The Calpain / Calpastatin System in TBI and Chronic Neurodegeneration

Kathryn E. Saatman, Ph.D.

Departments of Physiology and Neurosurgery

Spinal Cord and Brain Injury Research Center

Saatman lab:

Dr. Binoy Joseph
Dr. Sindhu Kizhakke Madathil
Dr. Diana Mathis Sama
Kathleen Schoch
Shaun Carlson
Amanda Bolton
Jen Pleasant Brelsfoard
Ben Tuttle
Shannon Swikert
Dr. Brantley Graham

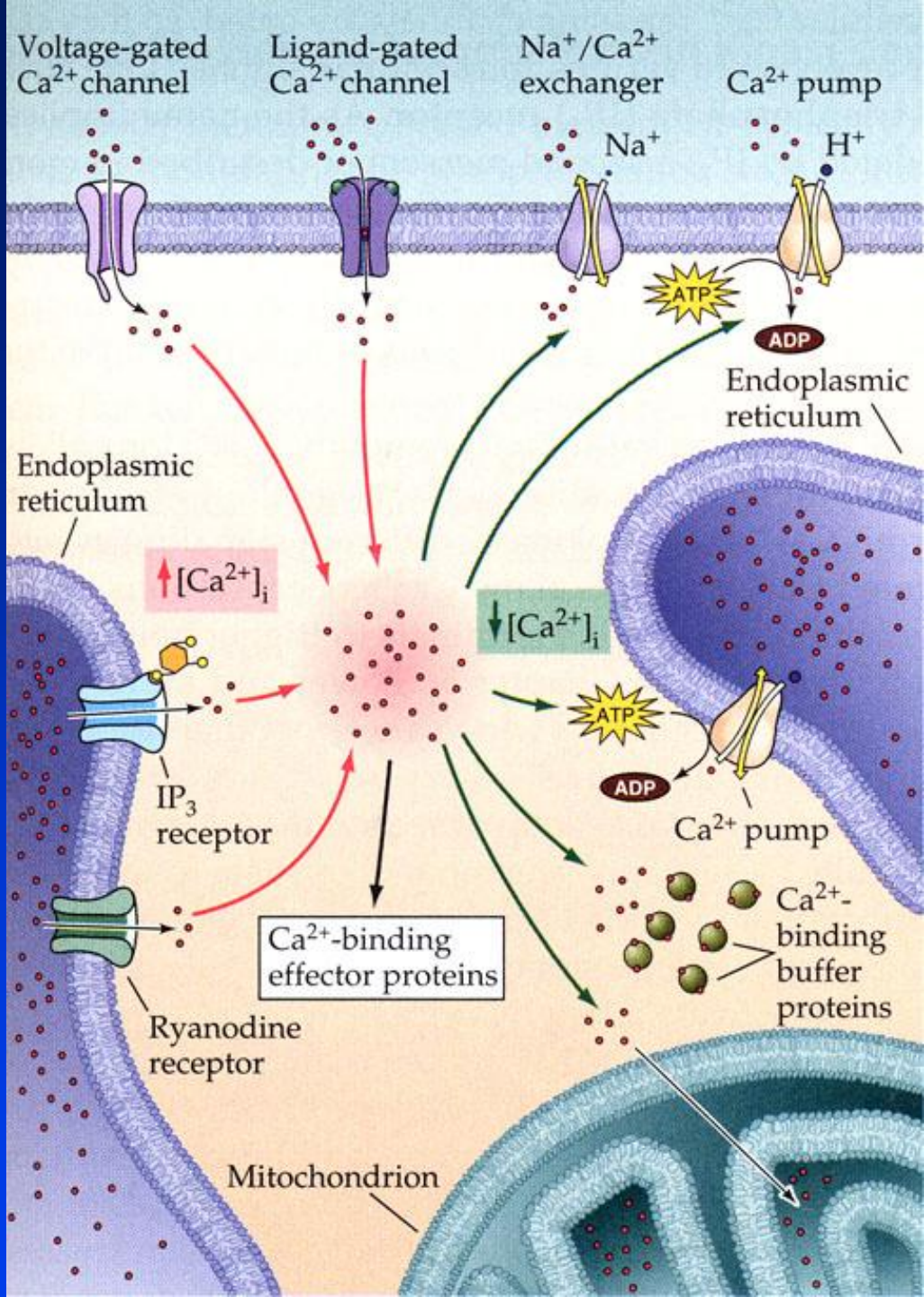
Heather Evans
Nathan Surles
Adam Benson

- Takaomi Saido and Jiro Takano, RIKEN Brain Science Institute
- Glenn Telling, Colorado State University
- David Meaney & Katie von Reyn, University of Pennsylvania

NIH NINDS R01 NS072302, R01 NS045131, P01 NS058484
KSCHIRT grants 6-12, 7-20, 9-13

- Traumatic neuronal injury triggers an acute increase in intracellular free calcium
- Magnitude and duration of calcium elevation proportional to initial injury severity and superposition of secondary insults
- Increased free Ca results in activation of calpains

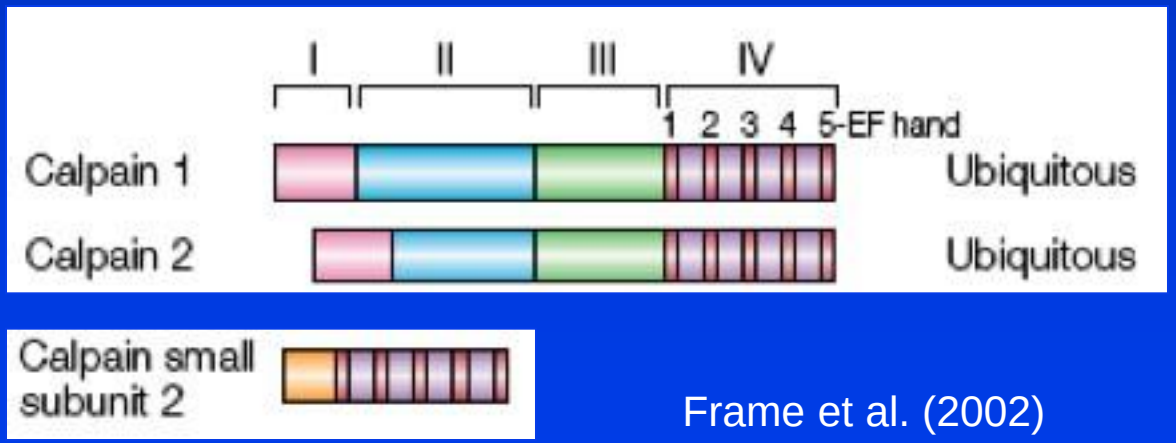
Taken from *Neuroscience* Purves, et al. editors



