Addiction Therapy-2014

Chicago, USA

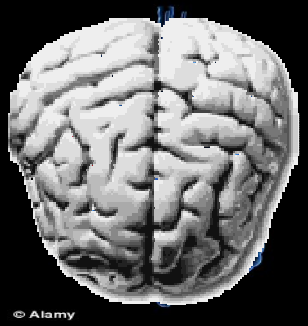
August 4 - 6, 2014





Bryan Yamamoto

Peripheral and Central Mechanisms of Methamphetamine Neurotoxicity: Connecting the Dots



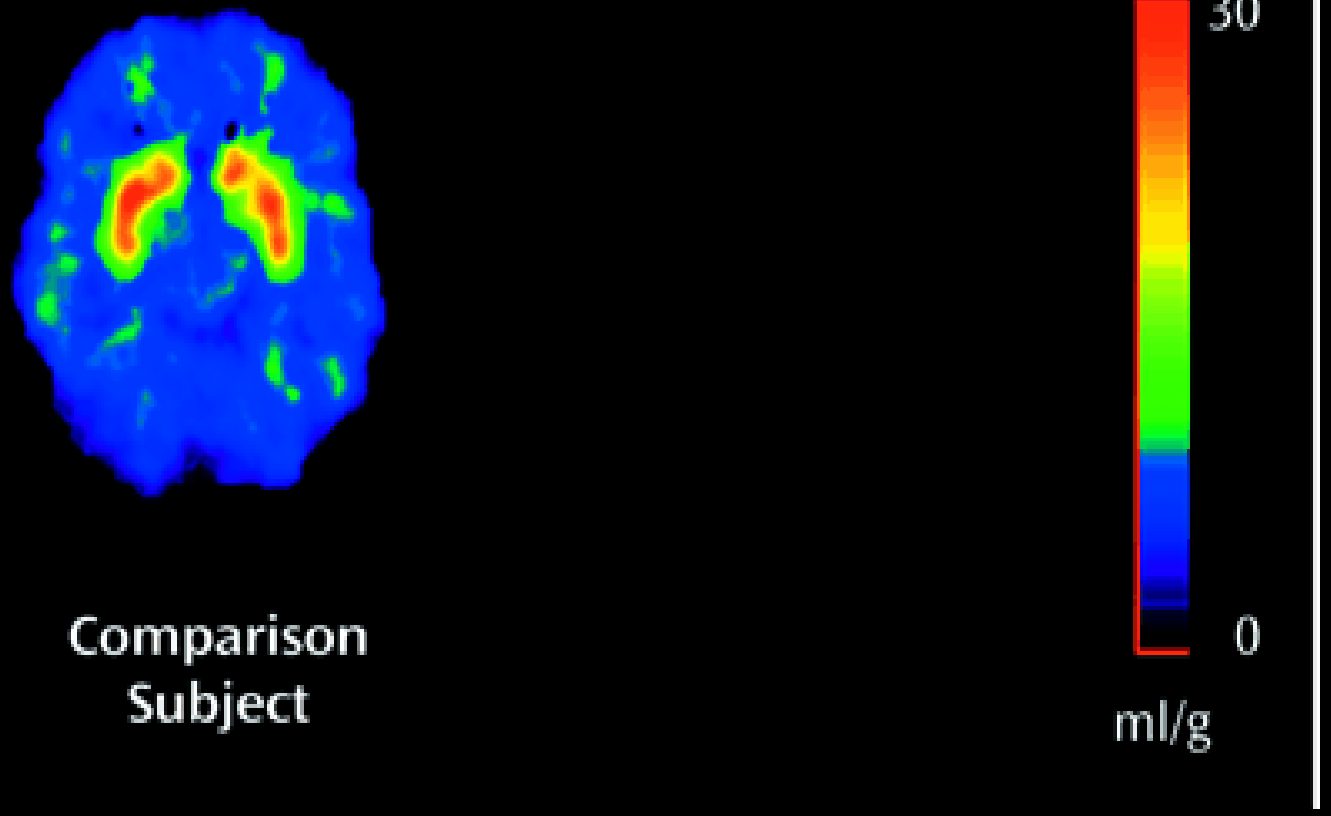


Bryan Yamamoto, Ph.D.
Department of Neurosciences
University of Toledo College of Medicine and Life Sciences
August 4, 2014

COLLEGE OF MEDICINE AND LIFE SCIENCES
THE UNIVERSITY OF TOLEDO

Methamphetamine Neurotoxicity in Humans

Volkow et al, Am. J. Psychiatry, 2001



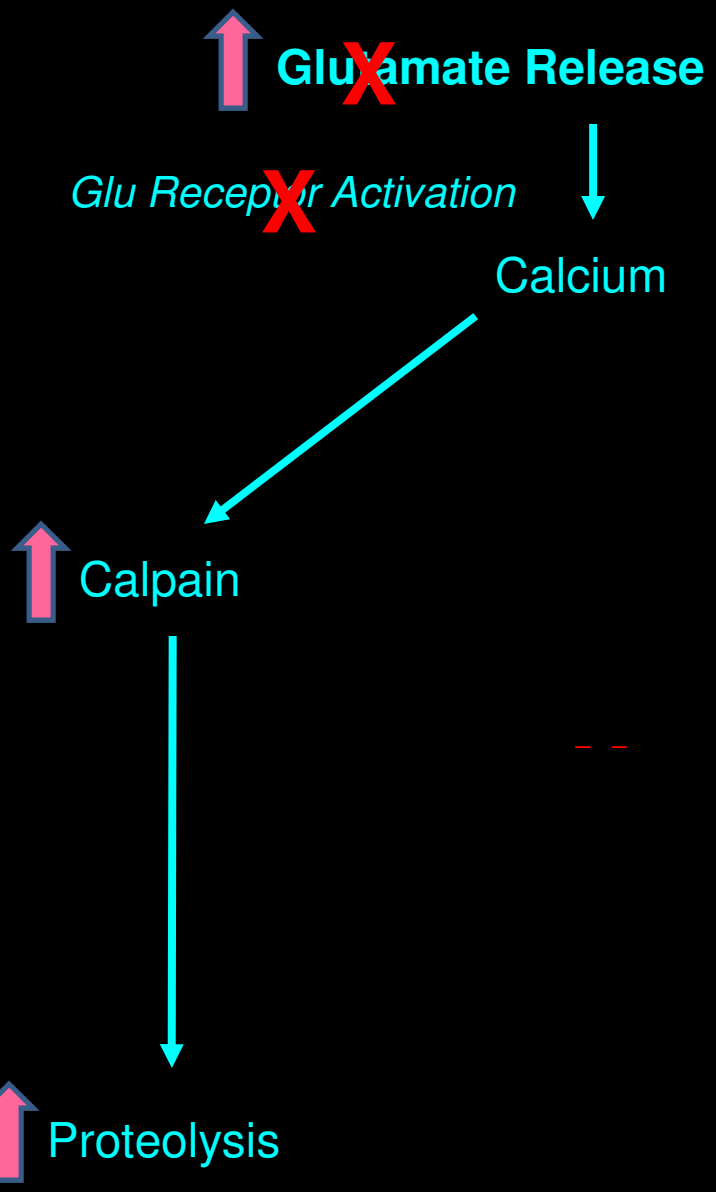
Callaghan et al., Drug and Alcohol Dependence, 2011

Meth abuse increases risk of Parkinson's Disease by 76% compared to age-matched controls and cocaine-abusers

Overarching Hypothesis

Excitotoxicity and oxidation of proteins and lipids are mechanisms underlying the neurotoxicity of Methamphetamine

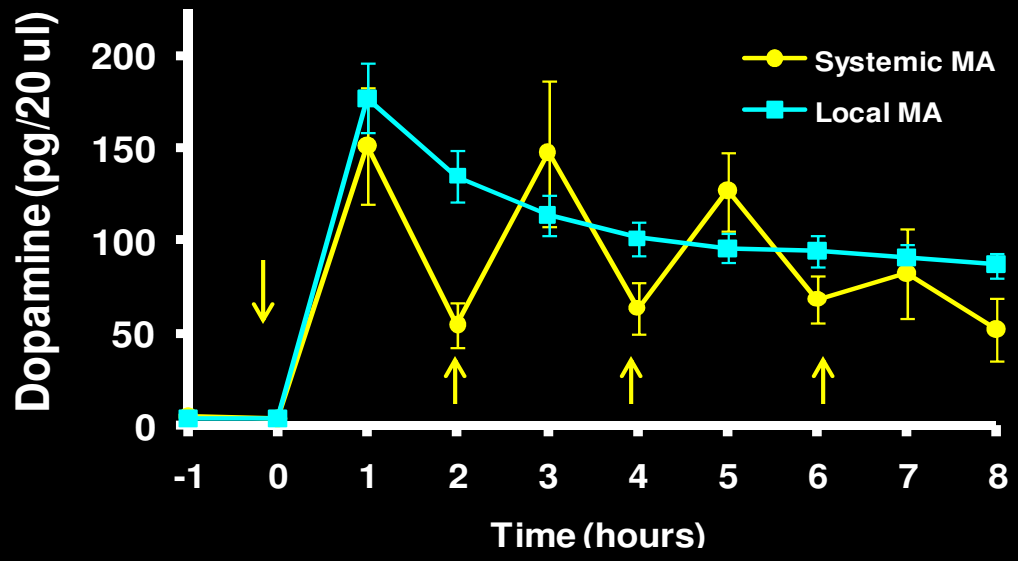
Identified Events Leading to a Loss of Dopamine and 5HT



But, there are caveats to the proposition that the neurotoxicity/excitotoxicity of METH is a result of its direct action on the brain……..

