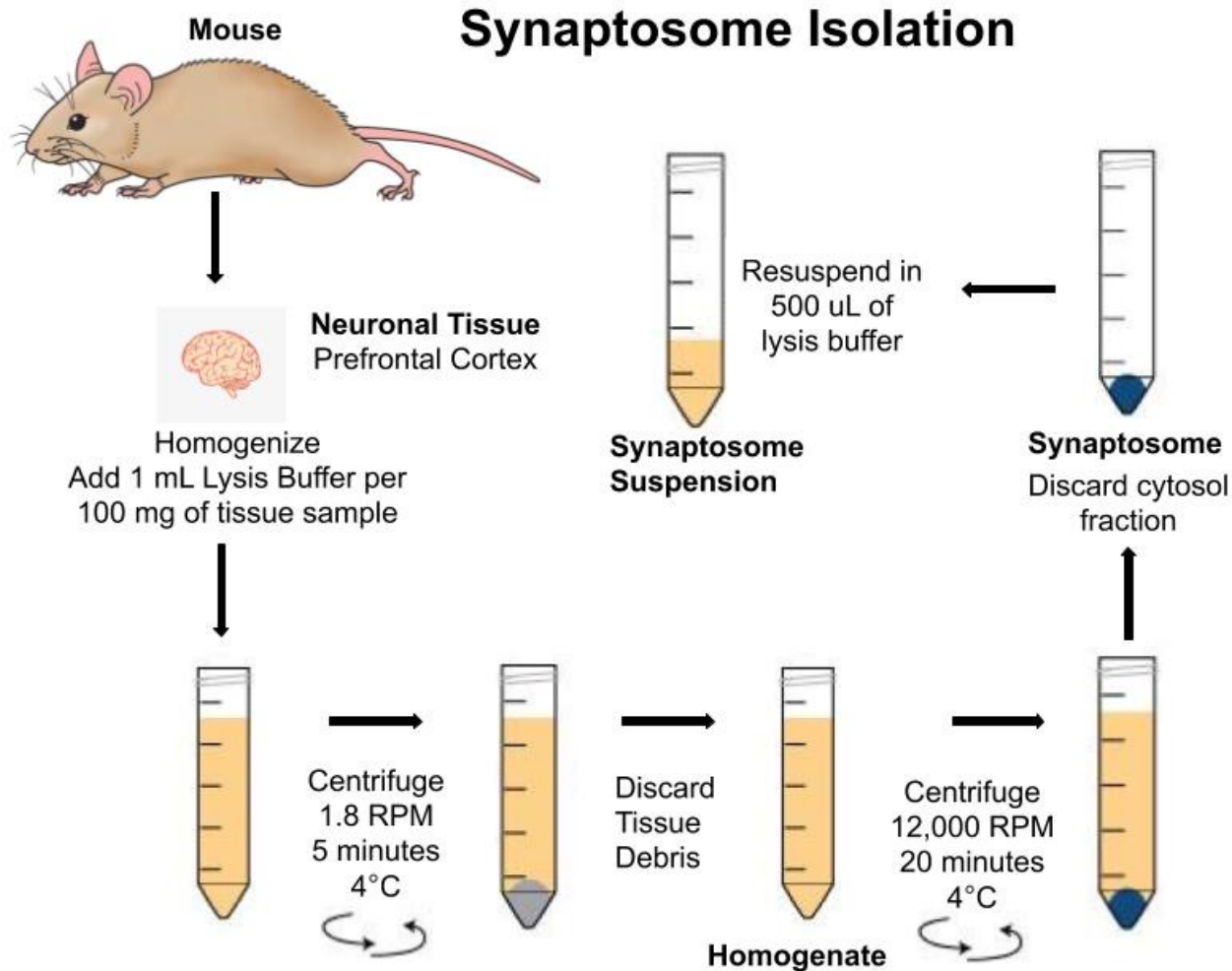
Synaptosome Overview

Represent pinched-off nerve terminals

- Serve as window into synaptic function
- Contain neurotransmitters and post synaptic cleft of isolated synapses from glial cells



