Alzheimer's Disease vs. Type 3 Diabetes:

Role of Impaired Insulin Actions in the Brain

de la Monte Laboratory
Rhode Island Hospital
Brown Medical School
Providence, RI

Early Abnormalities in AD

- Metabolic:
  - Reduced oxygen and glucose metabolism in the cerebral cortex
- Structural:
  - Dystrophic neurites and neurofibrillary tangles, phospho-tau, ubiquitin
  - Amyloid-β deposits
- Functional:
  - Acetylcholine deficiency and loss of cholinergic neurons

Fundamental Problems Behind the Scene

- Metabolic
  - Not known. Few studies showed improved cognition with insulin administration or cognitive impairment in Type 1 diabetes
- Structural
  - Gene mutations, oxidative stress including mitochondrial dysfunction, ischemia, unknown
- Functional
  - Loss of cholinergic neurons (why?)

Why Focus on Insulin Actions in the Brain?

- Studies linked neuronal thread protein (NTP) over-expression in AD to neuronal insulin resistance
- Ethanol-induced neurodegeneration caused by insulin resistance
- Chemical knock-out of insulin producing cells in the brain causes AD-type dementia

Questions Raised

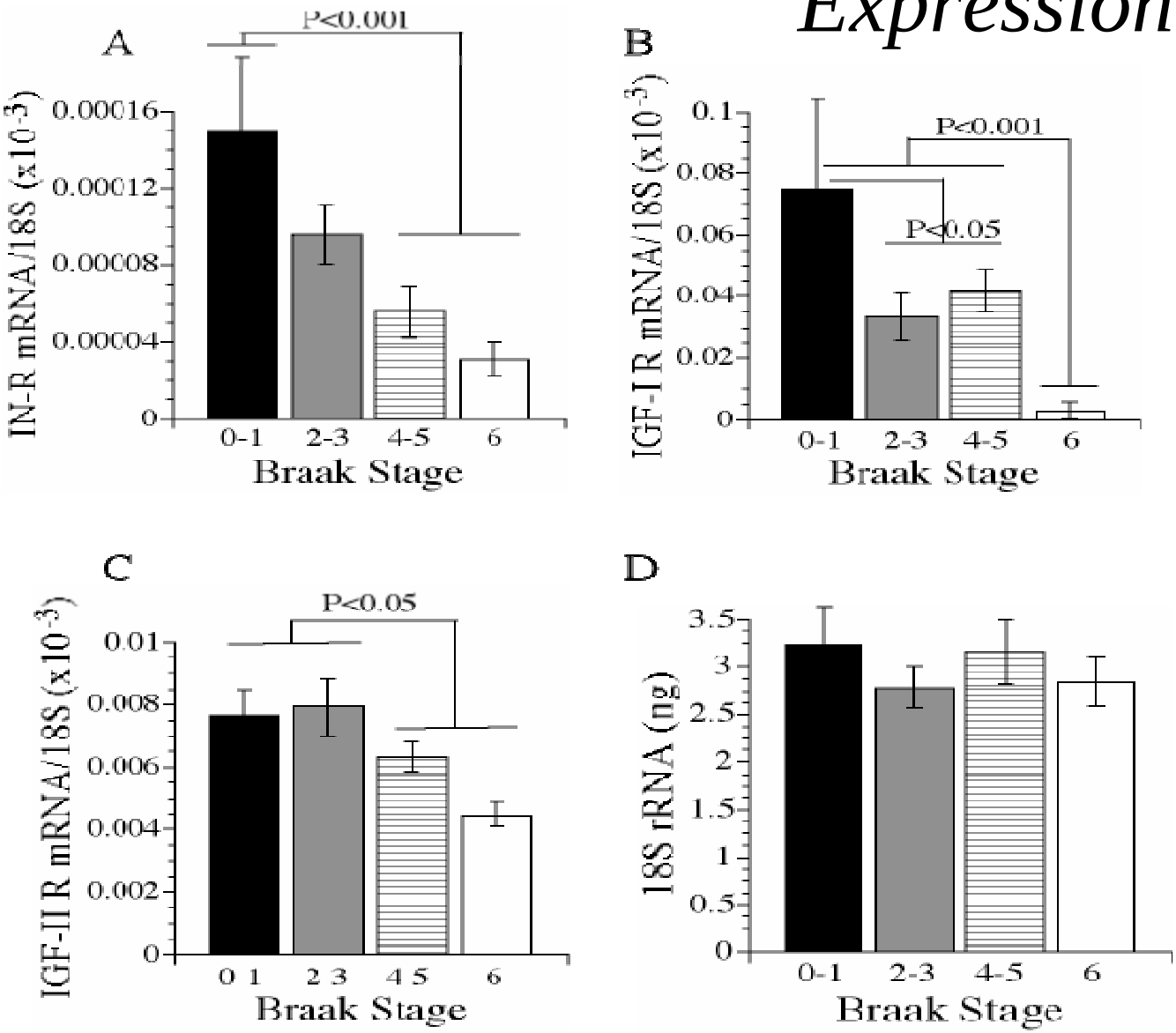
- Is Alzheimer's disease associated with abnormalities in insulin-mediated function in the brain?