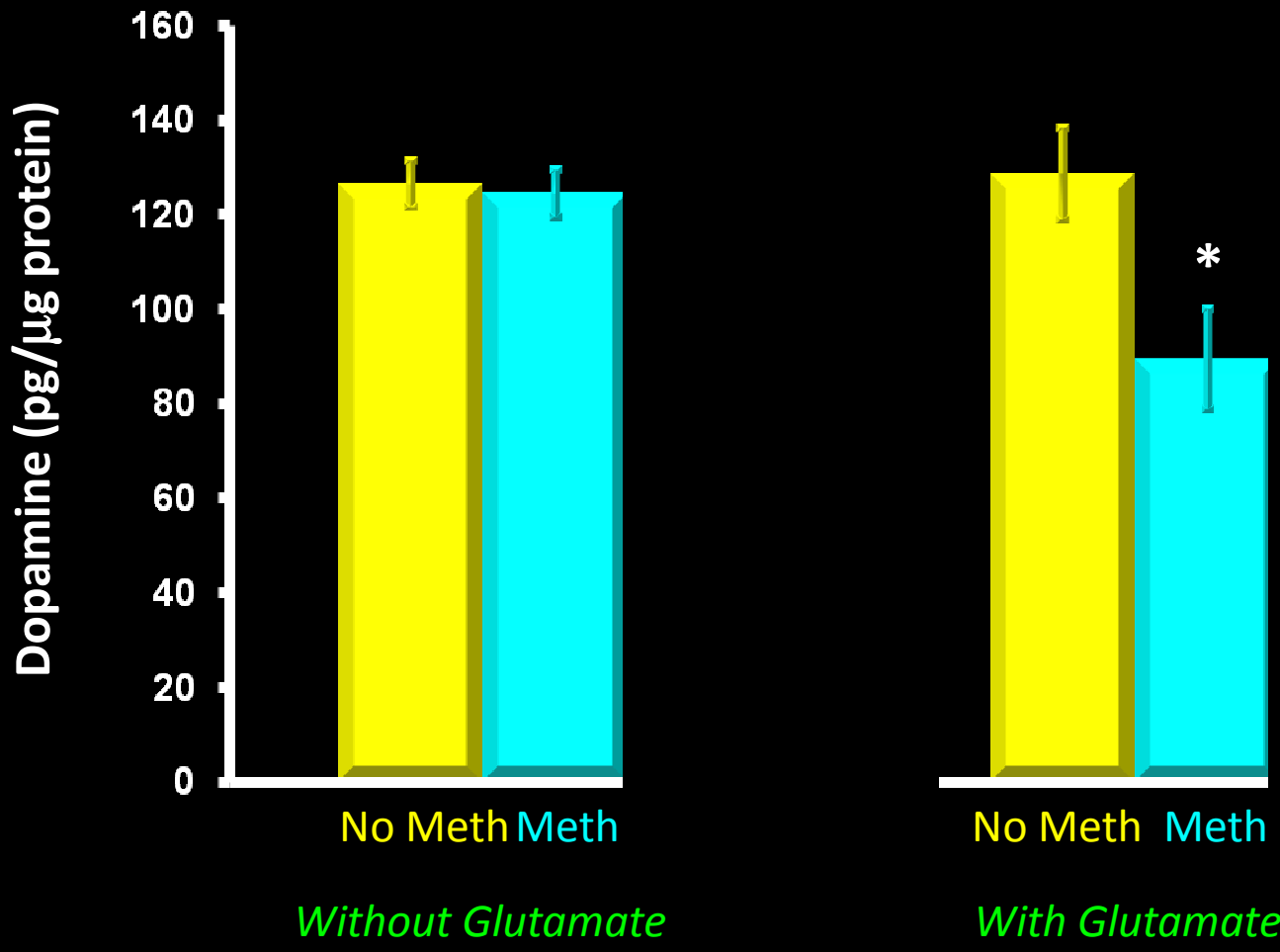
Systemic and Local Administration of METH:

Local administration of METH does not increase glutamate



Burrows

Glutamate Synergizes with Local METH To Deplete Dopamine Content



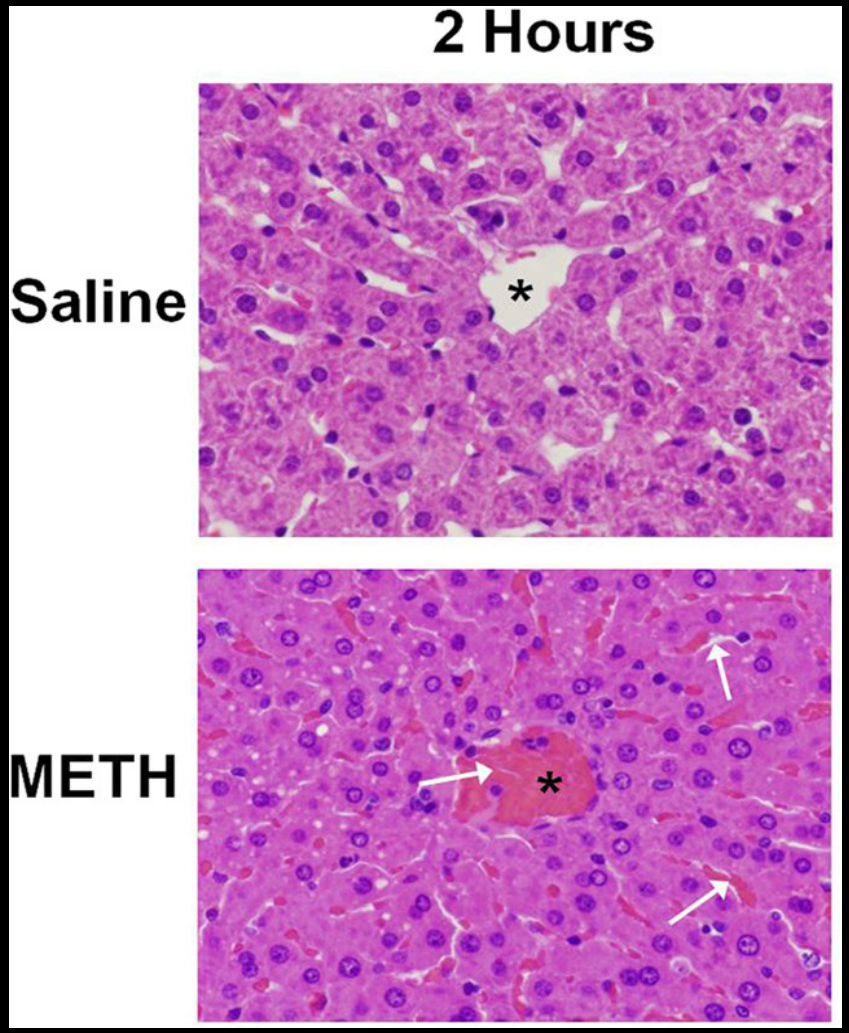
Burrows

Thinking Outside the Brain……

- If it is not the direct effect of METH alone on the brain (striatum), *what other systems could be responsible for the neurotoxicity?*

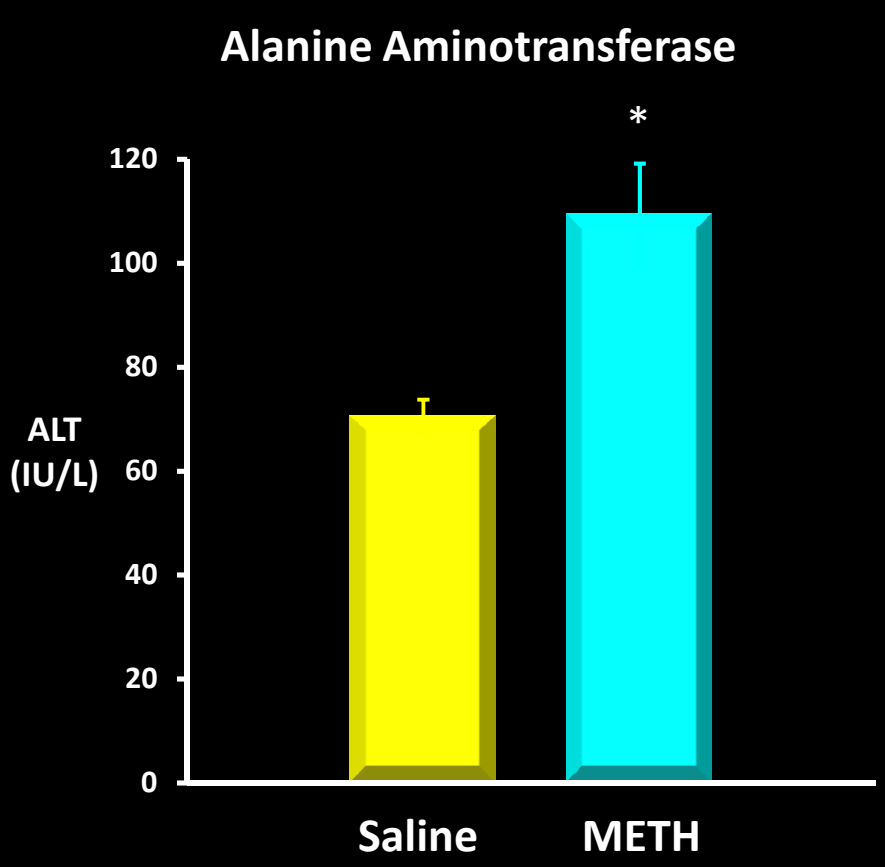
- Another target of METH is the liver
- Liver damage can produce encephalopathy (i.e. hepatic encephalopathy)
  - Tremor, movement disorders
  - Delirium, stupor, confusion, and coma

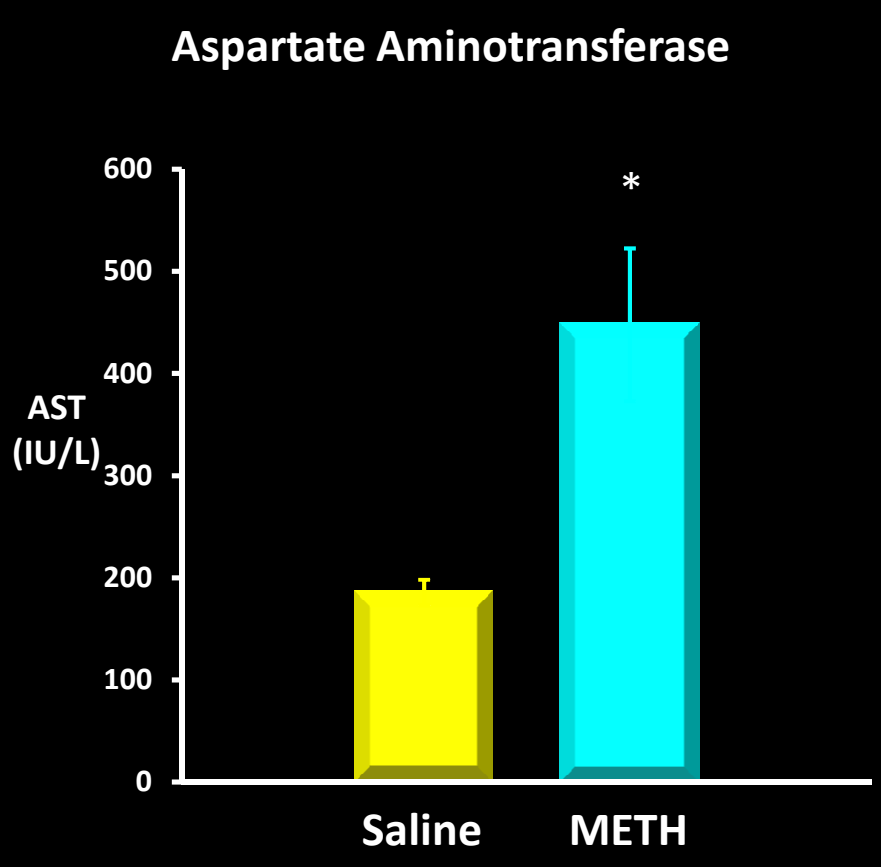
METH and Evidence of Hepatotoxicity



Halpin

Methamphetamine Increases Liver Enzymes in Plasma





Halpin

Liver Damage and Ammonia

- The liver normally removes excess ammonia from the blood via the urea cycle.
- This is important because ammonia is a neurotoxic byproduct of protein metabolism and other metabolic reactions.
- If the liver damaged, there is an accumulation of ammonia that is thought to cause hepatic encephalopathy