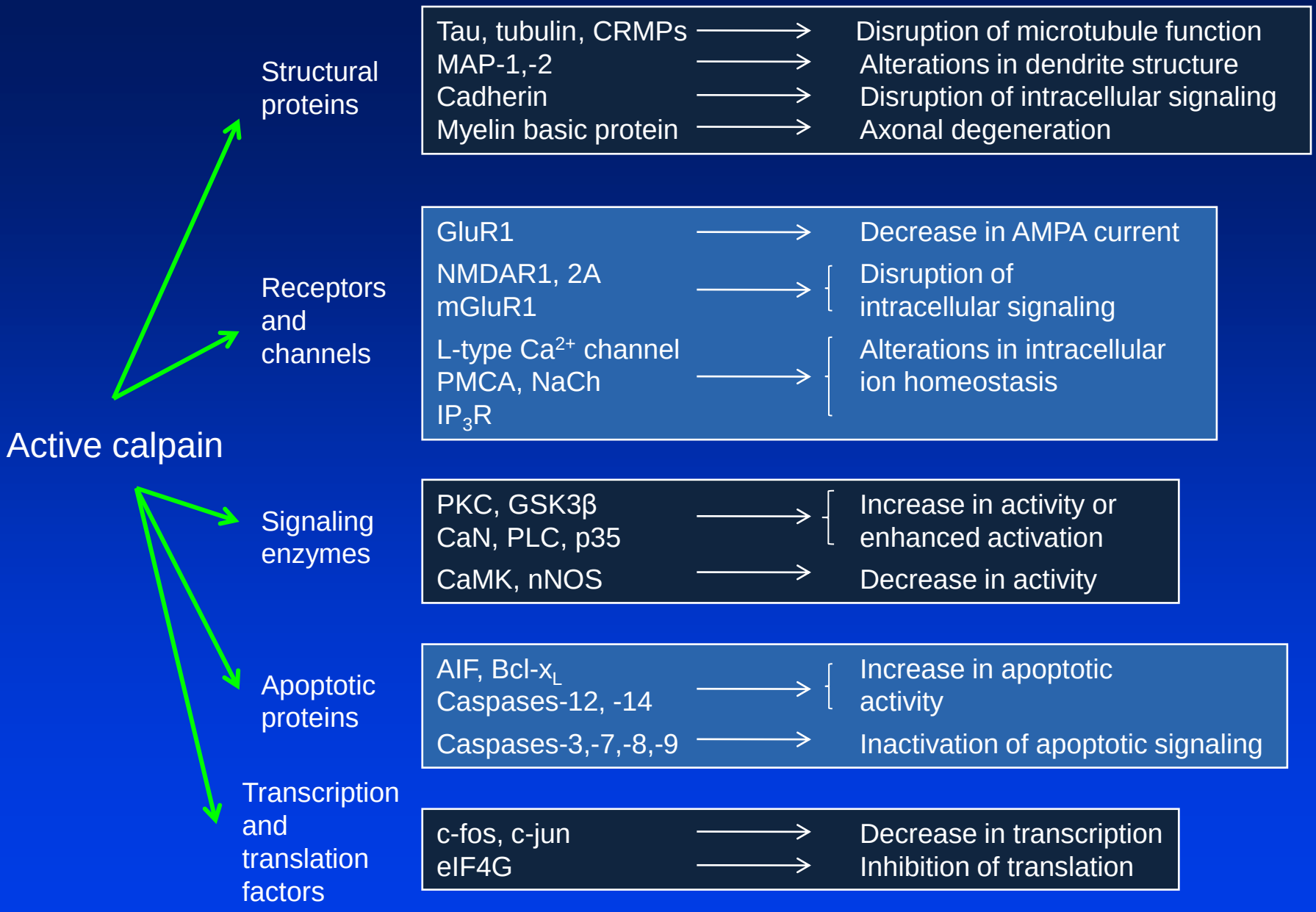
Calpains

Ca^{2+}-activated, neutral cysteine proteases

- Multiple isoforms
- μ-calpain and m-calpain expression ubiquitious
- Comprised of large (80 kDa) catalytic and small (30kDa) regulatory subunits
- Activated through autolysis and conformational change due to calcium binding



Frame et al. (2002)

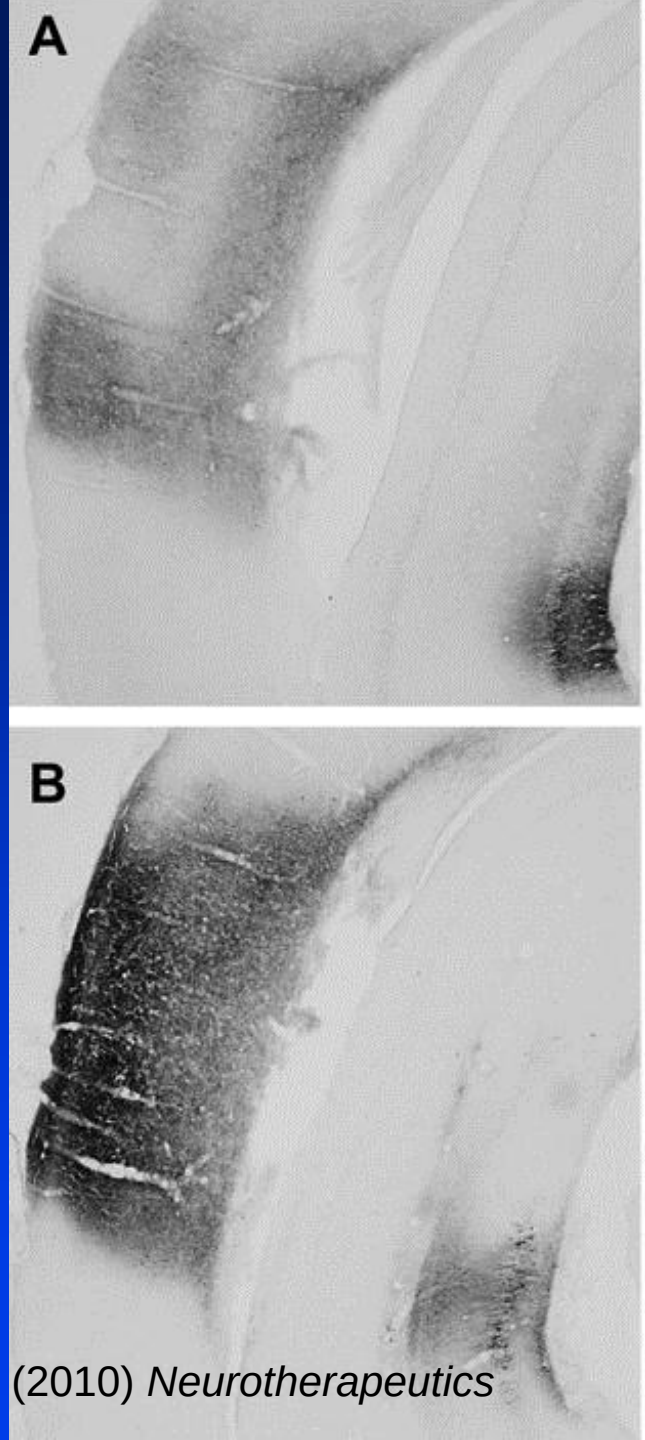


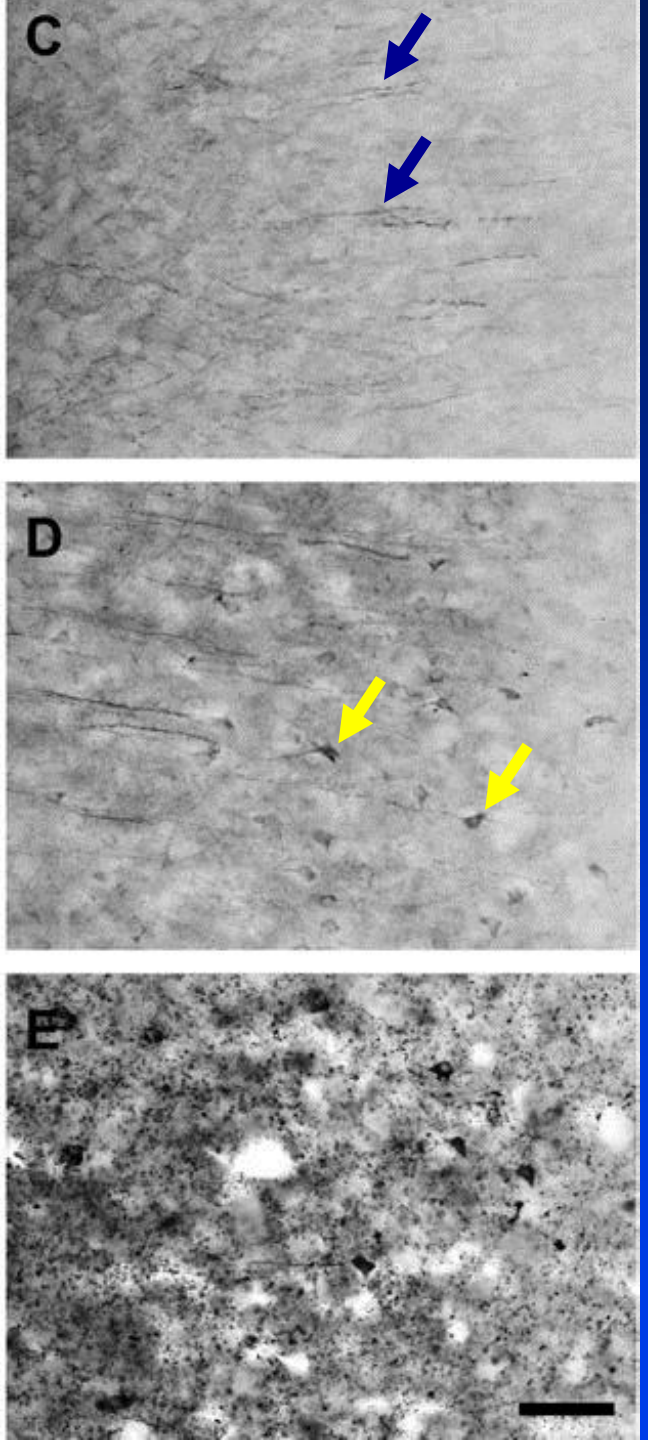
Saatman et al. (2010) *Neurotherapeutics*