- Are abnormalities in insulin-mediated functions detectable early in the course of AD, and do the abnormalities worsen with progression of neurodegeneration?

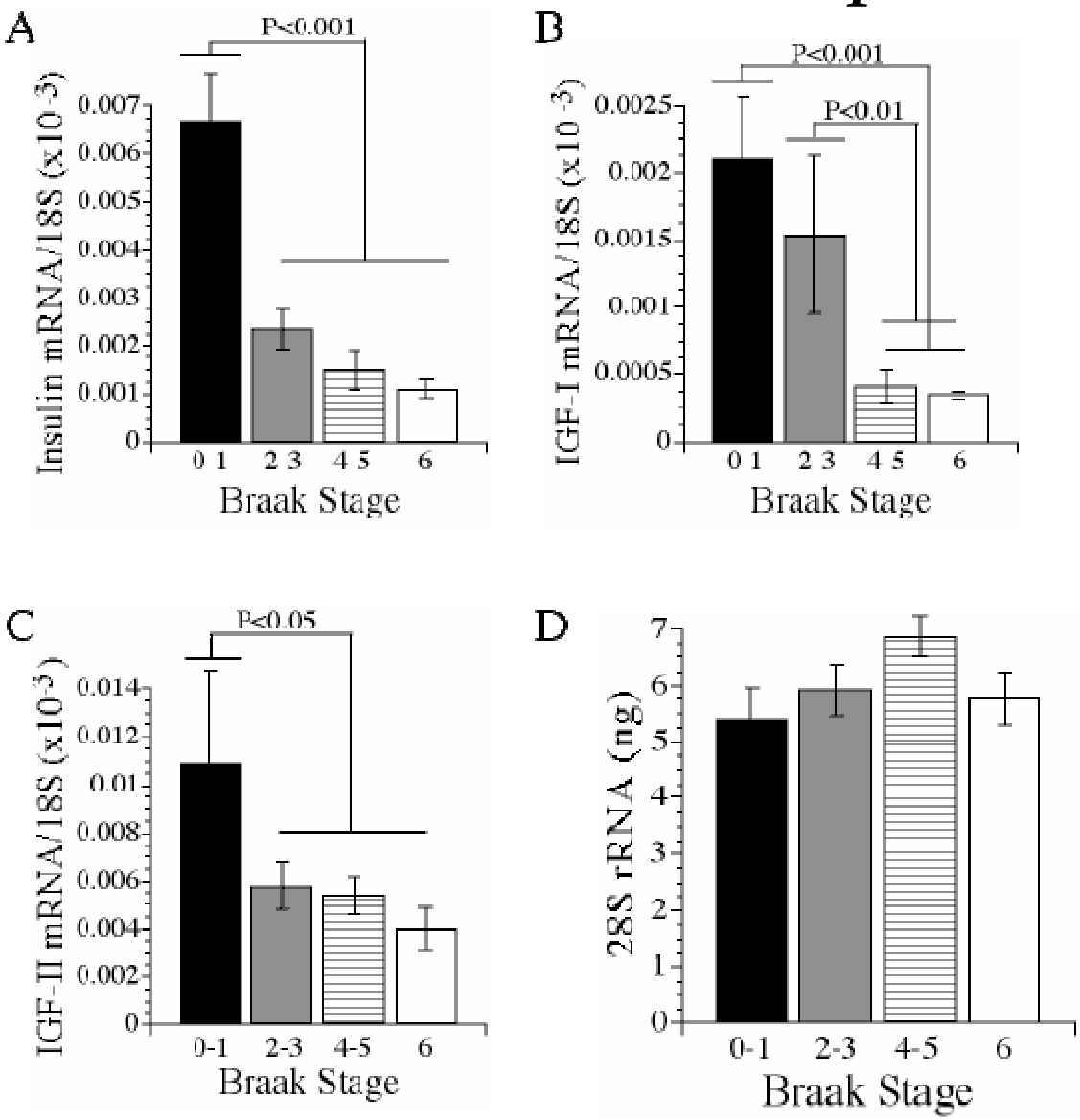
Study Design

- Postmortem banked human brain tissue
  - Different stages of AD or normal aging