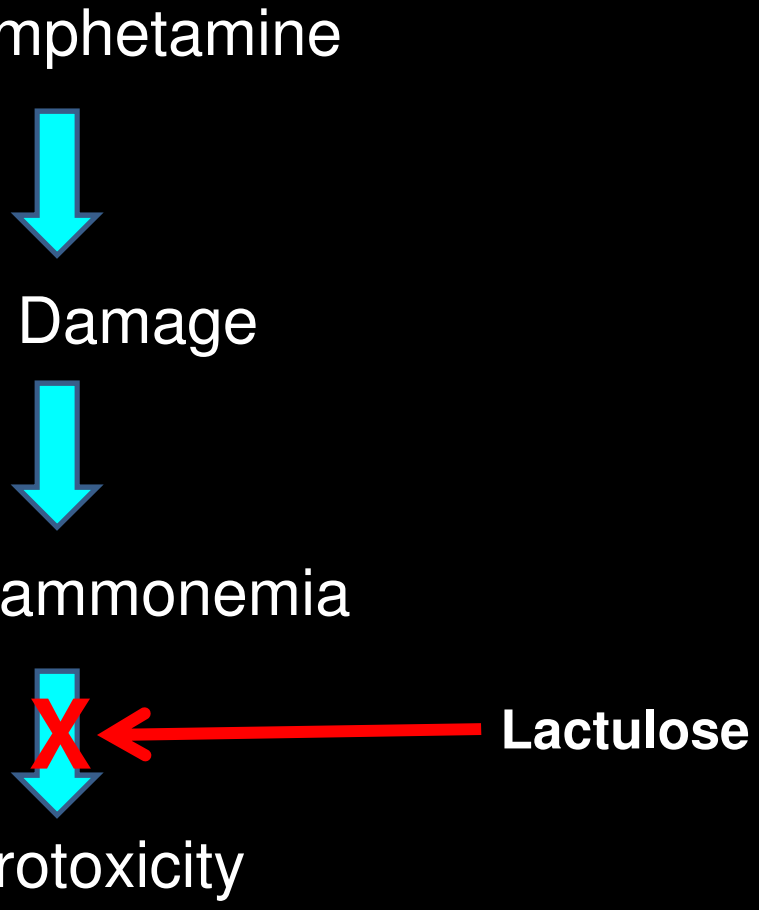
Ammonia Toxicity

- Excitotoxicity (Fan and Szerb, 1993, Hermenegildo et al., 1996)
- Oxidative stress (Kosenko et al., 1997 and Kosenko et al., 1995)
- Metabolic compromise (Hawkins et al., 1973, McCandless and Schenker, 1981)

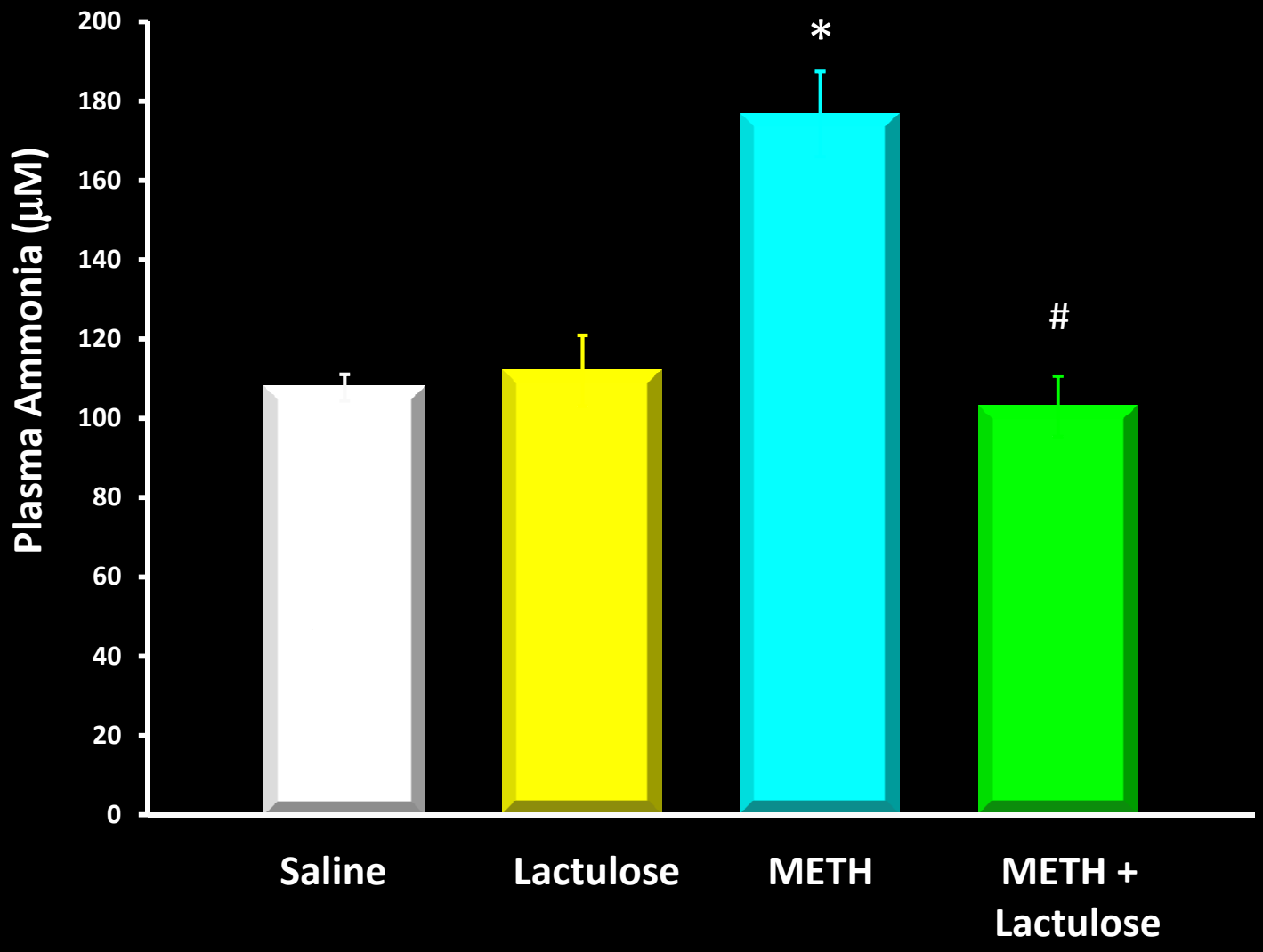
∴ *Similar mechanisms that mediate the toxicity to ammonia and the neurotoxicity to METH*

- Unknown whether peripheral organ (e.g. liver) damage is produced by METH and if it contributes to METH neurotoxicity