Calpain-degraded spectrin in TBI

4 hours

24 hours





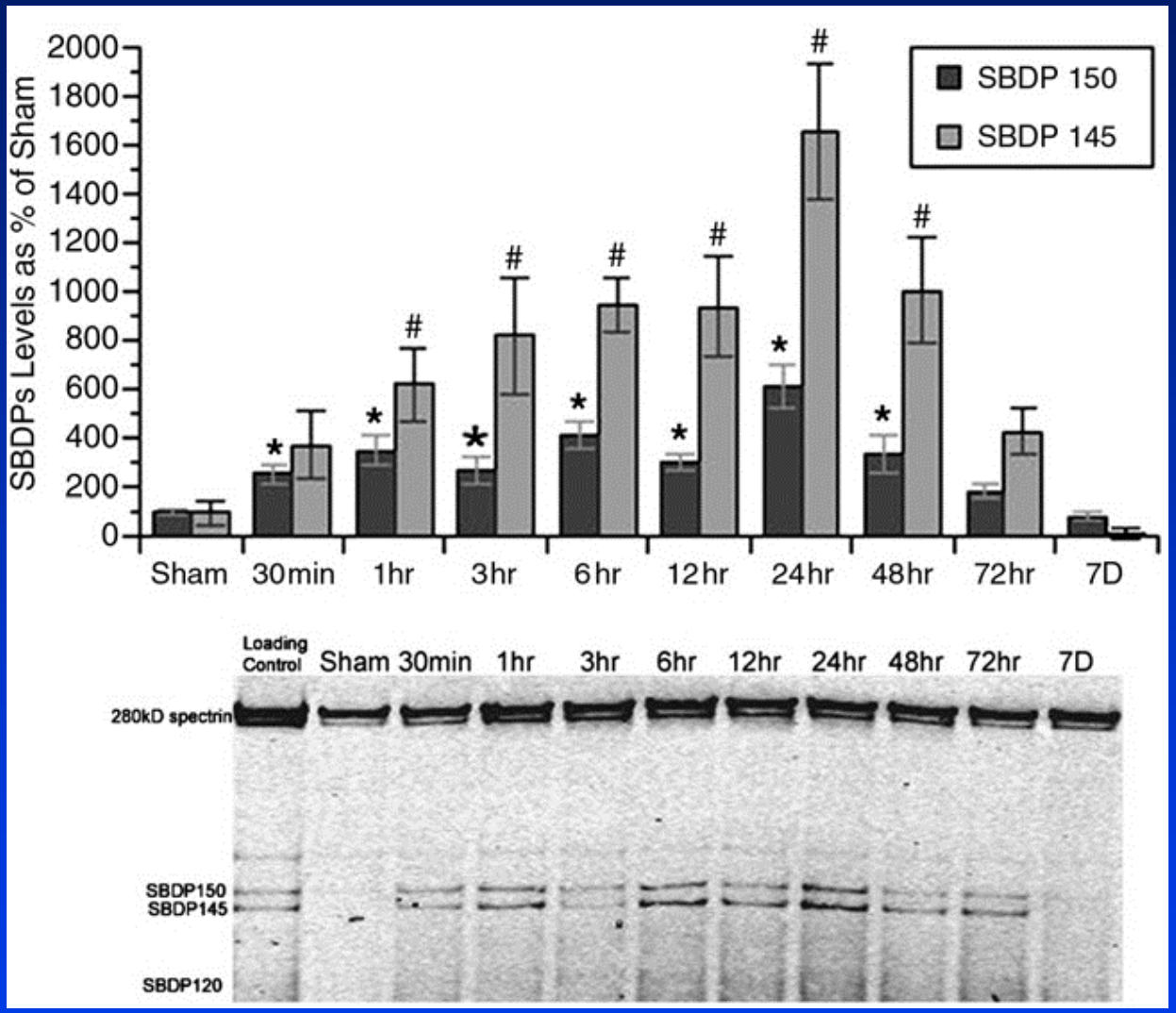
90 min

4 hours

24 hours

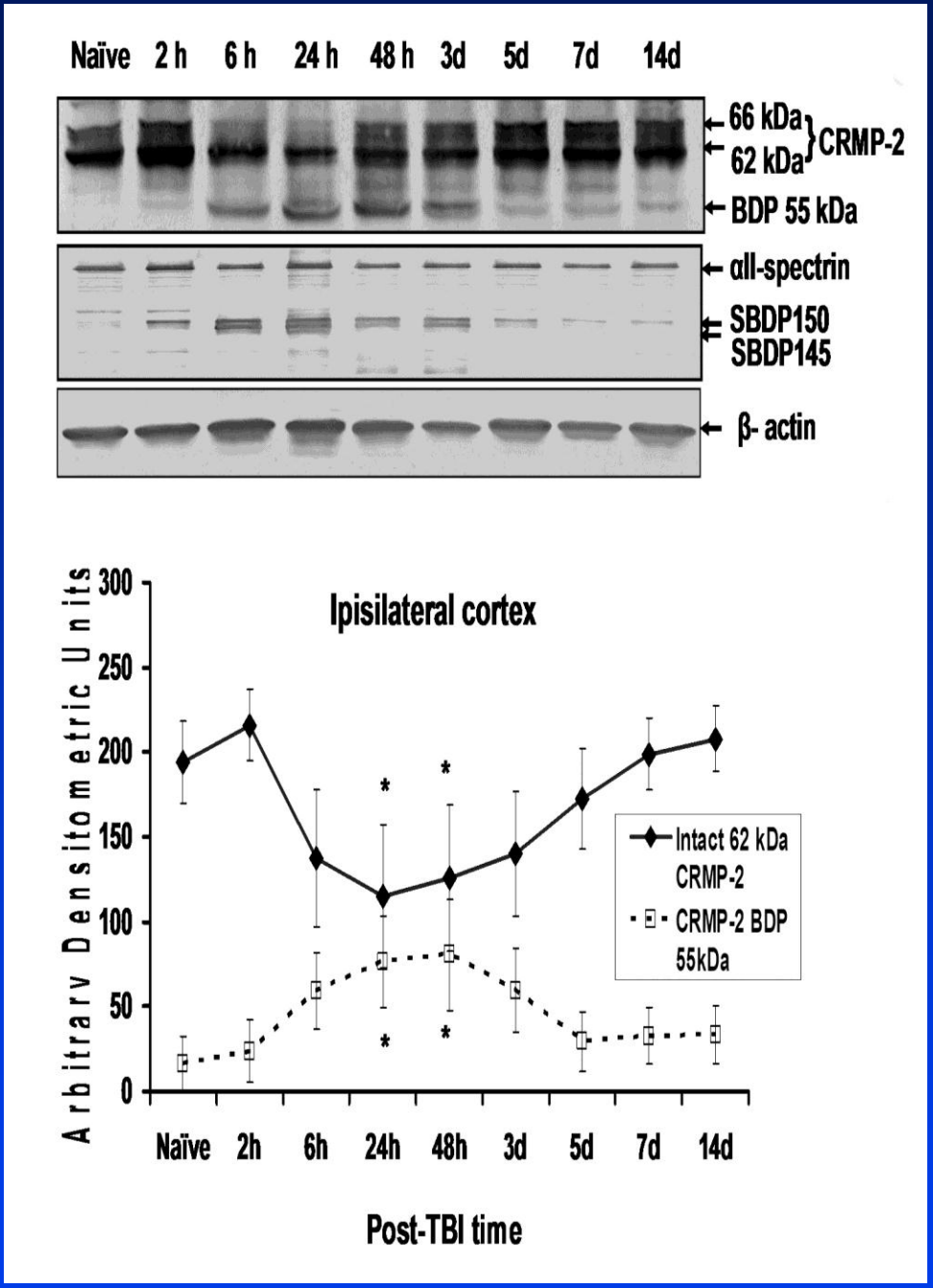
Saatman et al. (2010) *Neurotherapeutics*