    - Brown Brain Bank
    - Massachusetts General Hospital ADRC
    - Duke University
- RNA (PCR) and Protein (Western blots immunohistochemical staining, binding assays)
- Quantitative analysis of data

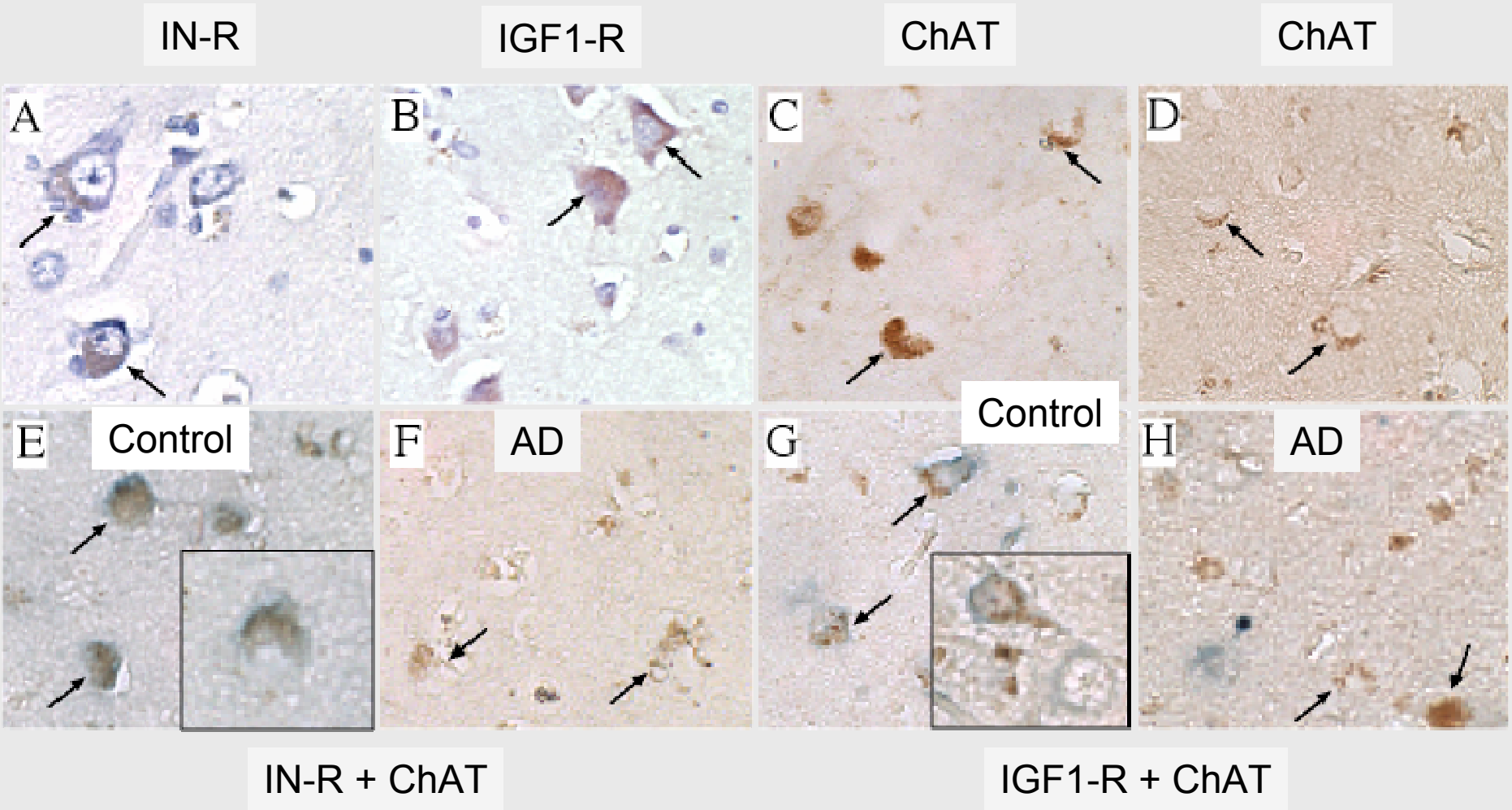
Decreased Growth Factor Receptor Expression in AD