Overarching Hypothesis

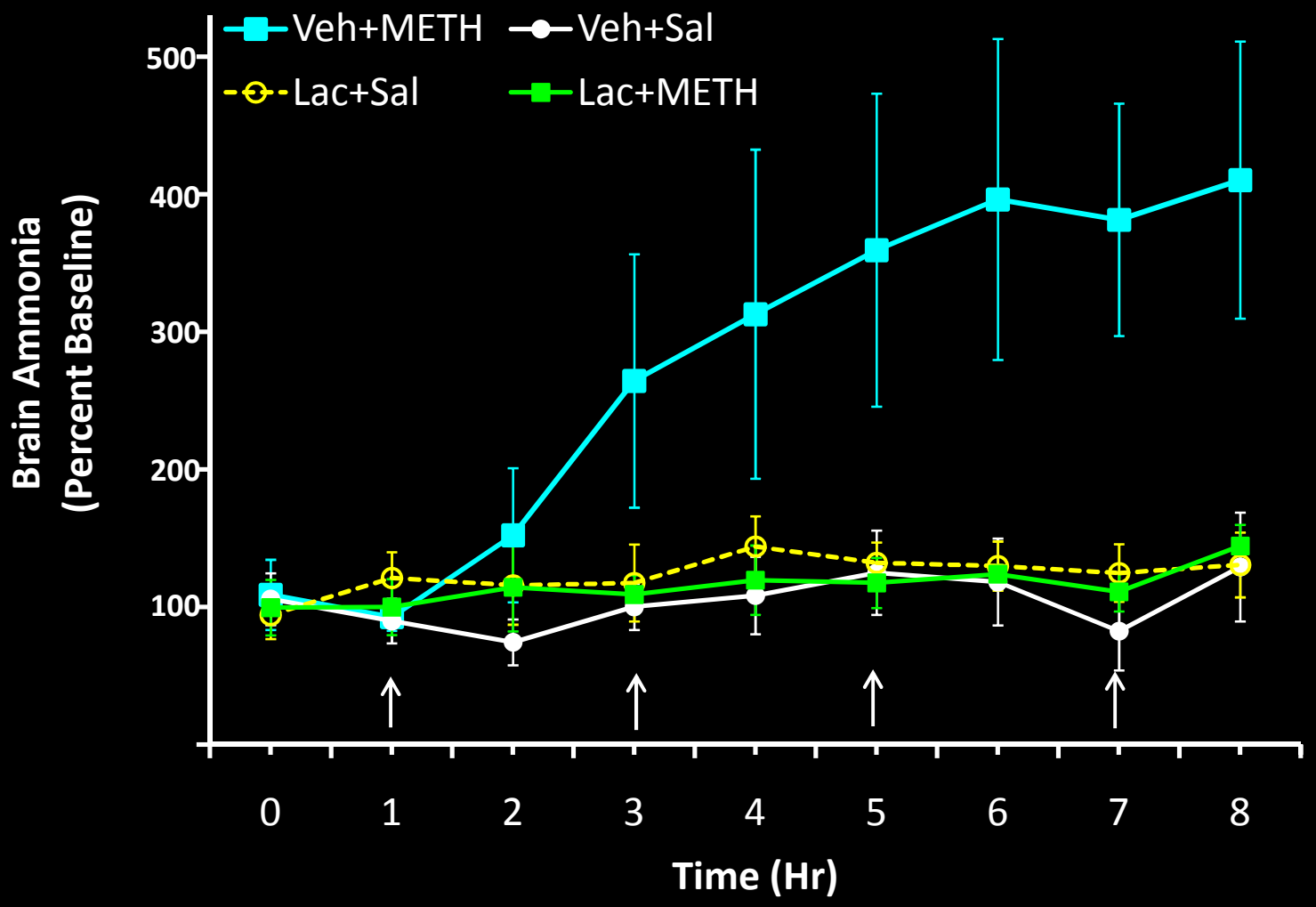


Methamphetamine Increases Ammonia in Plasma



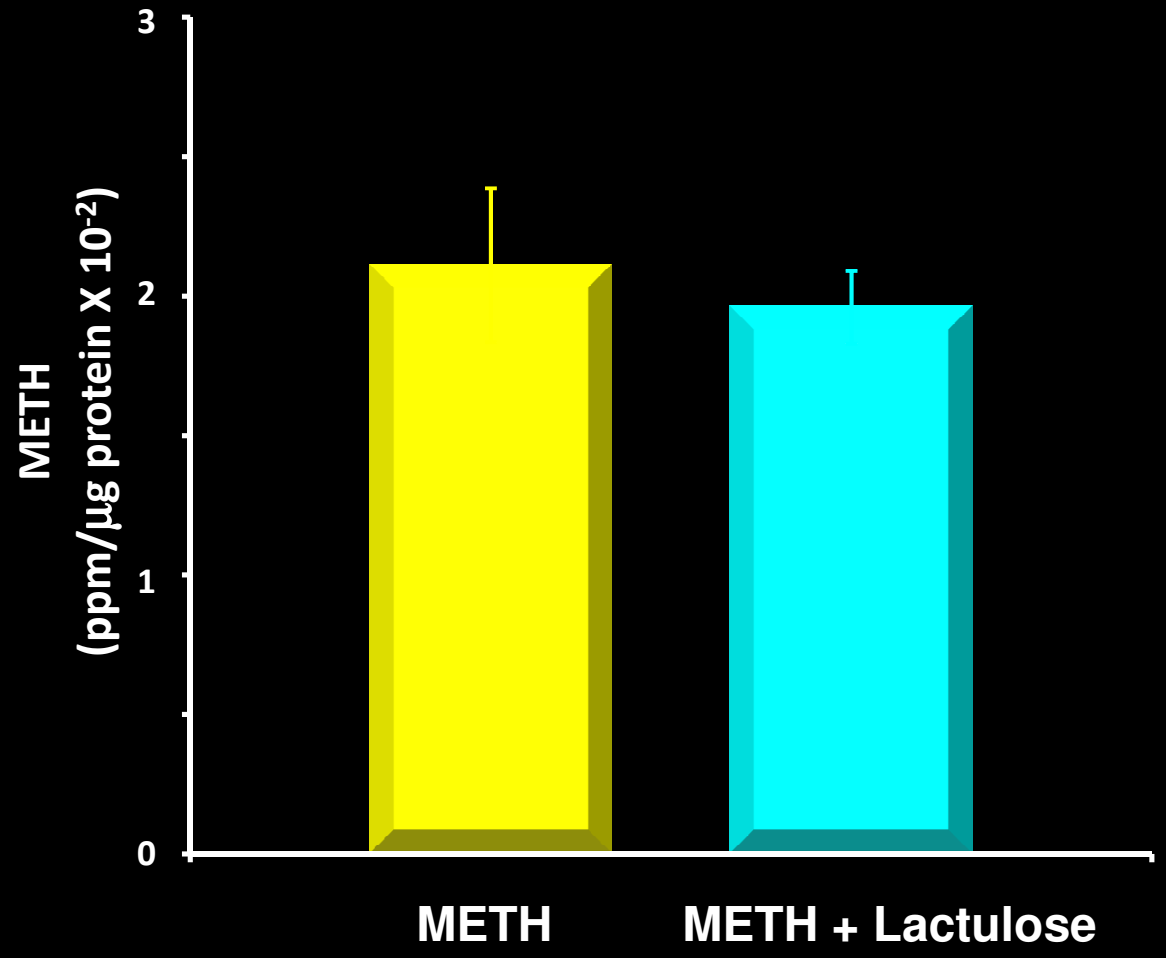
Halpin

Methamphetamine Increases Ammonia in Striatum: Blocked by Lactulose



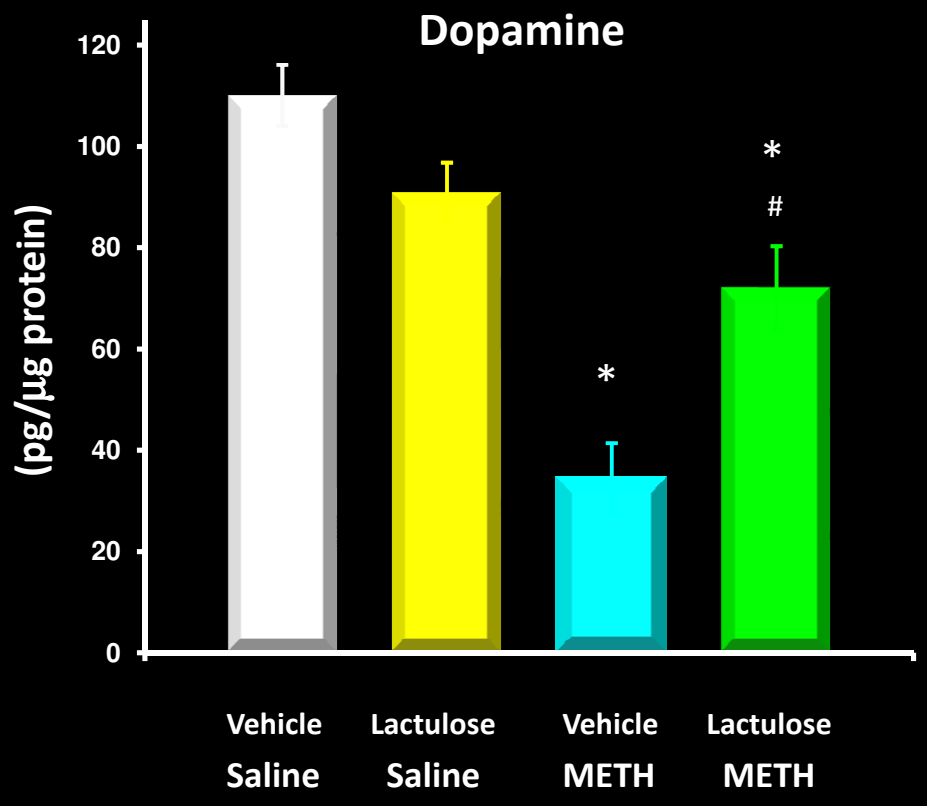
Halpin

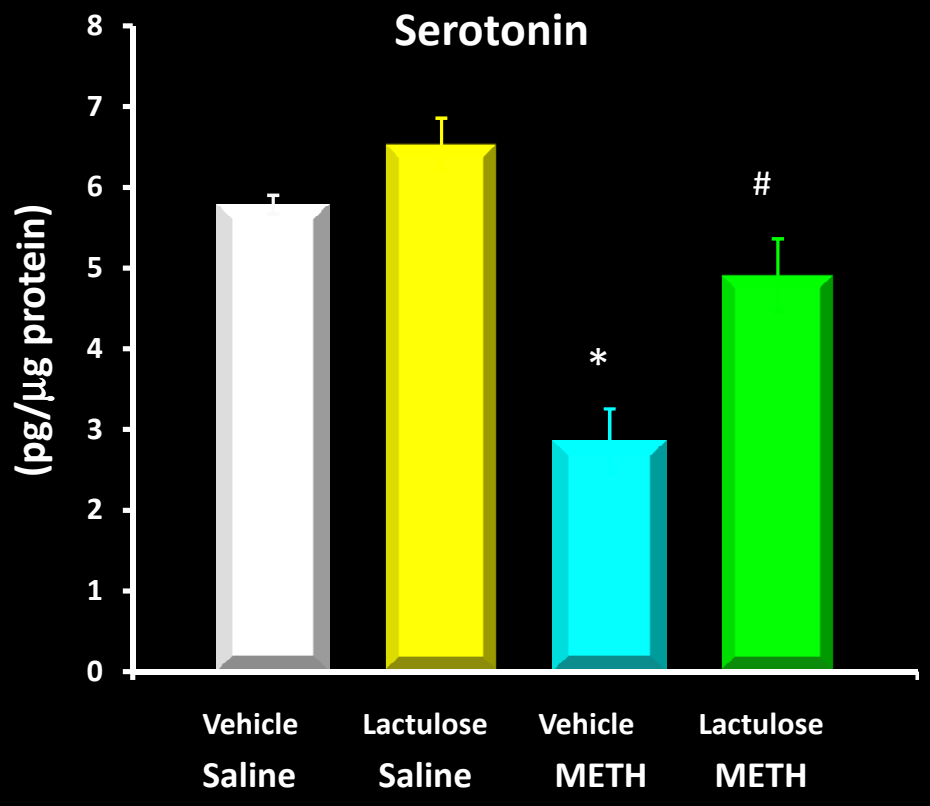
Lactulose Does Not Affect METH Concentrations in the Brain



Halpin

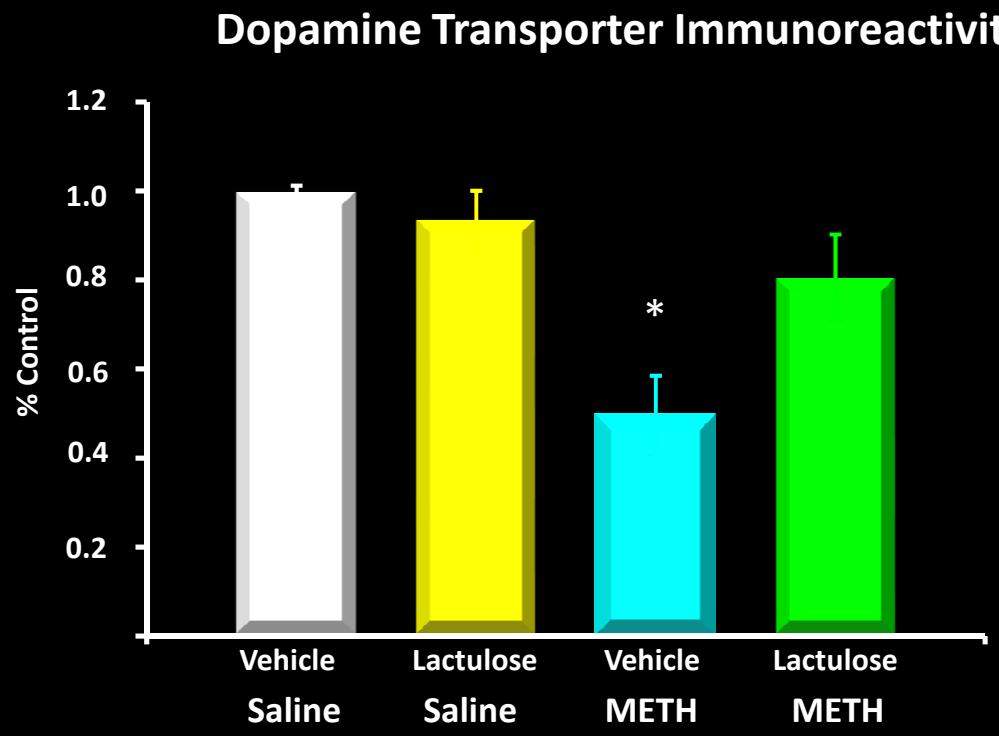
Lactulose Attenuates METH-induced Long-term Depletions of Dopamine and 5HT Content