Synaptosome Preparation



Results

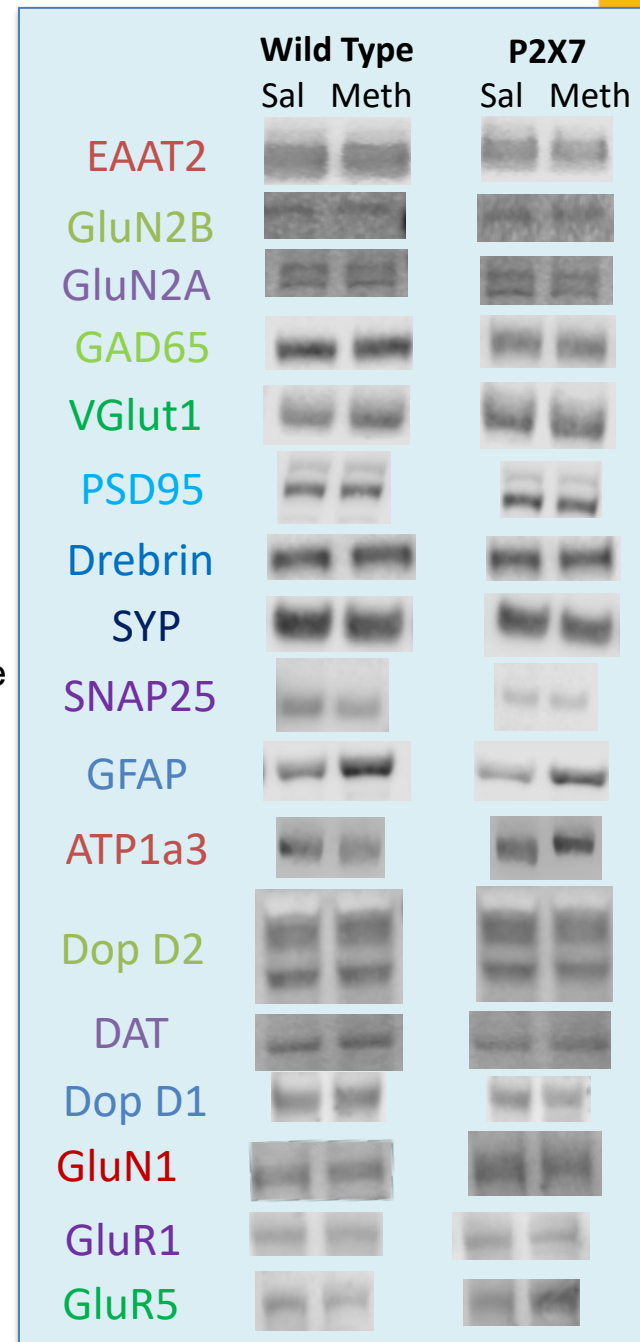
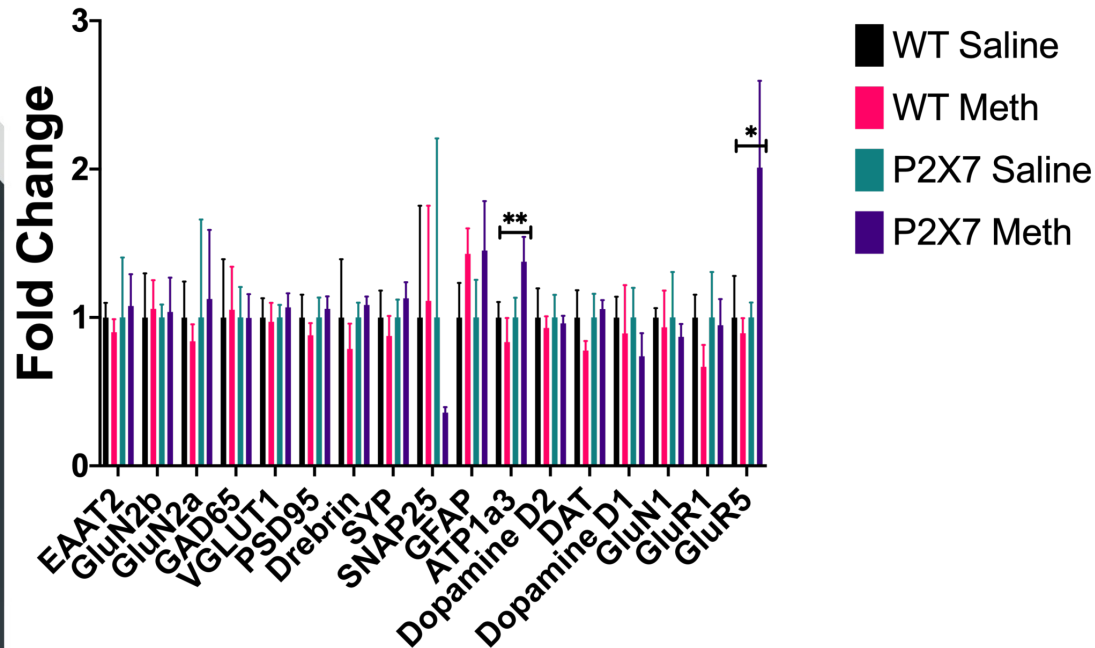
- Synaptic Differences
 - Synapse Counts
 - Protein Expression
- Sex Differences