Time course of calpain activation after contusion TBI in mice



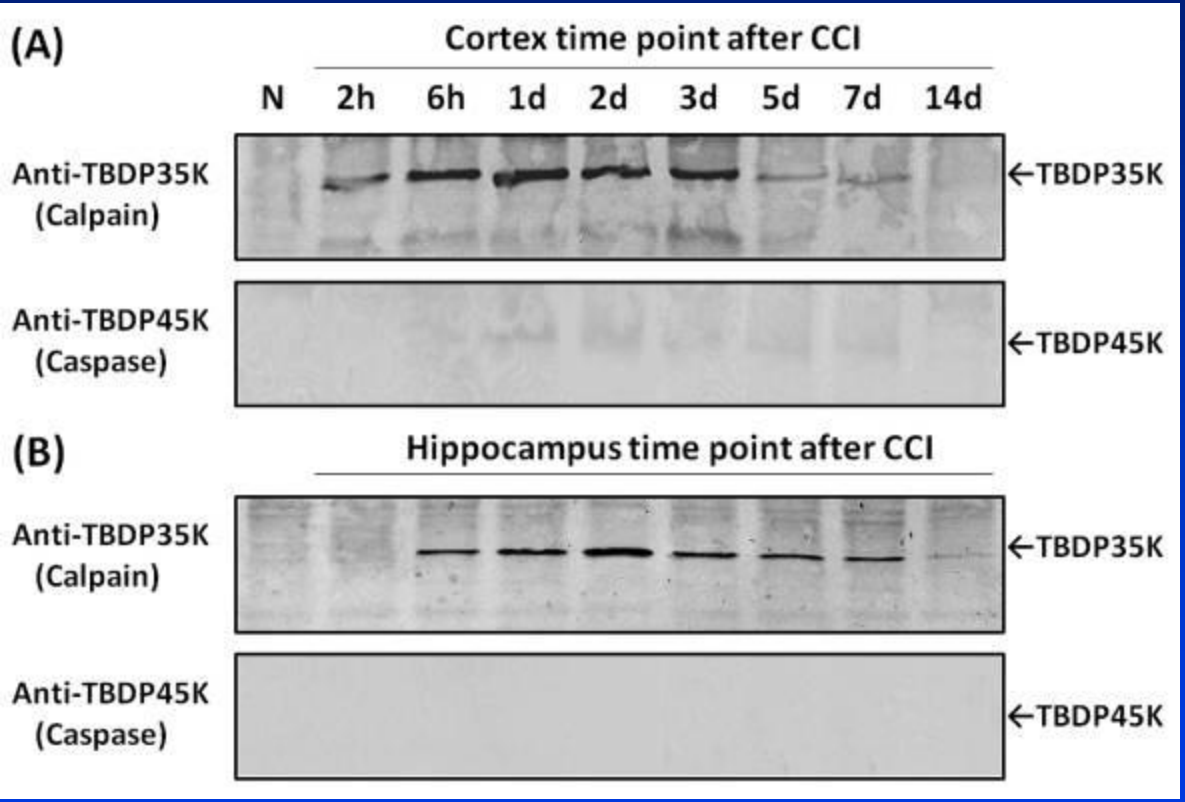
Deng et al. (2007) *Exp Neurol*

Loss of microtubule-associated protein CRMP-2 mirrors calpain-mediated spectrin proteolysis



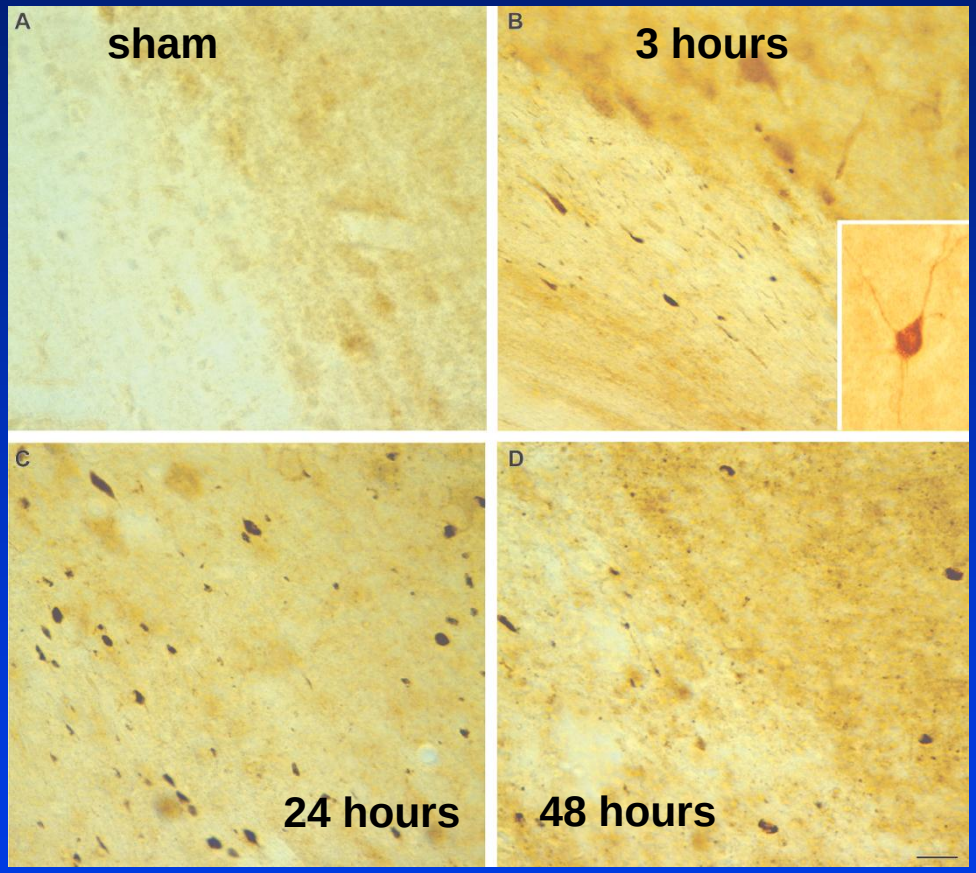
Zhang et al. (2007)
J Neurotrauma

Contusion brain injury results in calpain cleavage of tau



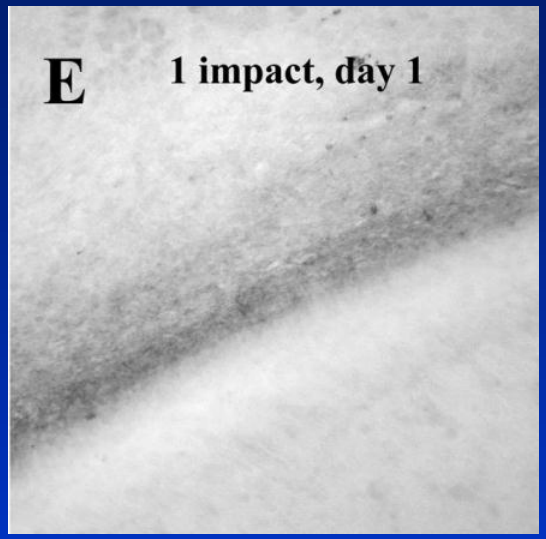
Lui et al. (2011) *ASN Neuro*

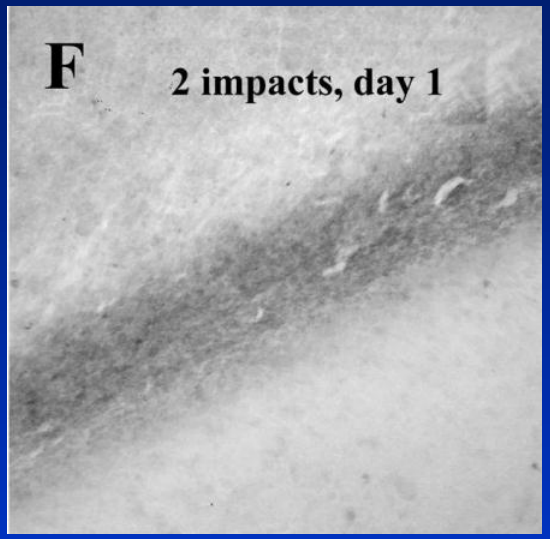
Axonal calpain activation in diffuse brain injury

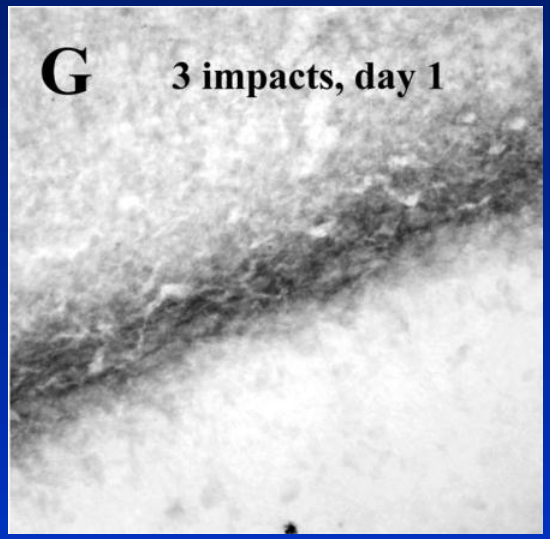


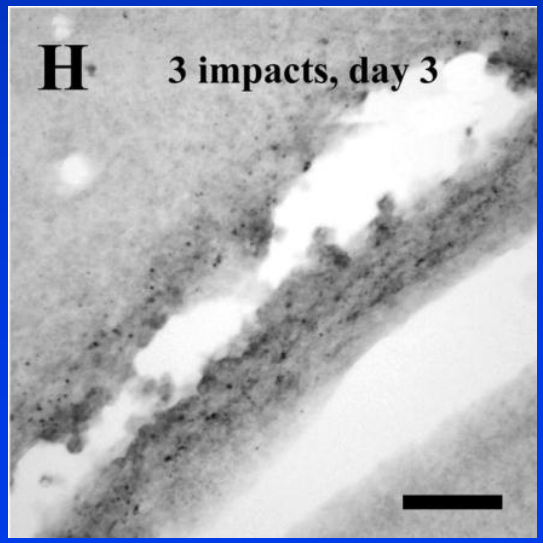
McGinn et al. (2009) *J Neuropathol Exp Neurol*