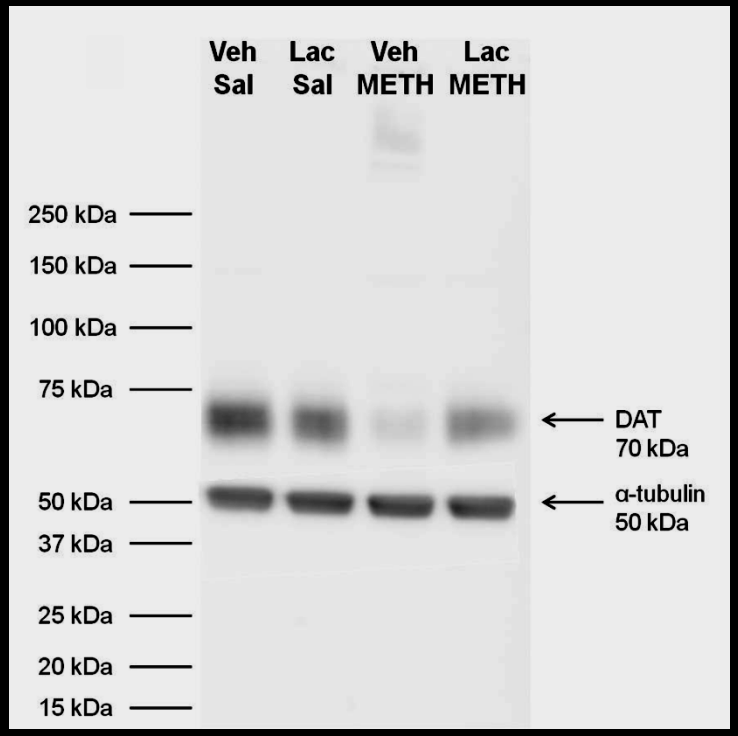




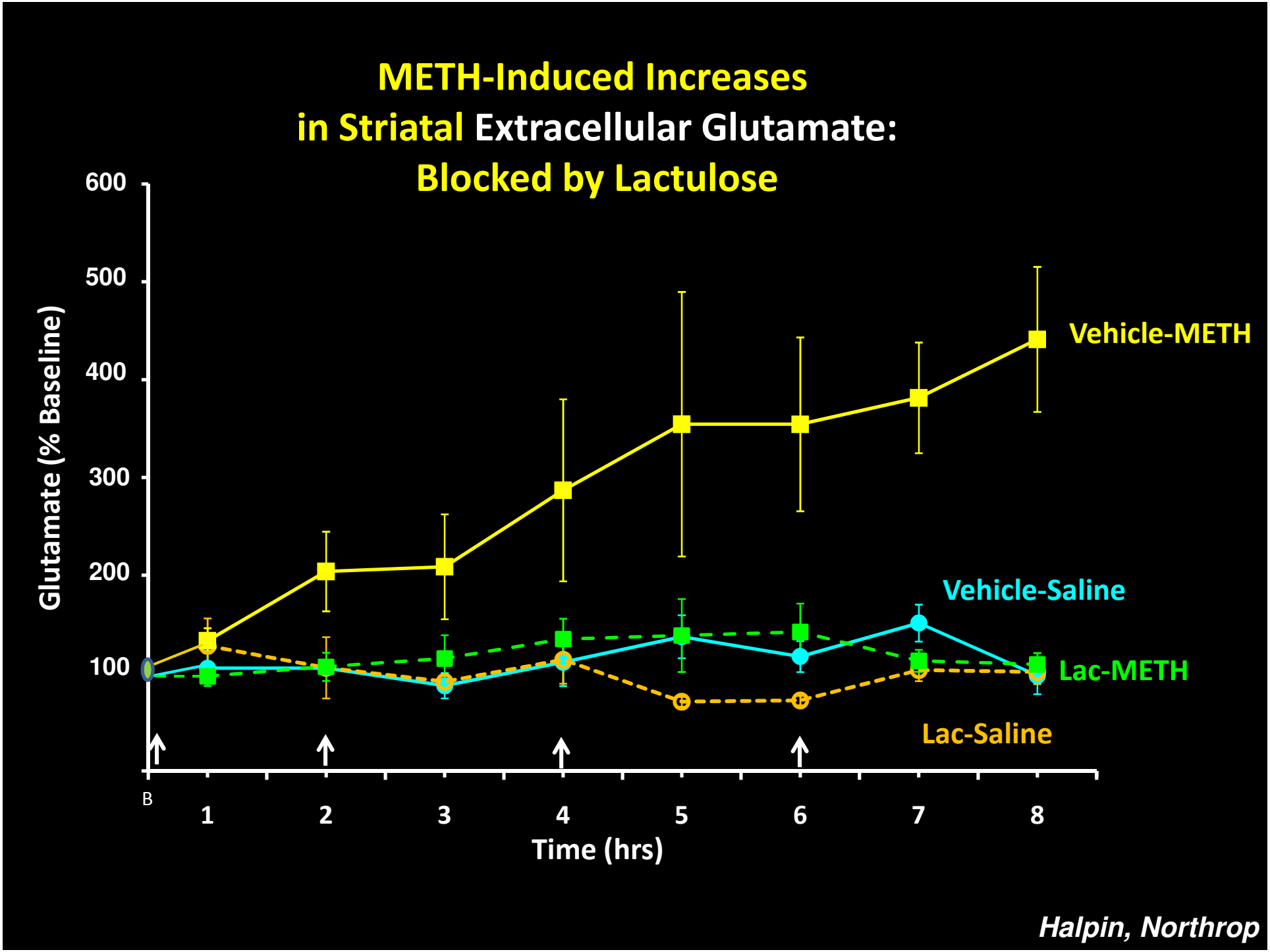
Halpin

Lactulose Blocks METH-induced Decreases in Dopamine Transporter Immmunoreactivity

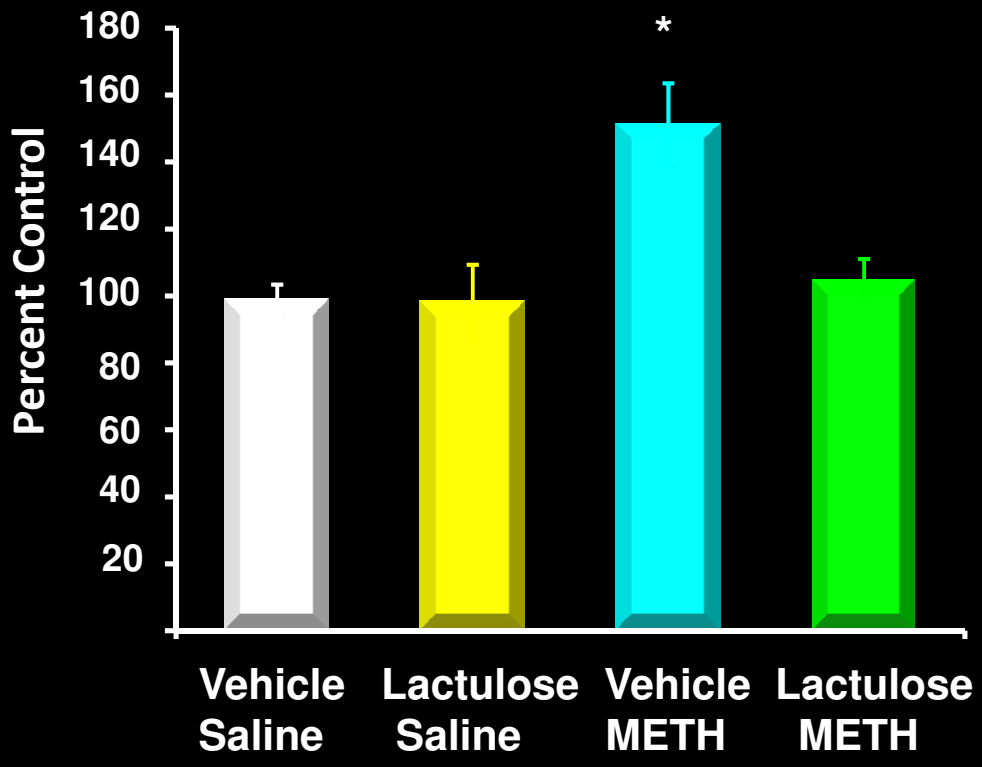


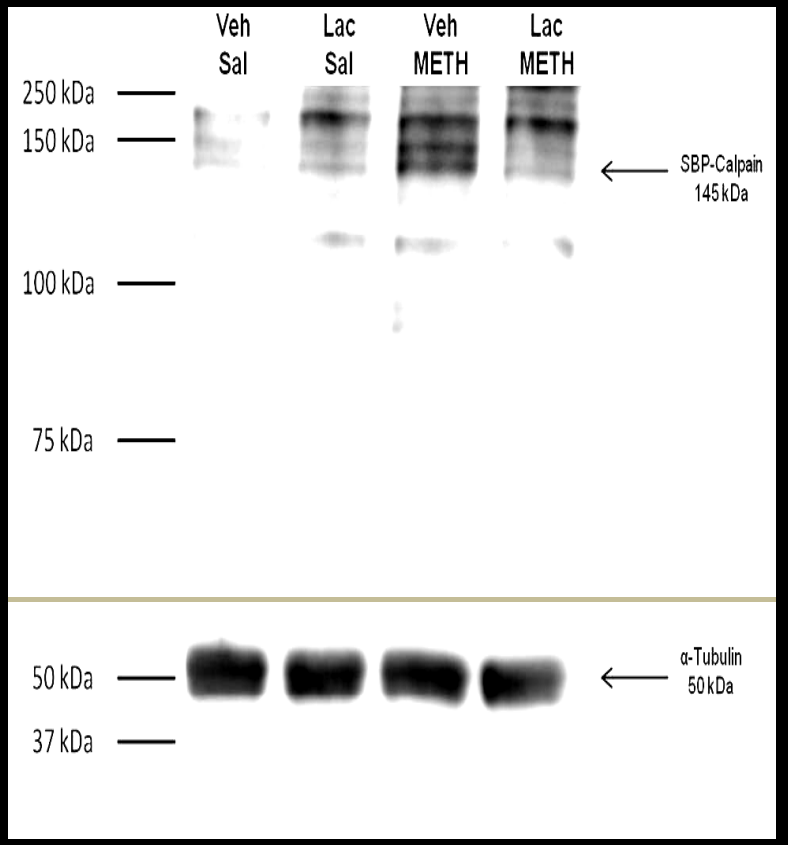


Halpin


METH-Induced Increases
in Striatal Extracellular Glutamate:
Blocked by Lactulose
Glutamate (% Baseline)
600
500
400
300
200
100
B
1
2
3
4
5
6
7
8
Time (hrs)
Vehicle-METH
Vehicle-Saline
Lac-METH
Lac-Saline
Halpin, Northrop

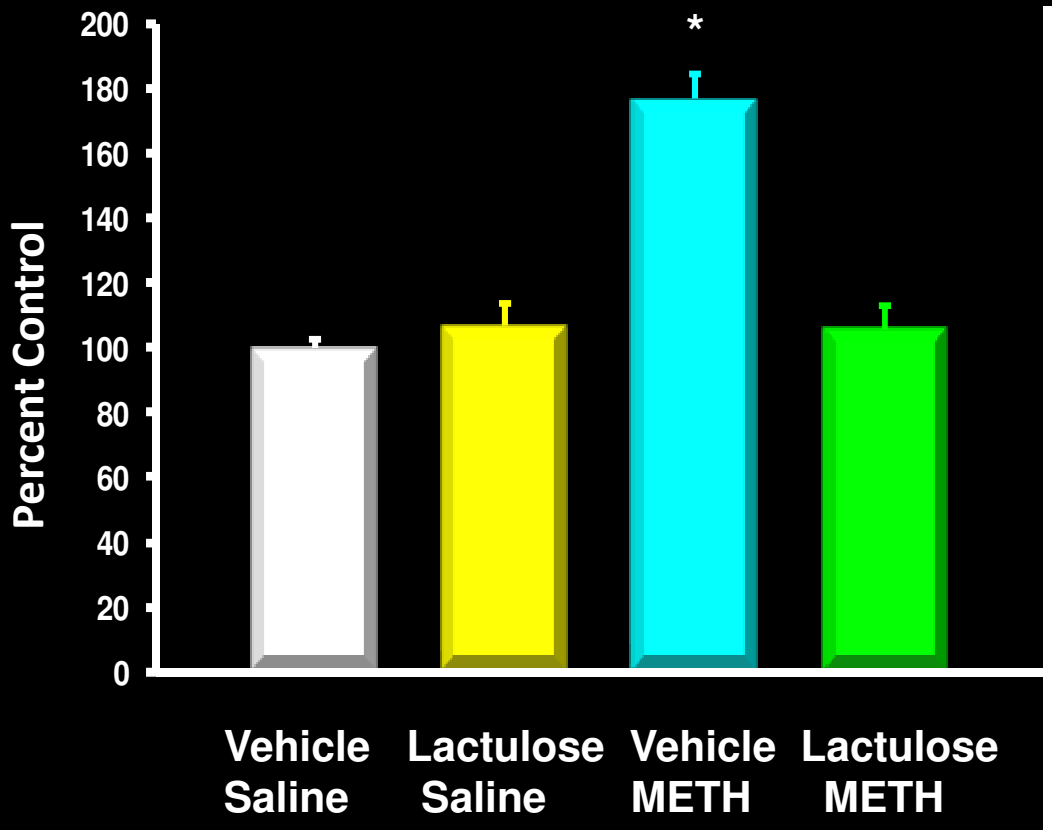
Lactulose Blocks METH-Induced Increases in Striatal Spectrin Proteolysis