Western Blot

Females Only

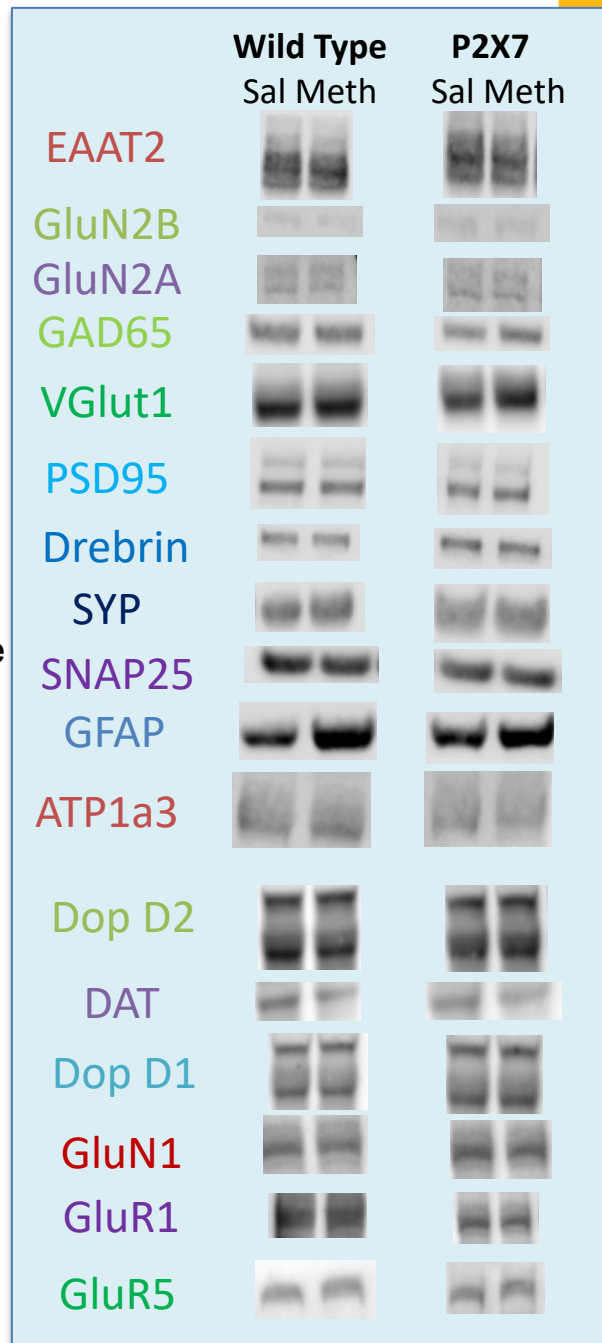
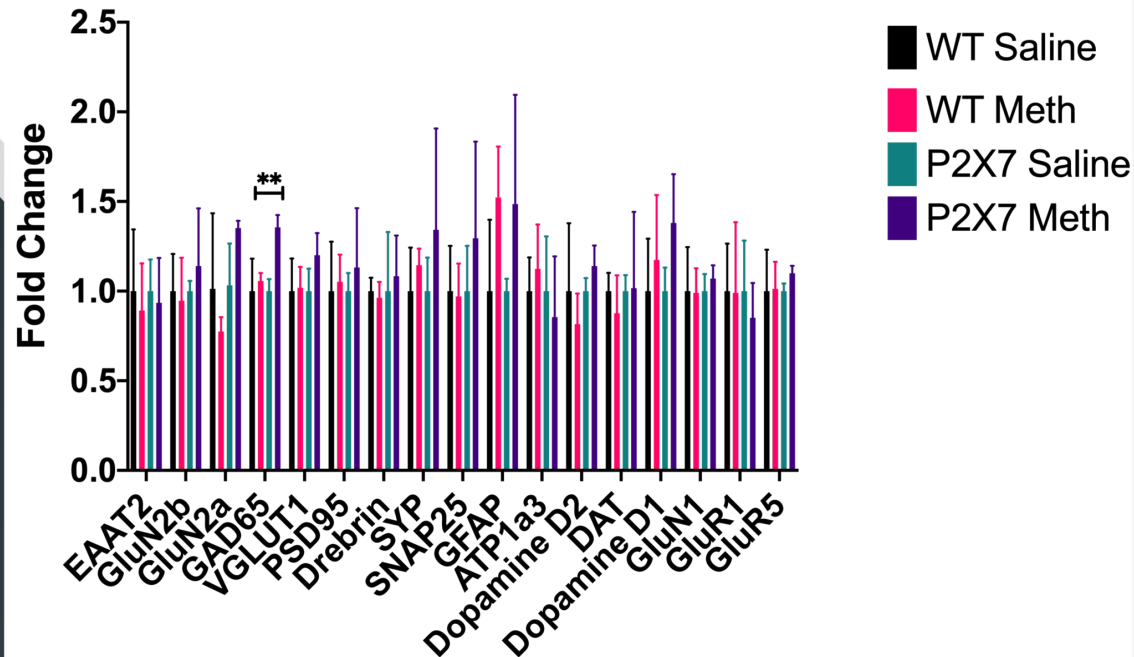
Chronic Females