Calpain-mediated proteolysis is enhanced with mild repetitive injury





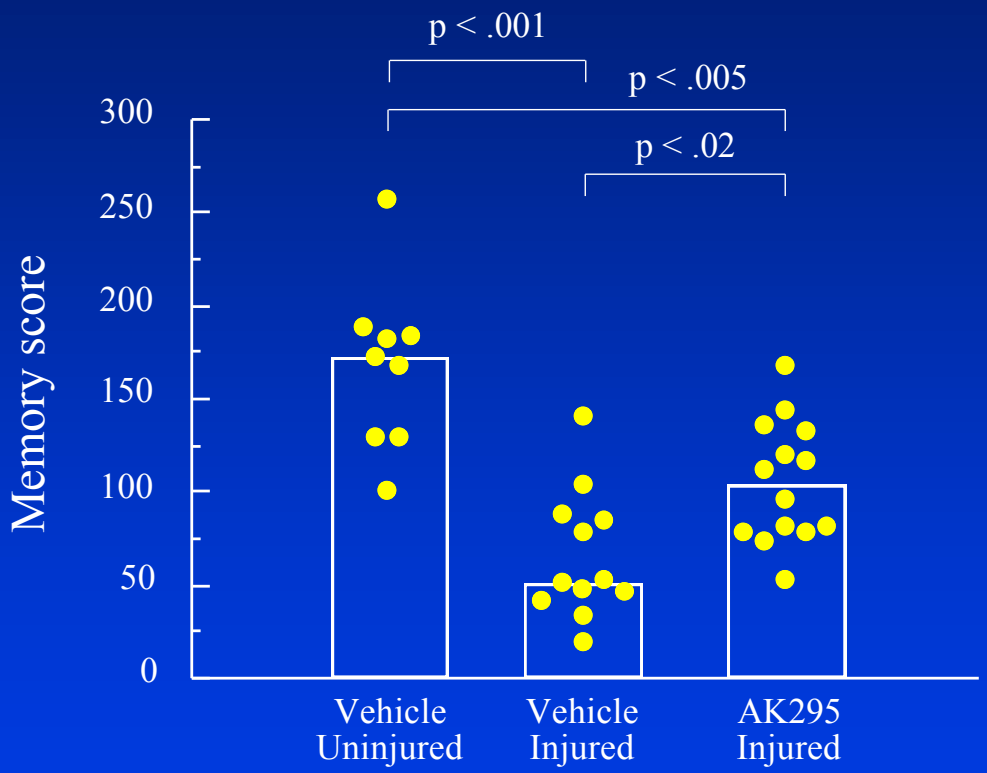


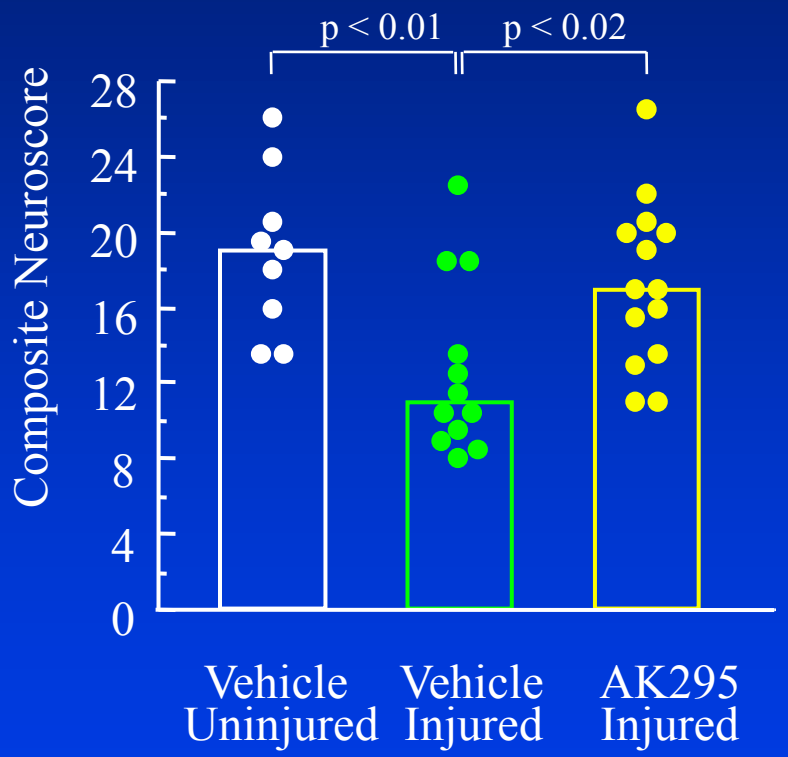


Lateral closed head injury in P11 rats

Huh et al. (2007) *J Neurotrauma*

Calpain inhibitor therapy attenuates behavioral deficits after TBI

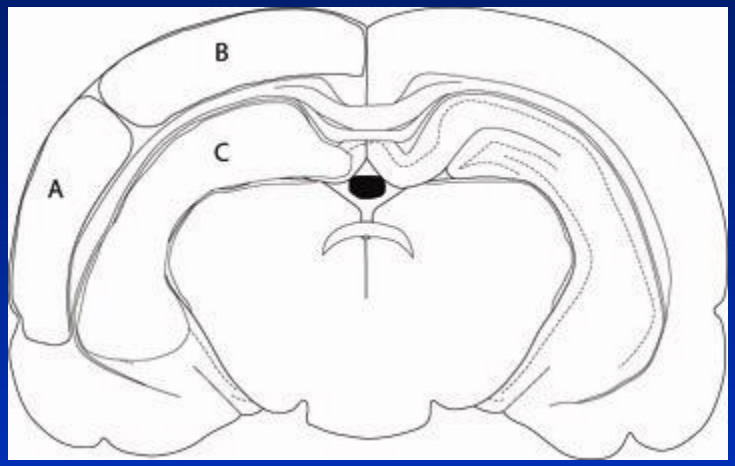


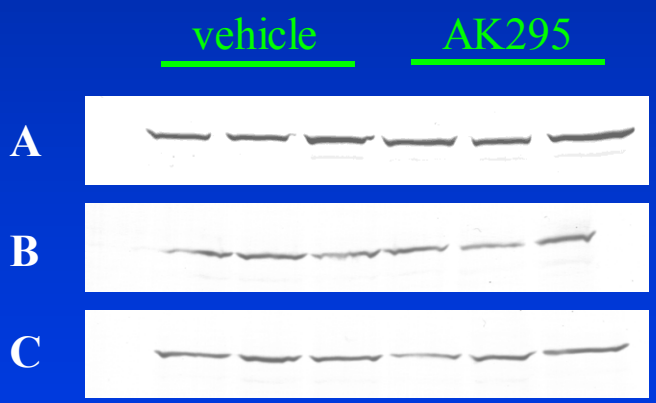


7 days post-injury

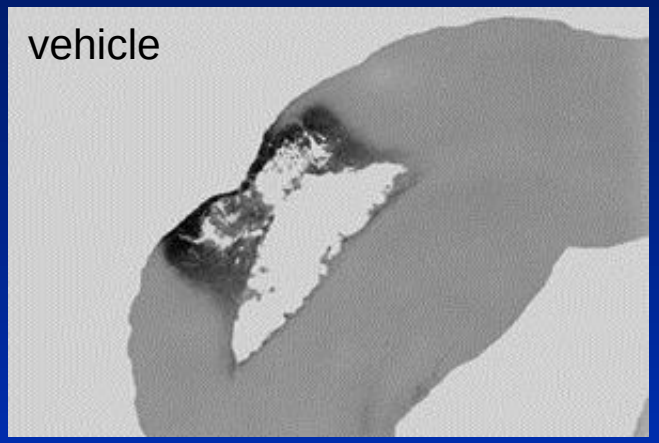
Saatman et al. (1996) *PNAS*

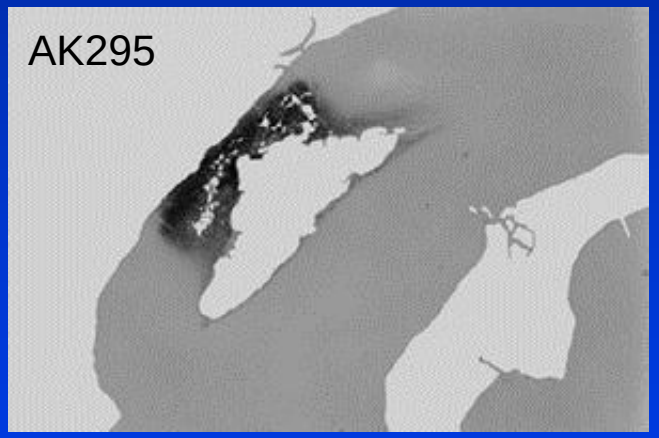
Effects of calpain inhibitor on spectrin proteolysis and cell death