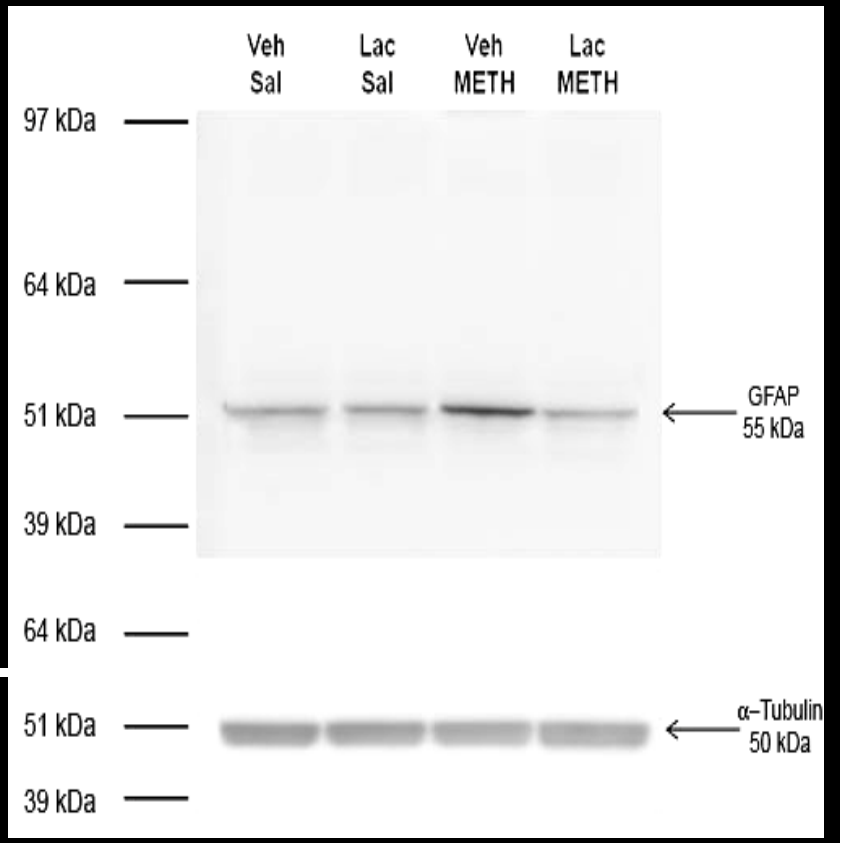




Halpin, Northrop

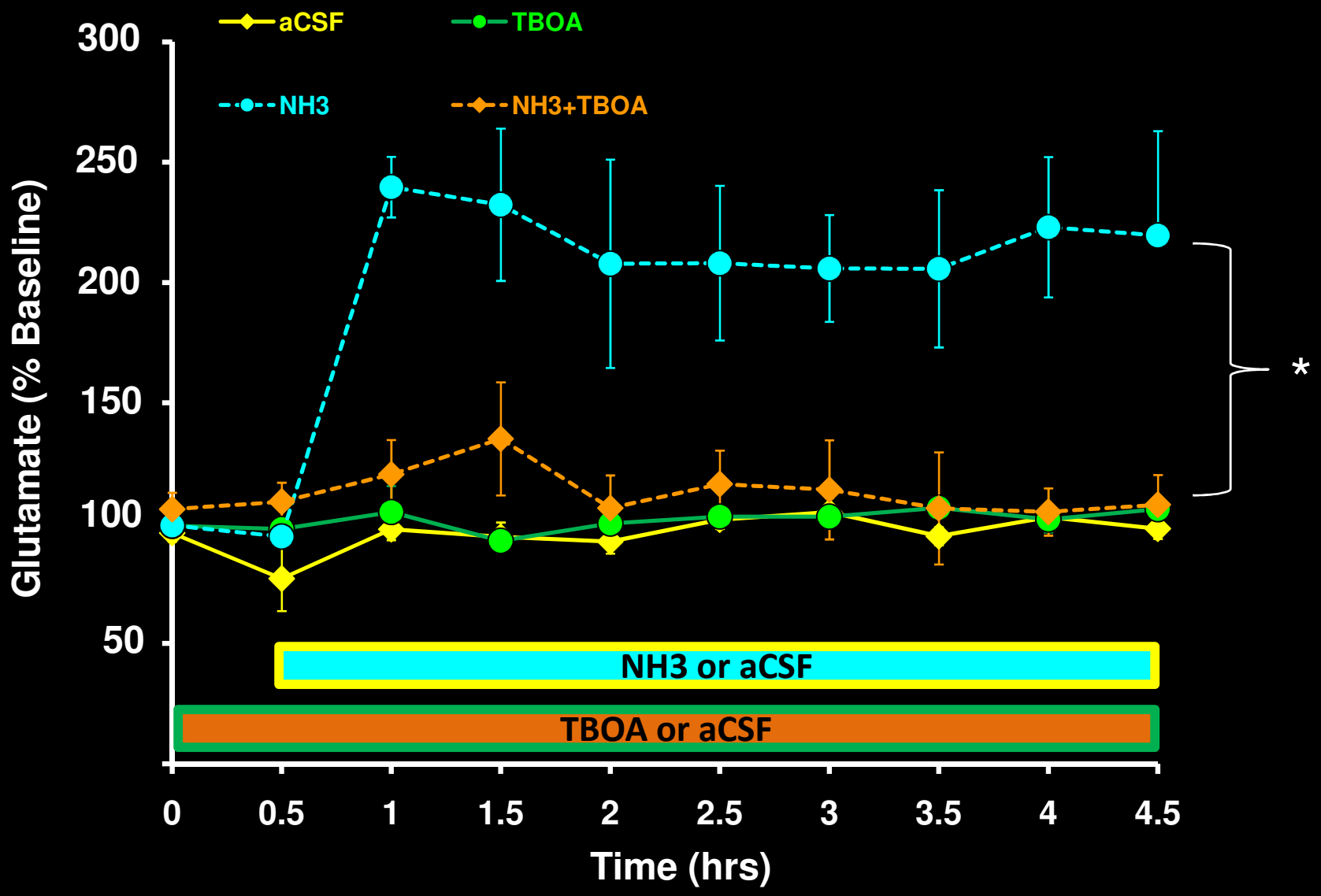
METH-Induced Astroglyosis (GFAP) is Blocked by Lactulose





Halpin, Northrop

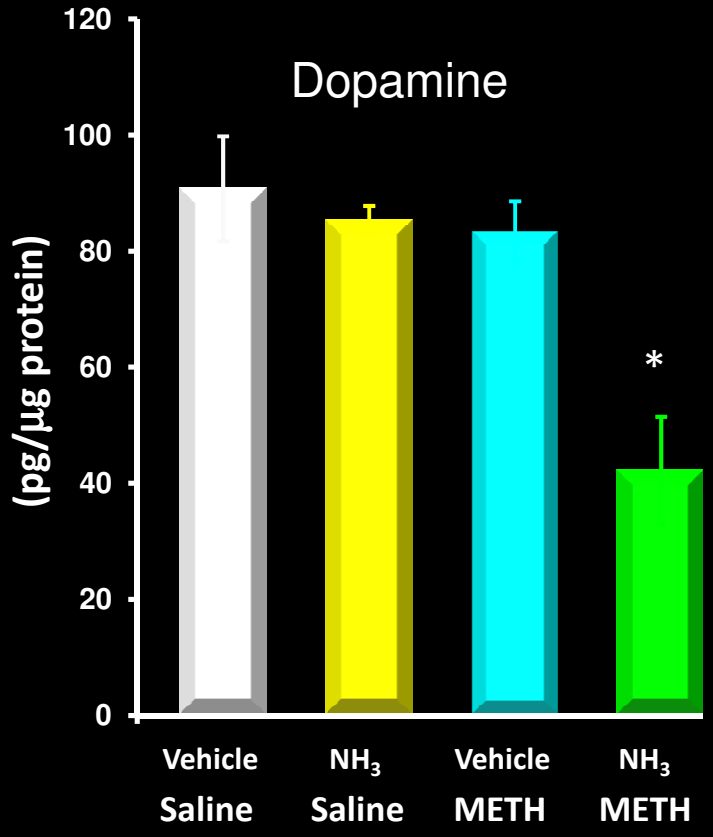
Local Perfusion of Ammonia on Glutamate:
Efflux Through Reversal of the Glutamate Transporter

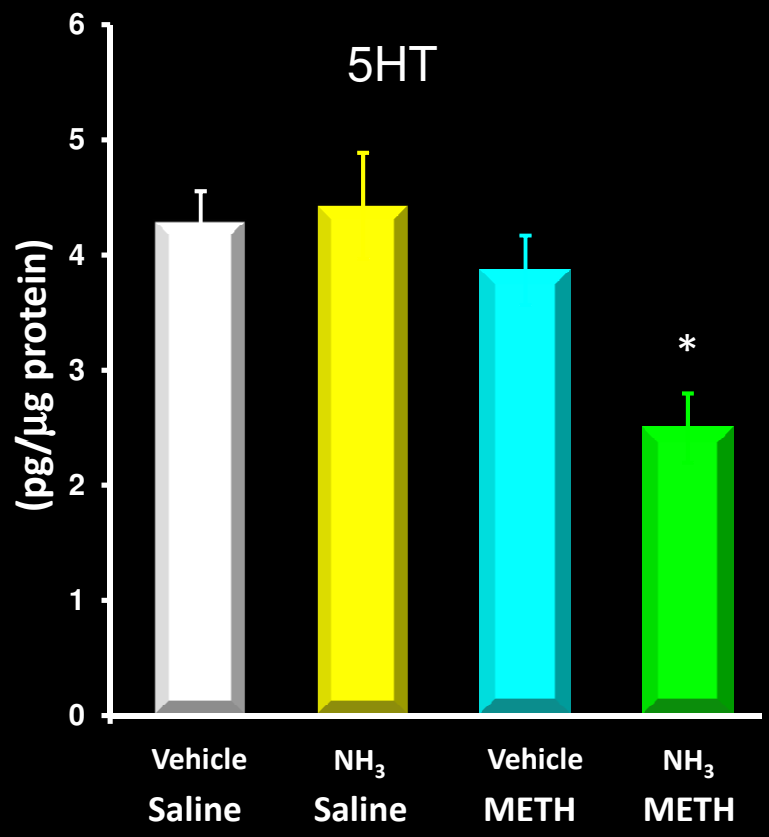


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Combined Local Perfusions of Ammonia and METH