Western Blot

Males Only

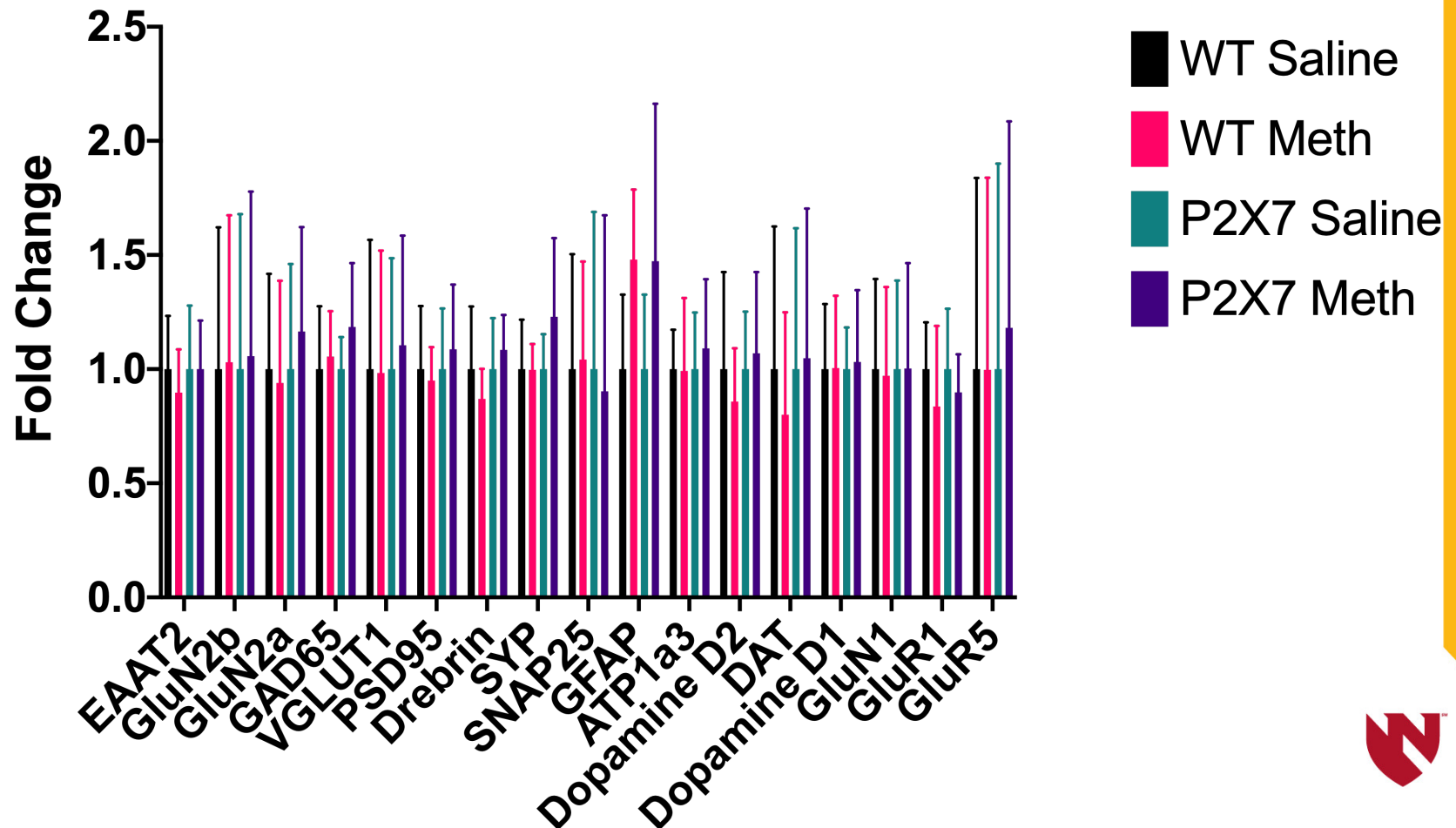
All Blots Males



Western Blot

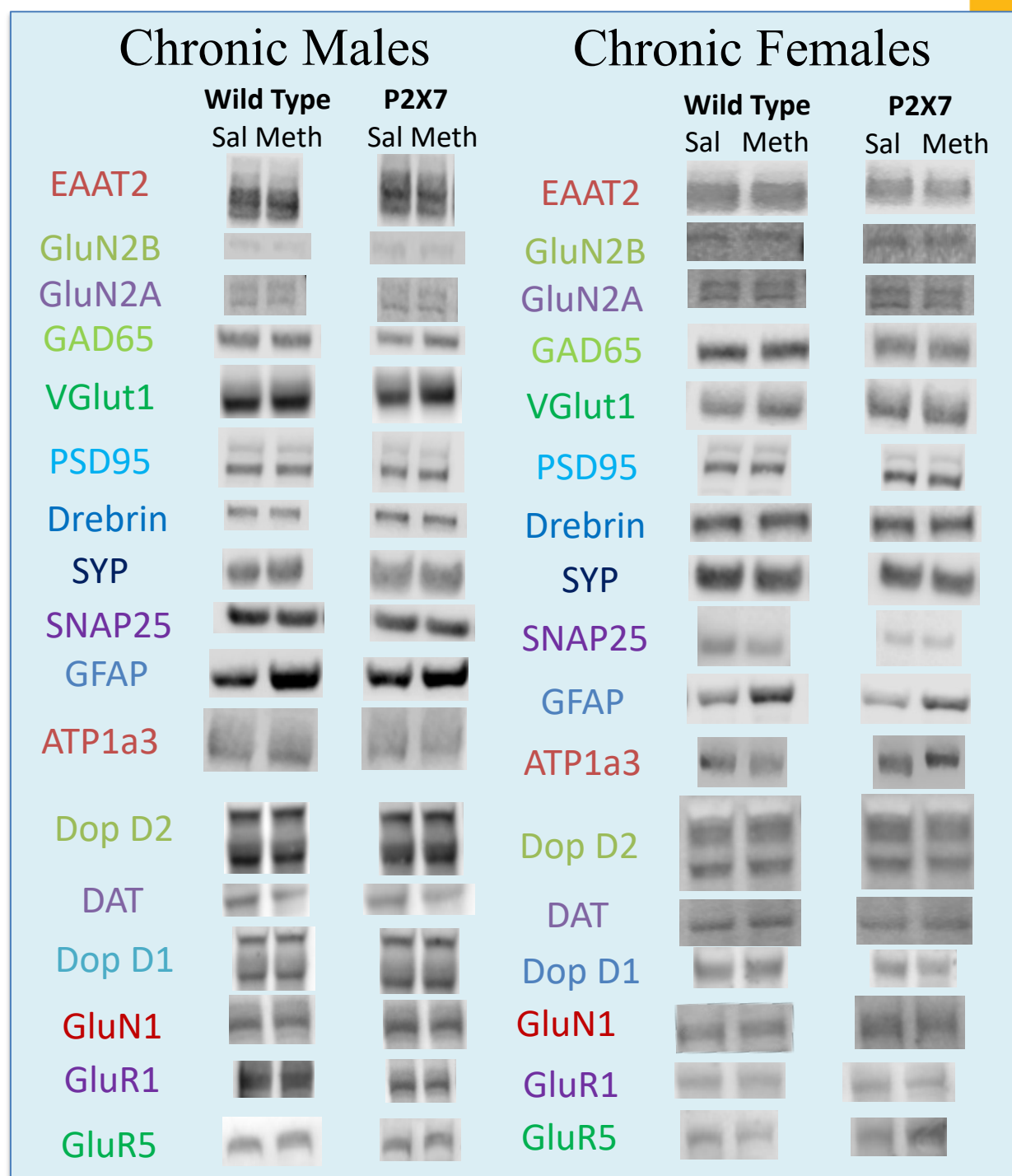
Males and Females