2 days after TBI

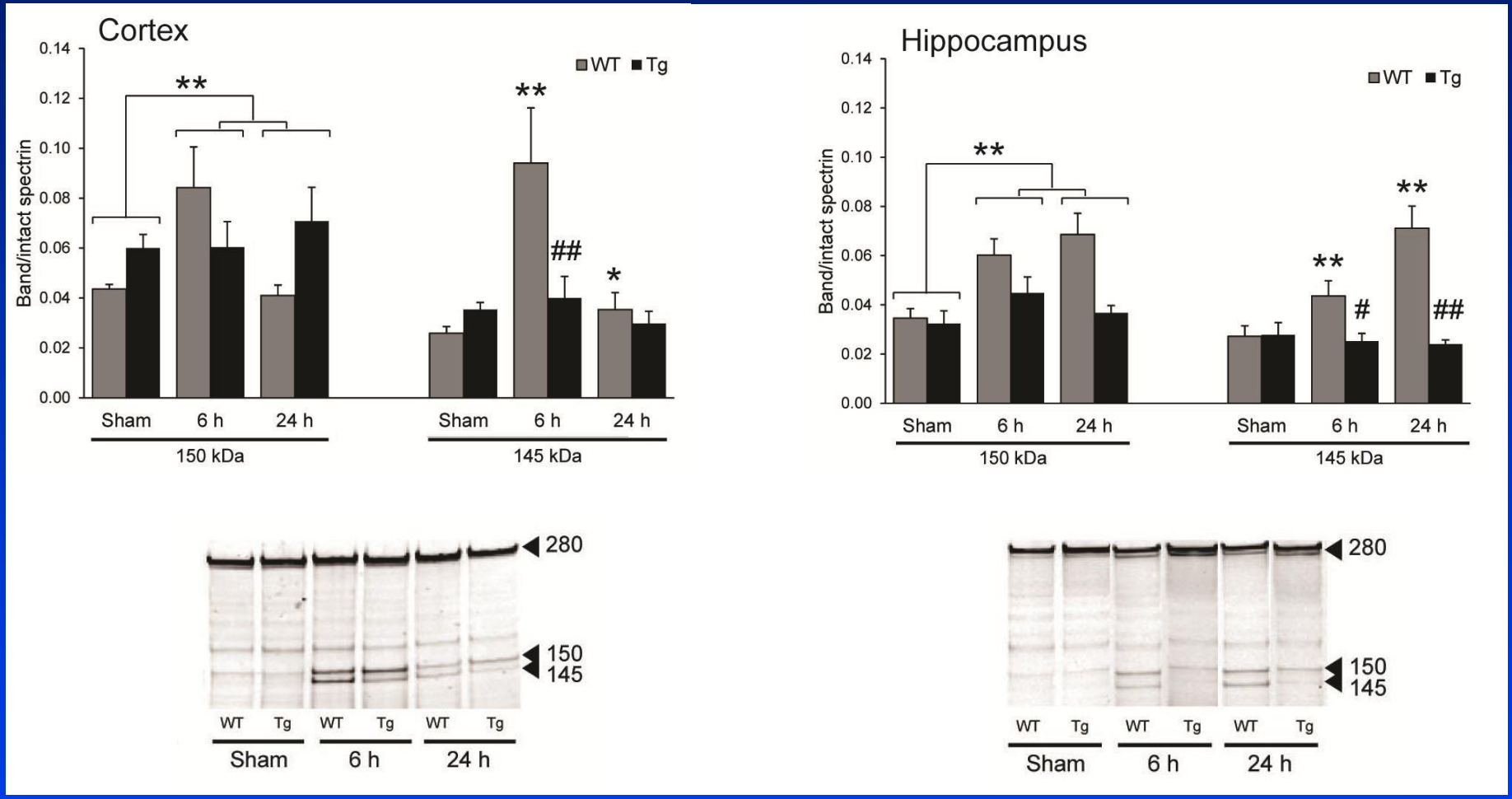




7 days after TBI

Saatman et al. (2000) *J Cereb Blood Flow Metab*

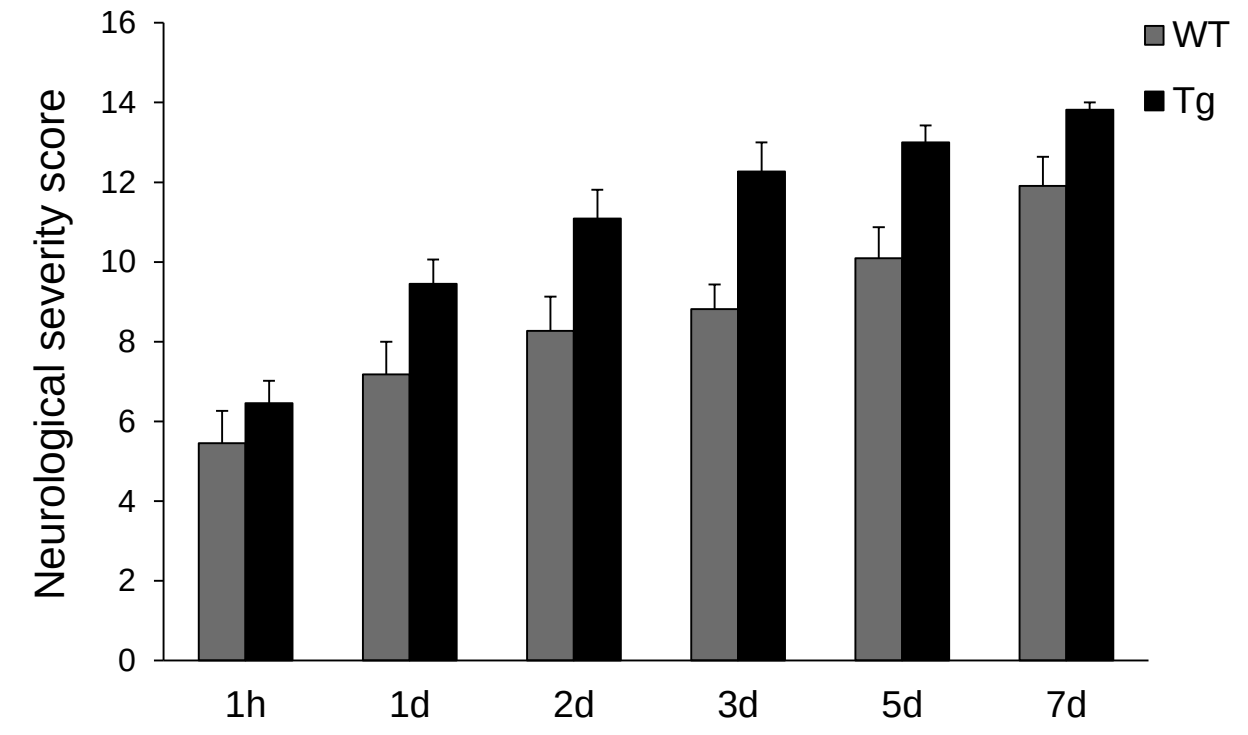
Calpastatin overexpression reduces cortical α-spectrin proteolysis after contusion brain injury