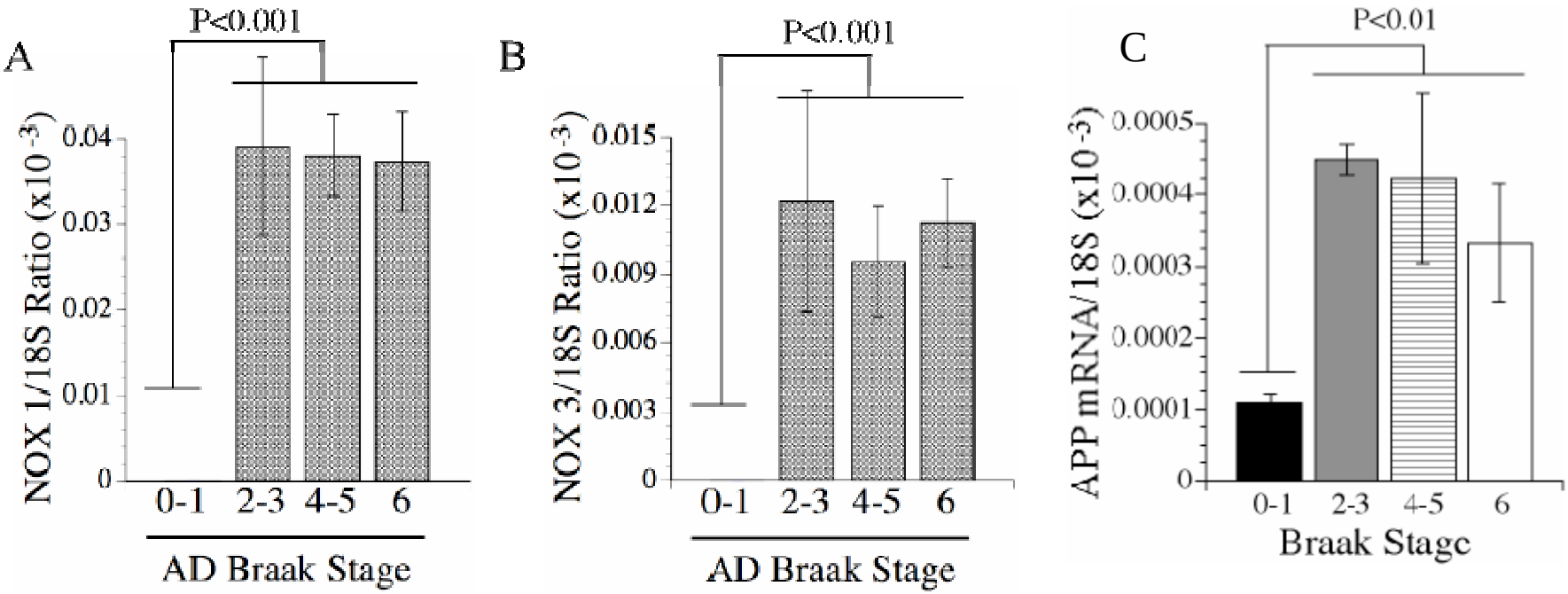
Decreased Growth Factor Gene Expression in AD



Loss of Cholinergic Neurons in AD Linked to Death of Insulin & IGF-1 Receptor^{+} Neurons