Chronic Males and Females



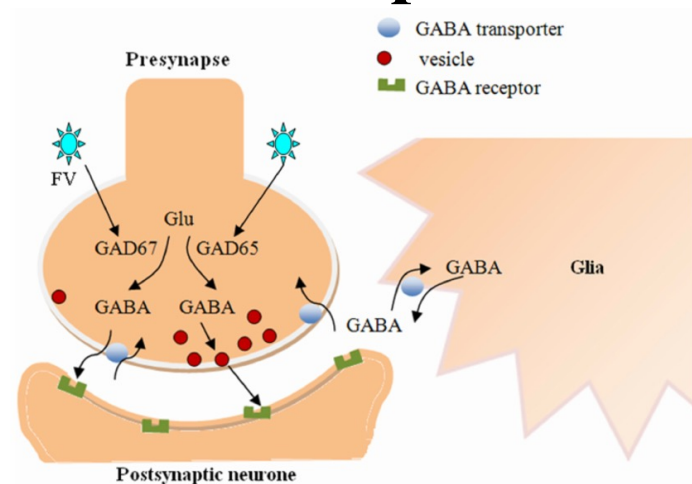
Western Blot

Males and Females



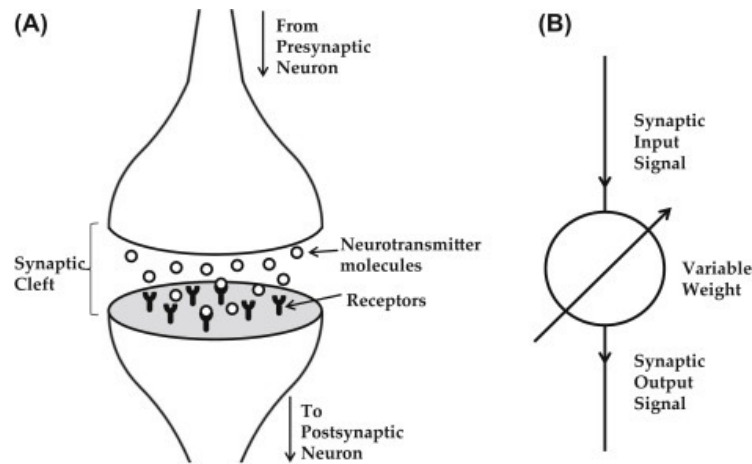
GAD65

- Synthesizes the inhibitory neurotransmitter GABA
- Higher expression in P2X7 KO meth group > meth wild type group
 - **Higher levels of GABA needed to counteract increased dopamine release**