* p<0.05, ** p<0.0005 vs. sham; # p<0.05, ## p<0.0005 vs. WT

Schoch et al. (2012) *Exp Neurol*

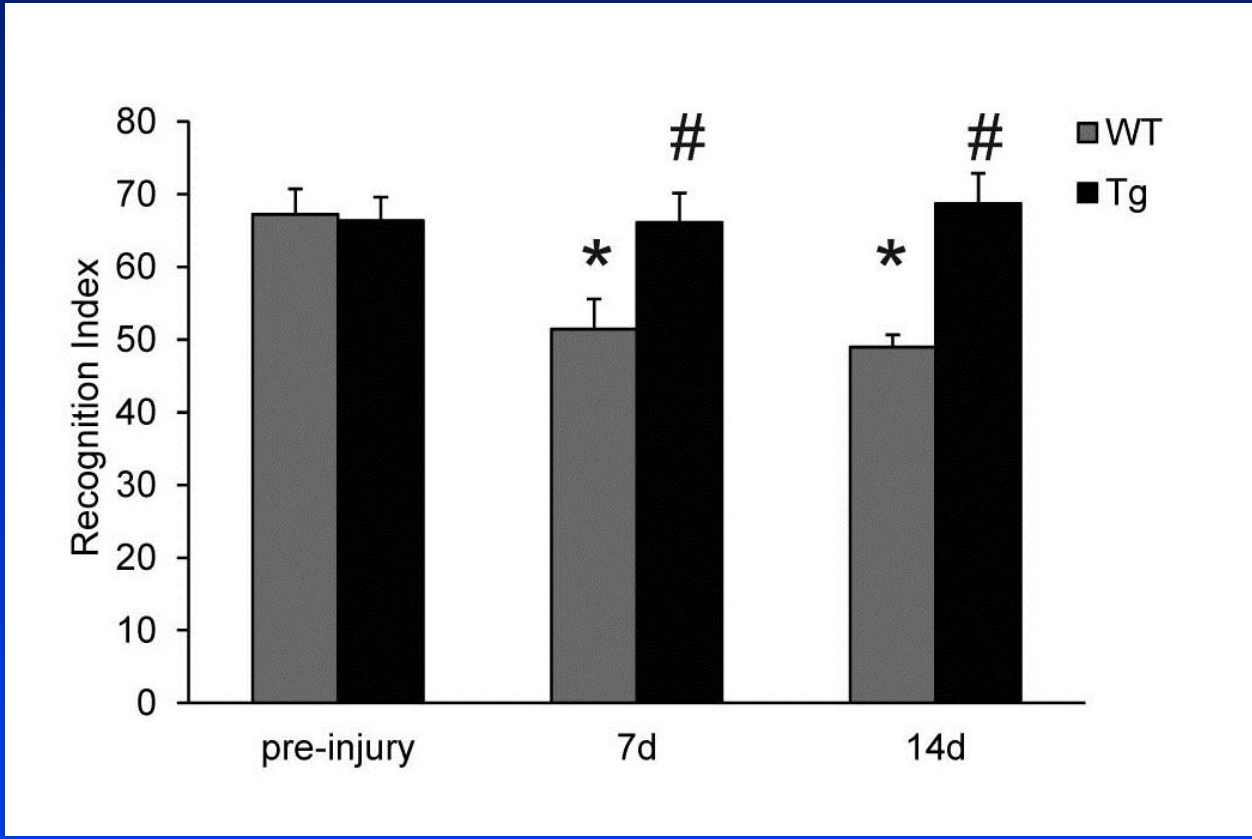
Calpastatin overexpression improves recovery of motor function after contusion brain injury



Genotype effect: $p<0.01$

Schoch et al. (2012) *Exp Neurol*

Calpastatin overexpression attenuates memory impairment after contusion brain injury



* p<0.05 vs. pre-injury

# p<0.01 WT vs. TG

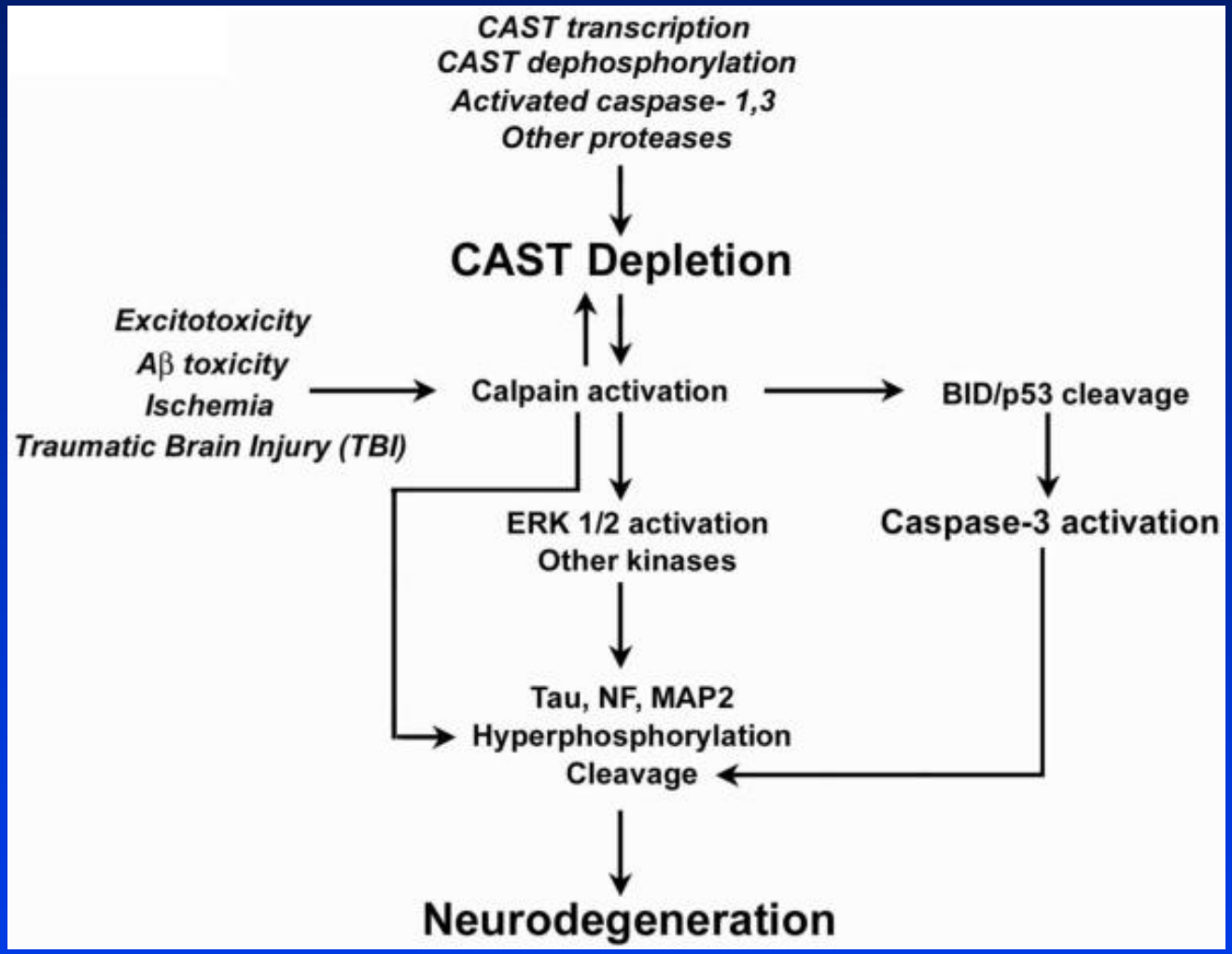
Schoch et al. (2012) *Exp Neurol*

Calpain/Calpastatin in TBI

- Acute activation in contusion TBI in rodents
- Axonal calpain activation in diffuse TBI
- Potential roles in neuron death and axonal injury
- Exacerbation of axonal calpain activation with repeated mTBI
- Unknown involvement in chronic neuropathology of TBI

- Calpain inhibitor treatments improve behavioral function but do not reduce contusion size
- Calpastatin overexpression reduces substrate proteolysis
- Calpastatin overexpression attenuates motor and cognitive dysfunction after contusion TBI

Calpain/Calpastatin in chronic neurodegeneration



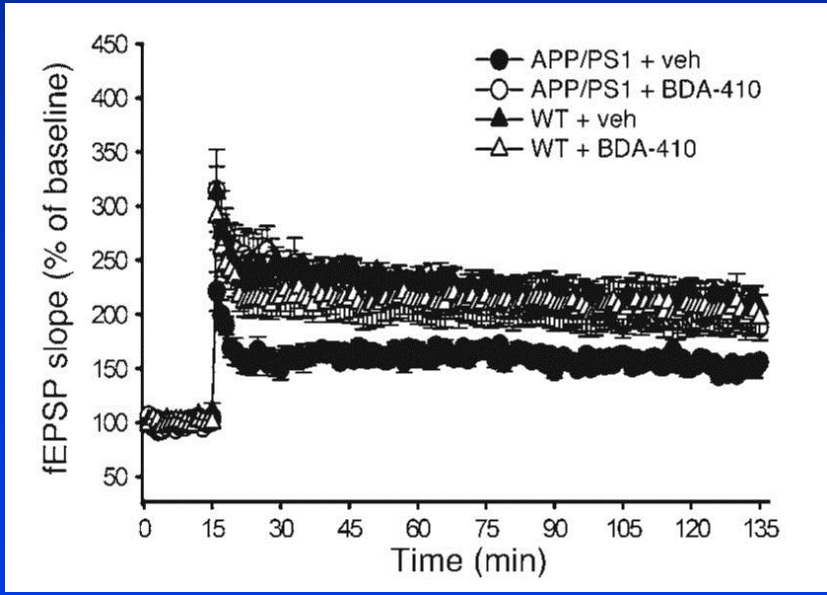
Rao et al. (2008) *J Neurosci*

J Clin Invest (2008)