Increased Oxidative Stress in AD- Second Arm of Neurodegeneration

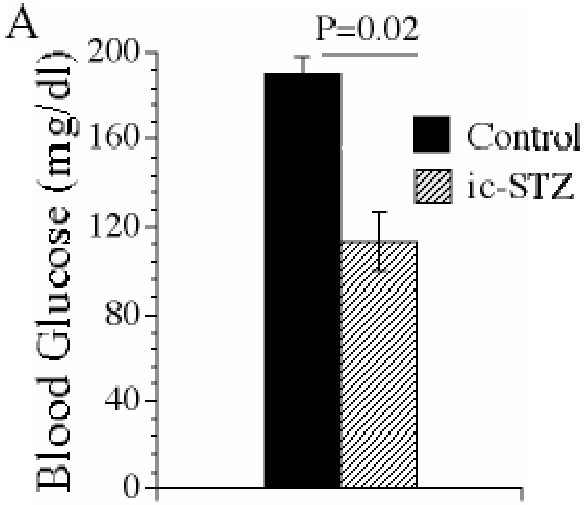


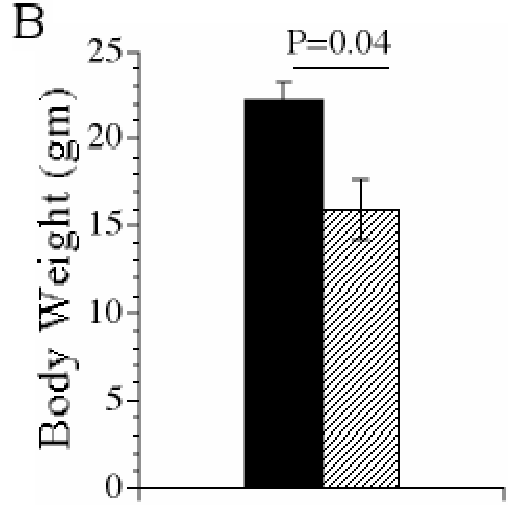
NOX1