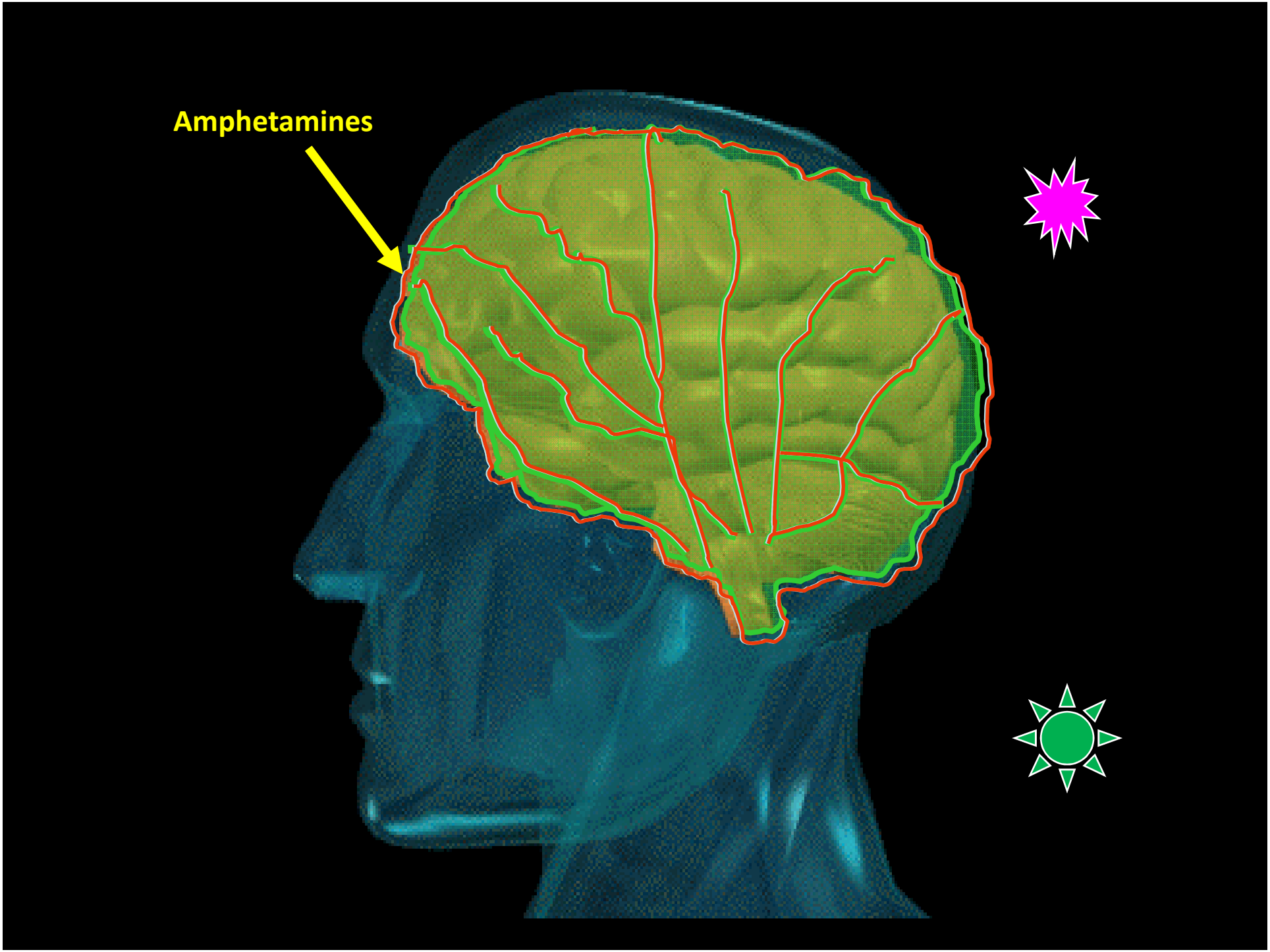
Dopamine and 5HT Content in the Striatum





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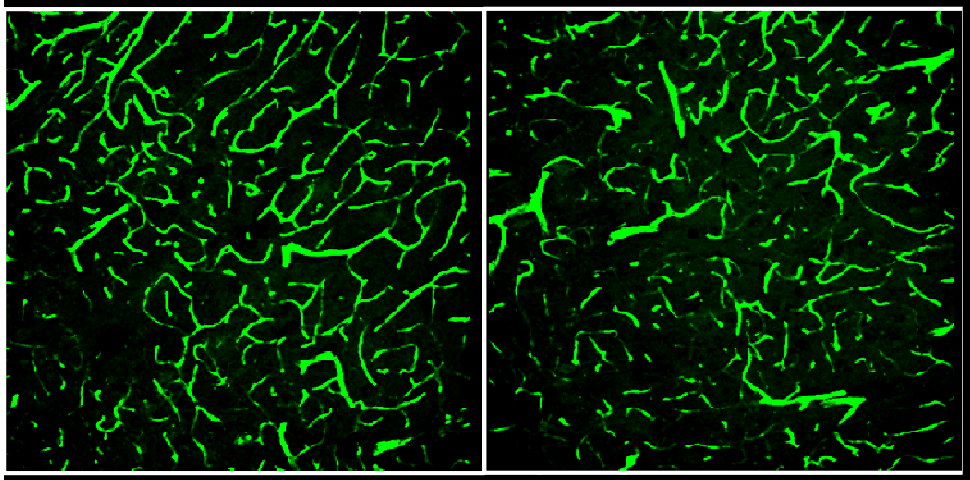
Are there other targets of ammonia?

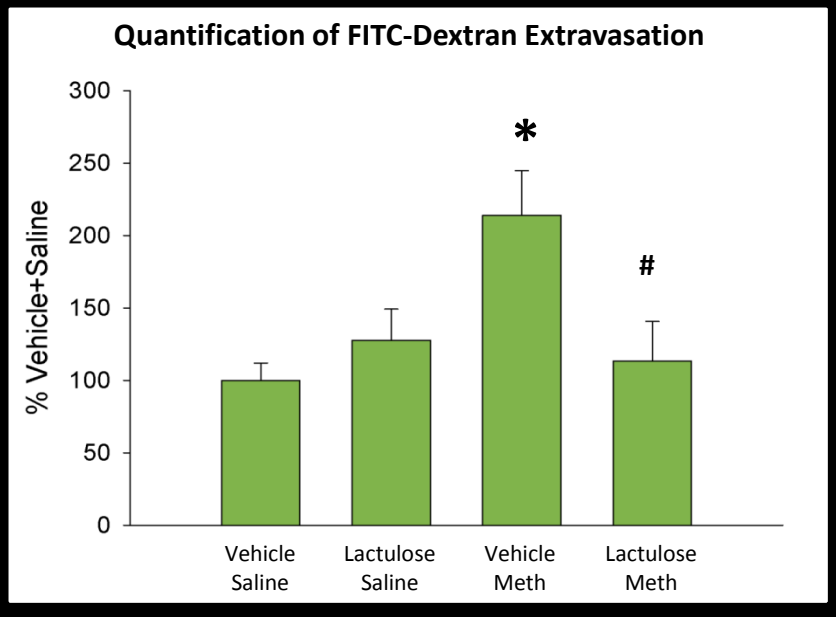

Amphetamines

BBB Function in Cortex After Meth

Vehicle+Saline

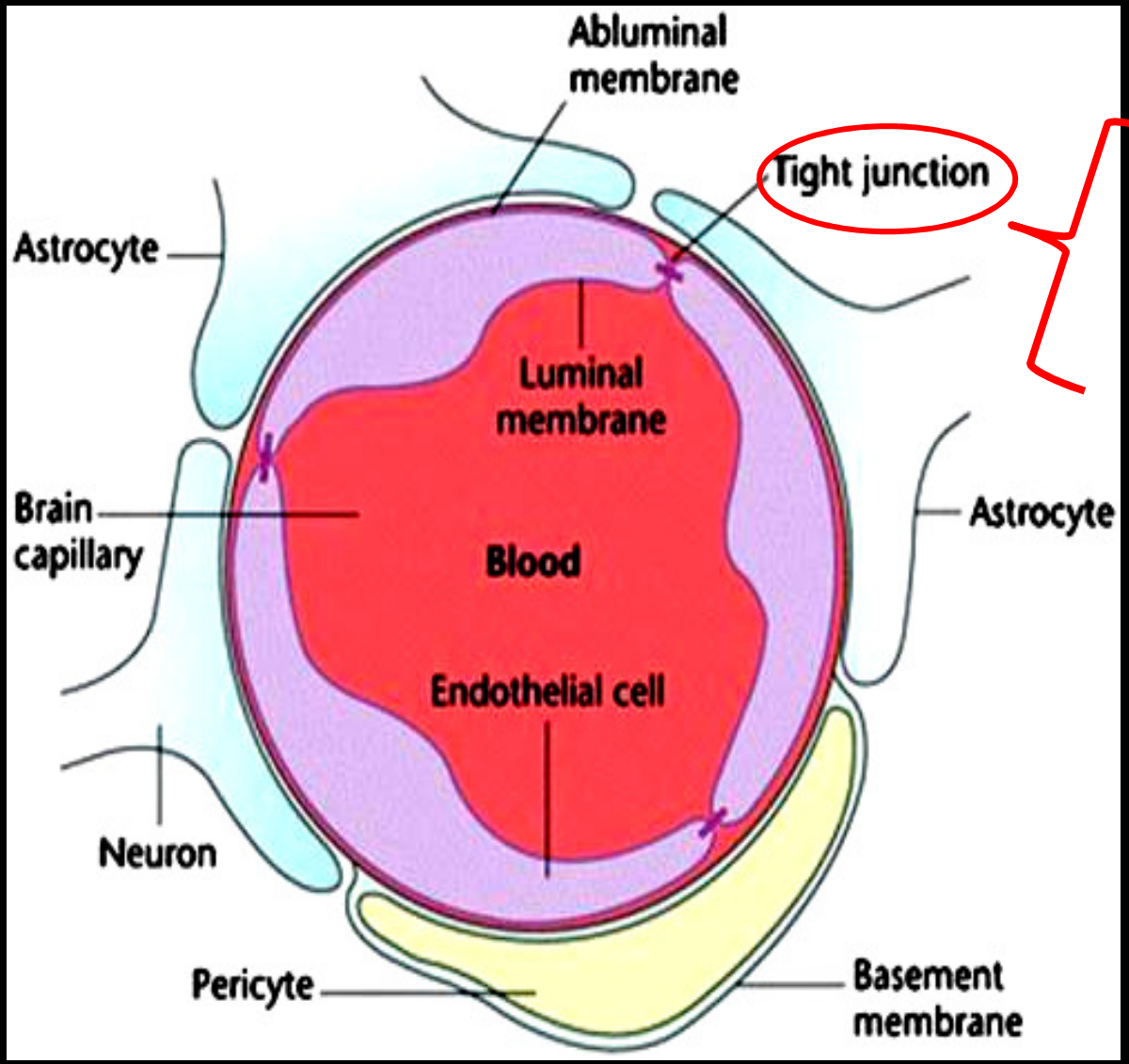
Lactulose+Saline





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Blood-Brain Barrier
Tight Junctions