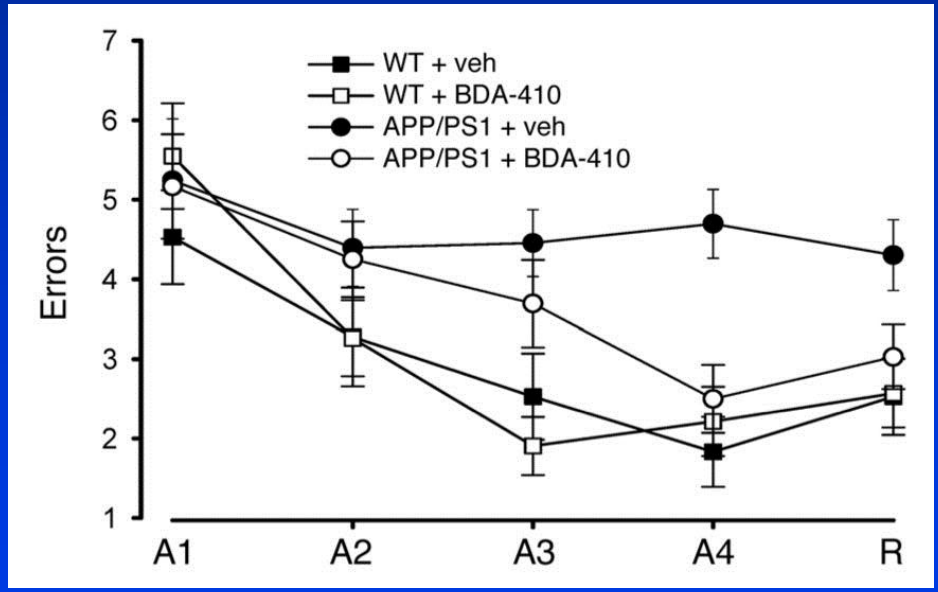
Research article

Inhibition of calpains improves memory and synaptic transmission in a mouse model of Alzheimer disease

Fabrizio Trinchese,[1] Mauro Fa',[1] Shumin Liu,[1] Hong Zhang,[1] Ariel Hidalgo,[1] Stephen D. Schmidt,[2,3] Hisako Yamaguchi,[4] Narihiko Yoshii,[4] Paul M. Mathews,[2,3] Ralph A. Nixon,[2,3,5] and Ottavio Arancio[1]



Hippocampal LTP



Radial arm water maze

Daily treatment from 2-7 months of age

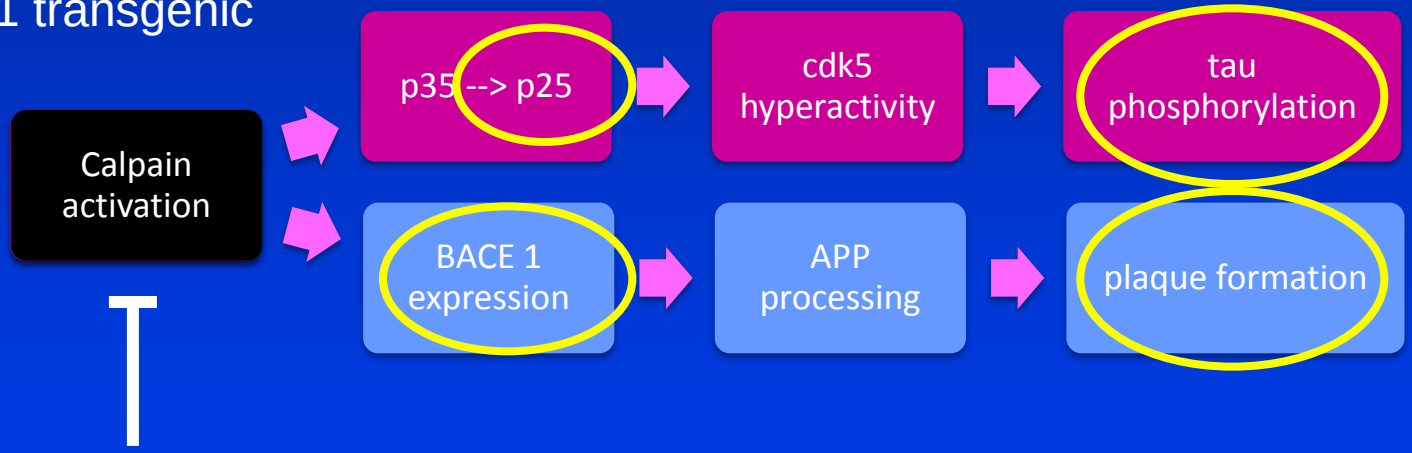
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 285, NO. 36, pp. 27737–27744, September 3, 2010

Calpain Activation Promotes BACE1 Expression, Amyloid Precursor Protein Processing, and Amyloid Plaque Formation in a Transgenic Mouse Model of Alzheimer Disease*

Received for publication, February 25, 2010, and in revised form, June 27, 2010 Published, JBC Papers in Press, July 1, 2010, DOI 10.1074/jbc.M110.117960

Bin Liang, Bao-Yu Duan, Xiu-Ping Zhou[1], Jia-Xin Gong, and Zhen-Ge Luo[2]

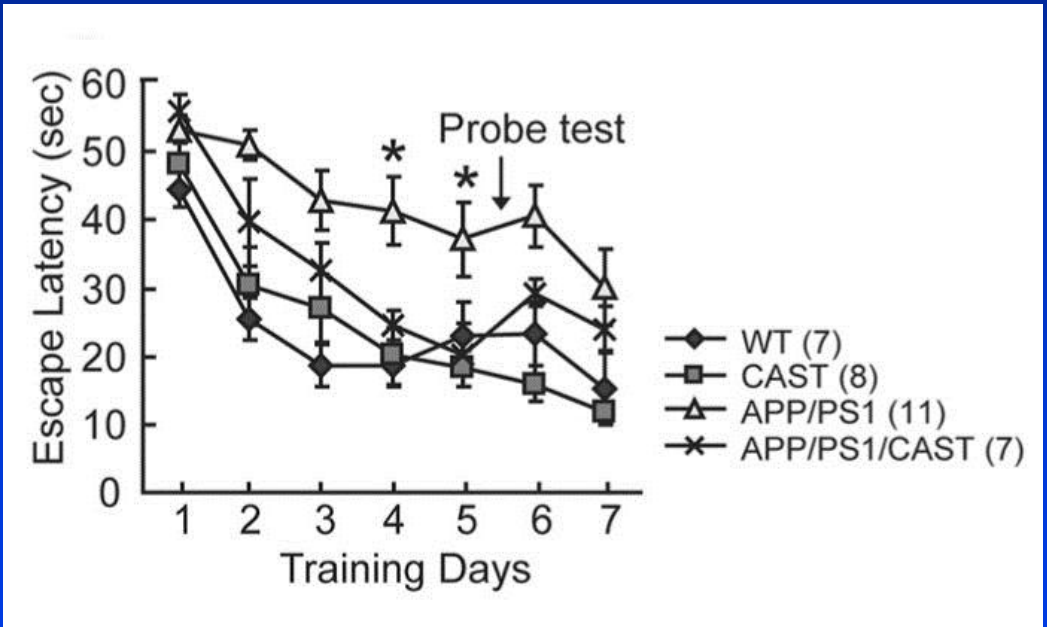
APP/PS1 transgenic



calpastatin overexpression (hCAST Tg x APP/PS1)

Calpastatin overexpression:

- prevented decrease in phosphorylation of CREB and ERK1/2 in APP/PS1 mice
- attenuated spatial learning deficits in APP/PS1 mice



Liang et al. (2010) *J Biol Chem*

Calpain/Calpastatin in AD neuropathology

- Mild chronic activation of calpains
- Downregulation of calpastatin expression
- Dysregulation of multiple calpain substrates:

  kinases/phosphatases
- Role in tau hyperphosphorylation
- Role in APP processing or regulation
- Upstream or downstream?
- Protective effects of calpain inhibition or calpastatin overexpression