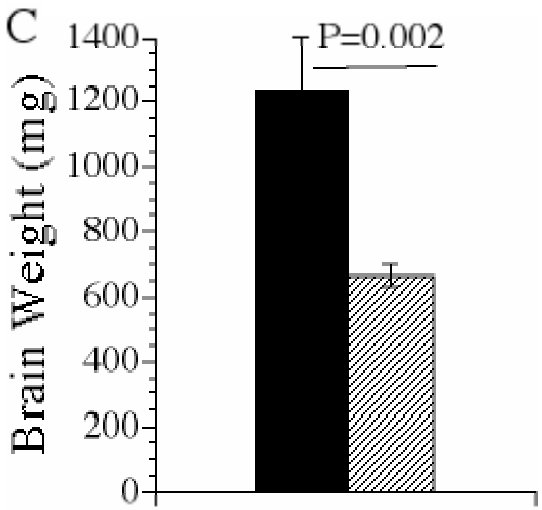
NOX3

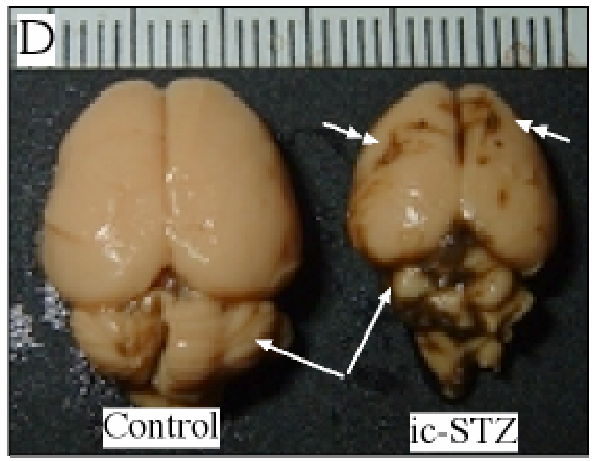
APP

Animal Model of Type 3 Diabetes/AD

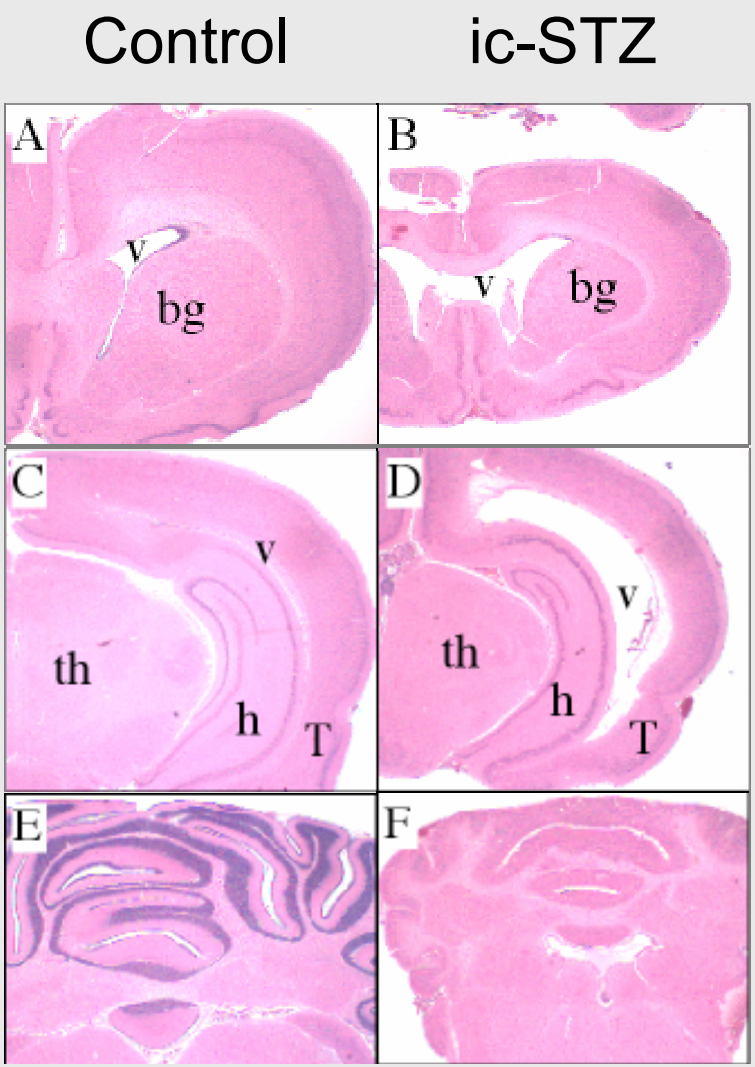