ATP1a3

- Known as Na^+/K^+ ATPase or the sodium pump
- ATP1a3 uses ATP as an energy source for pumping ions and out of cells
- Increase in ATP1a3 could be a complimentary effect of high levels of meth-induced ATP released into the cell system



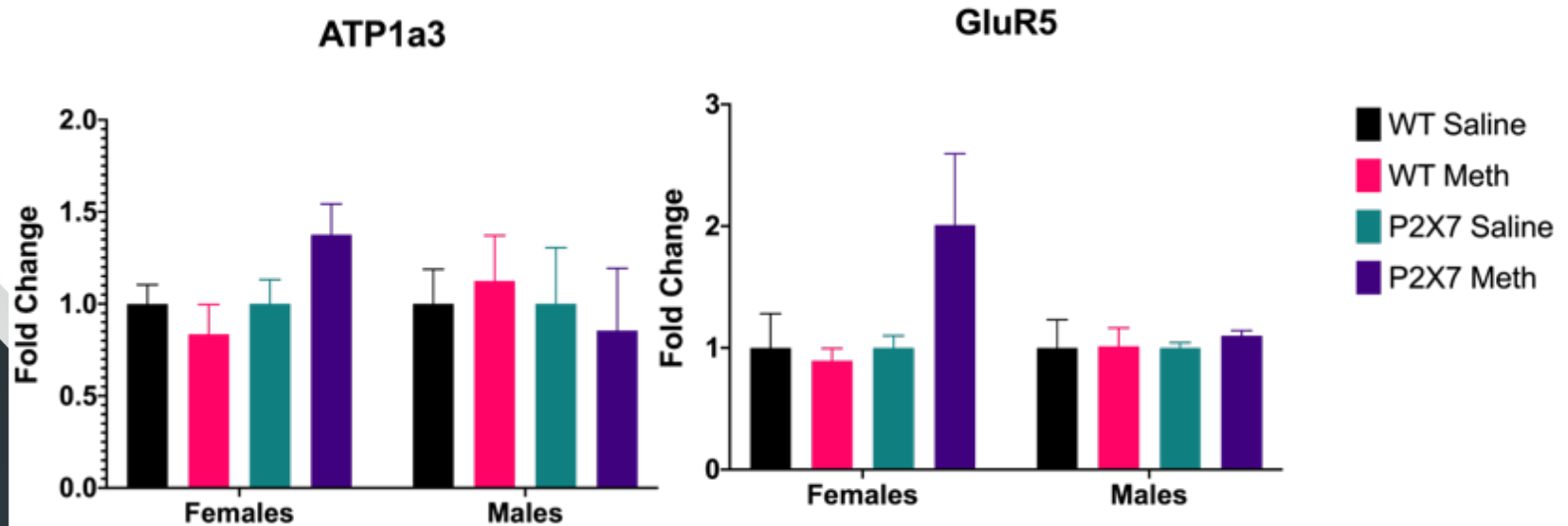
GluR5

- Ionotropic glutamate receptor
- L-glutamate acts as excitatory neurotransmitter in synapses of CNS
 - **Induces conformation change, thereby opening the cation channel** Glutamatergic transmission is a key component in psychostimulant addiction
- mGluR5 receptors play an important role in methamphetamine reinforcement and methamphetamine-seeking behavior (Herald et al, 2012)



Sex Differences

P2X7 KO Meth Group



- Female rats are far more responsive to anti-inflammatory effects induced by the P2X7 receptor blockade than male rats



Future Directions

- Behavior Testing- GluR5 CPP testing sex differences
 - Hot Cold Plate
 - CPP
- Further investigation of the hit markers, GAD65, ATP1a3, GluR5, from our findings
- Ongoing acute studies, waiting to increase sample size
- Increasing the male sample size to see if GAD65 remains significant
- Increasing female sample size to see if ATP1a3 and GluR5 remain significant



Acknowledgments

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Citations

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