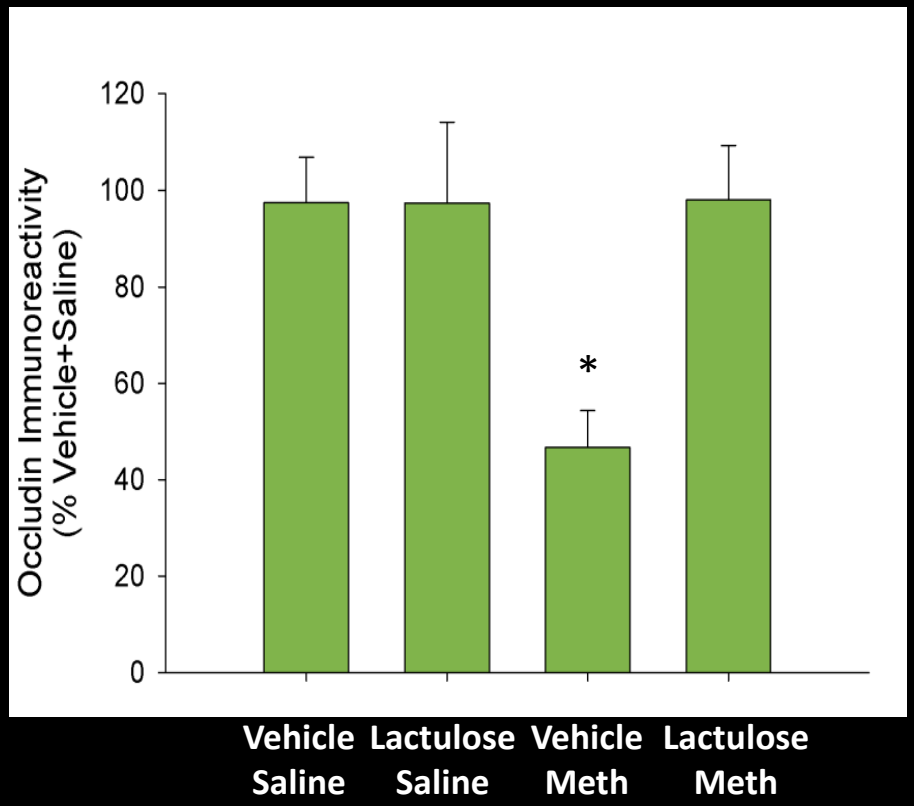


Occludin
Claudin 3, 5, 12
JAM

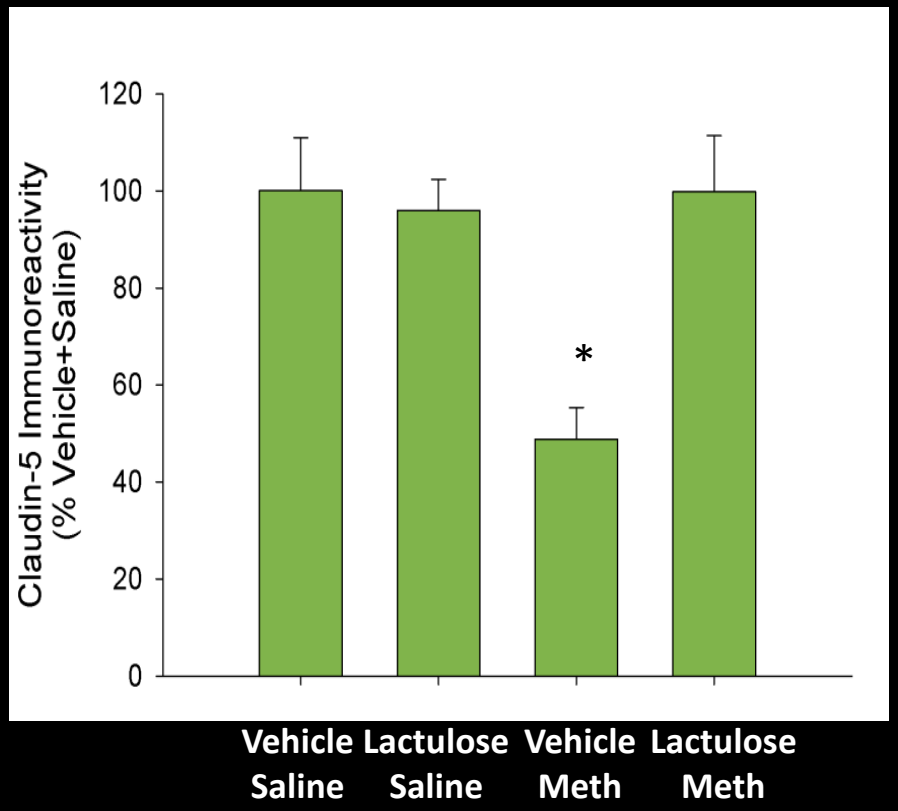
Meth-Induced Disruption of BBB Structure in Cortex

Isolated Brain Capillaries

Occludin



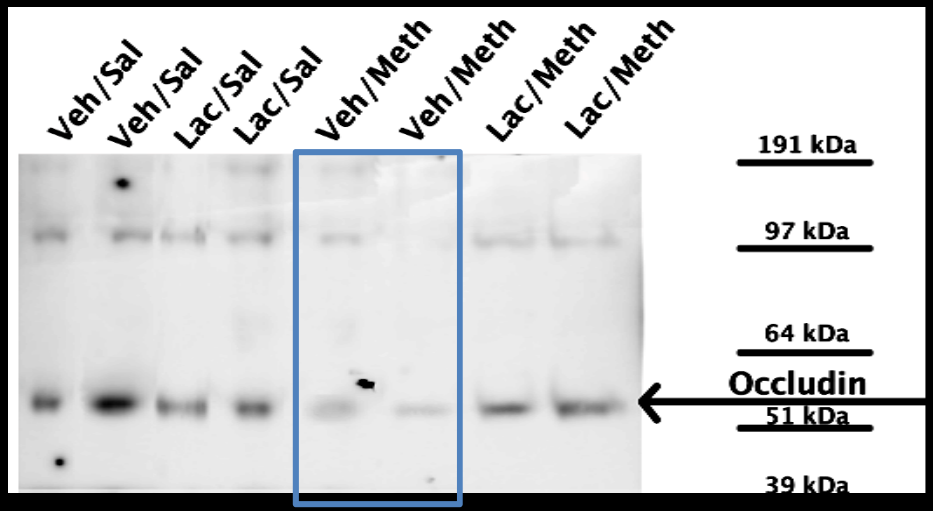
Claudin-5



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Ammonia as a Pro-Oxidant?

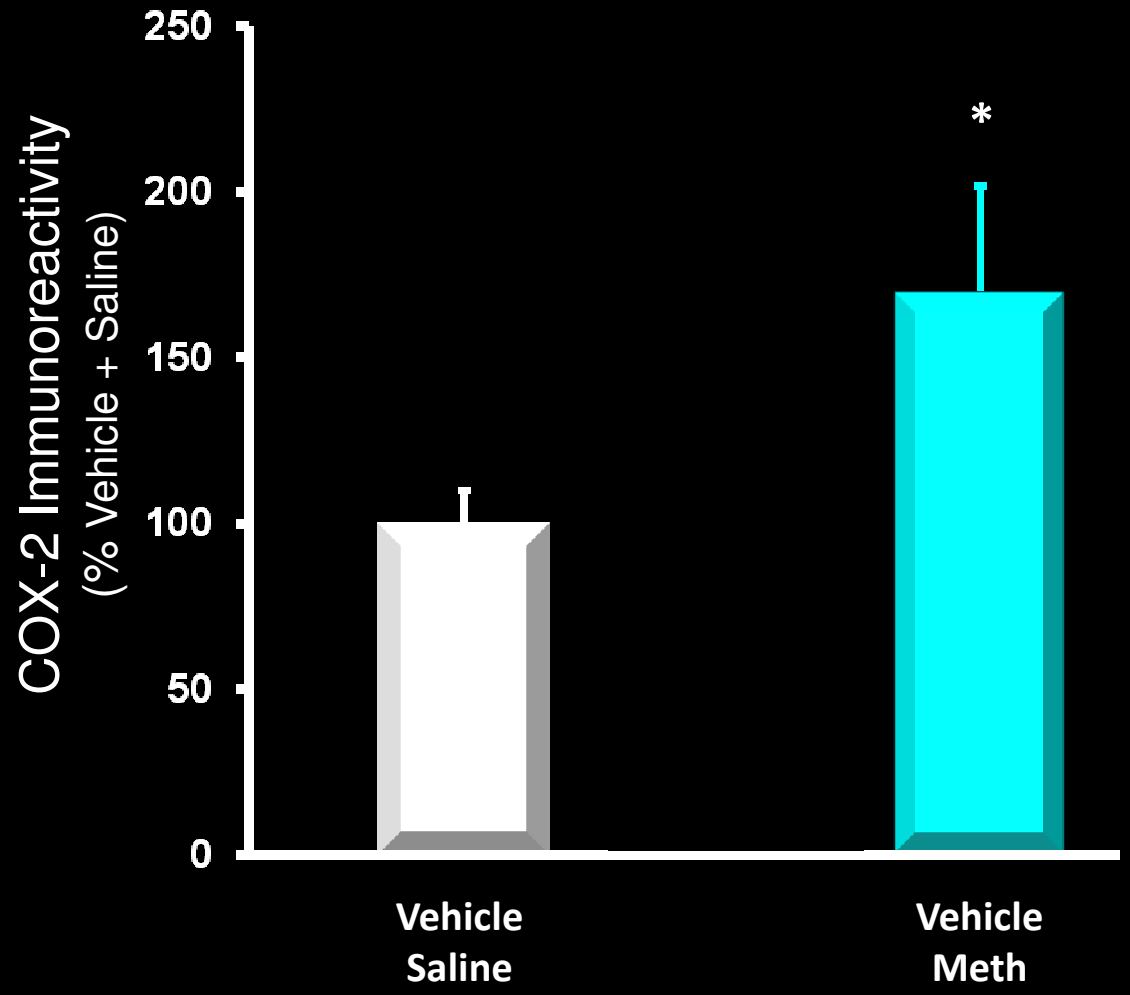
Representative Blot for Tight Junction Proteins



Isolated Brain Capillaries from Cortex

Ammonia as a Pro-Inflammatory Agent?

Cyclooxygenase-2



Northrop

Summary and Conclusions

Effects of METH:

- Increases in extracellular glutamate and evidence of excitotoxicity and oxidative degradation of proteins
- Causes hepatotoxicity and increases ammonia concentrations in peripheral plasma and brain to mediate excitotoxicity
- Damages the BBB via ammonia, oxidative stress, and inflammation (COX2-dependent prostaglandin synthesis?)
- Opening of the BBB can render the brain vulnerable to toxins by that would otherwise by restricted to the periphery.
- Peripheral organ effects should be considered as possible causes of the neurotoxicity associated with psychostimulant drug use

Collaborators

Methamphetamine Project

Past and Current

- Jeffrey Brown, Ph.D.
- Kristan Burrows Cline, Ph.D.
- David Eyerman, Ph.D.
- Amy Ferng, M.S.
- Laura Halpin, Ph.D.
- John Irlam, D.O.
- J. F. Nash, Ph.D.
- Arunan Nadarajah, Ph.D.
- Nicole Northrop, Ph.D.
- Robert Staszewski, M.S.
- Despina Tata, Ph.D

Other Current Lab Members

- Amanda Blaker
- Veronica Chiu, Ph.D.
- Stuart Collins
- Nicole Harless
- Katelyn Marchal
- Carmen Mitchell
- Reka Natarajan, Ph.D.
- Allen Schroering, M.S.
- Erin Semple
- Branden Stansley

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Florida, USA

August 3 - 5, 2015

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