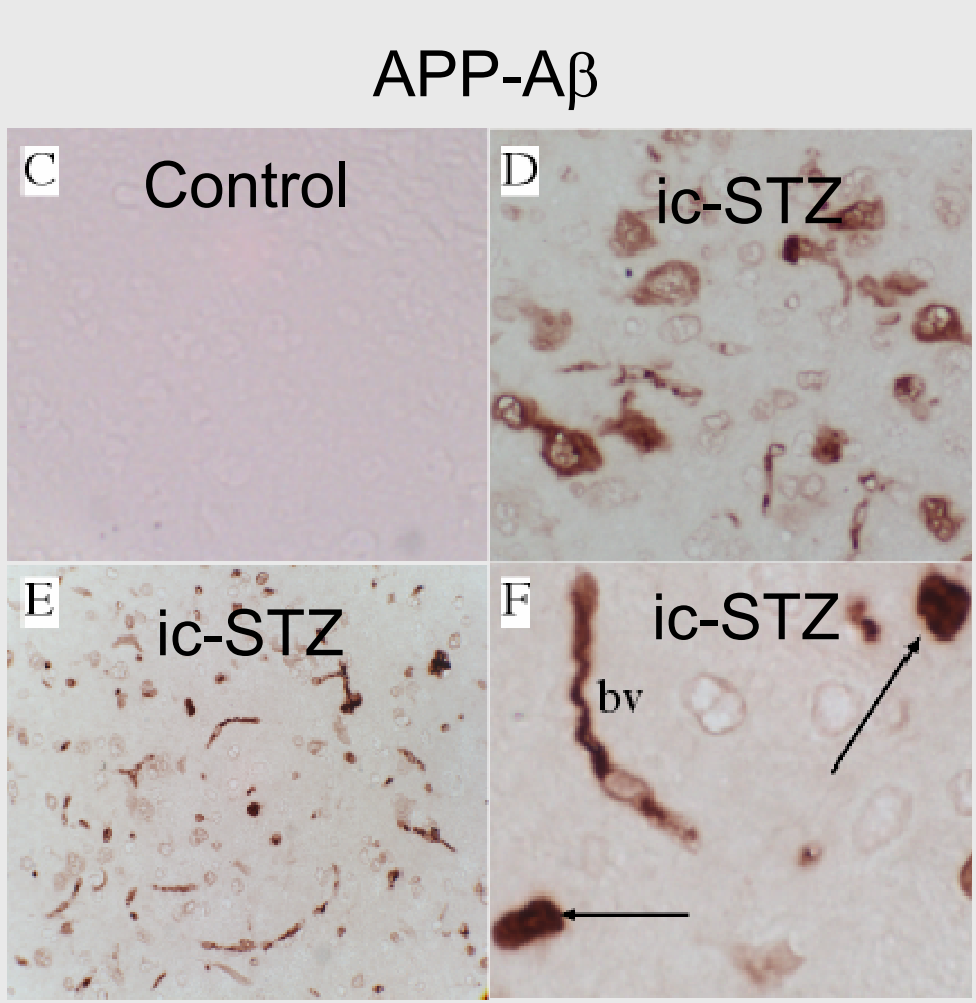




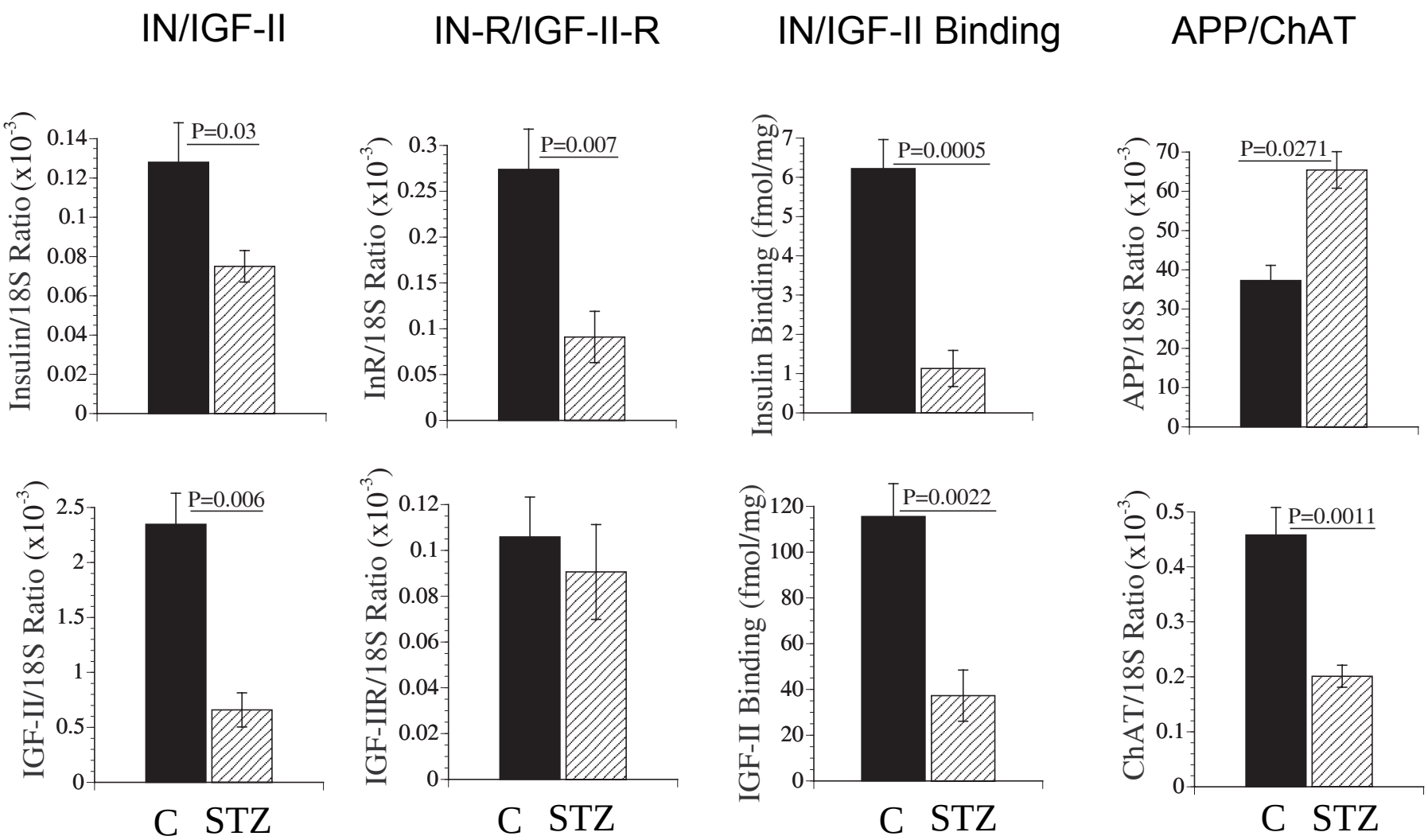


AD-Type Neurodegeneration in Experimental Type 3 Diabetes Model

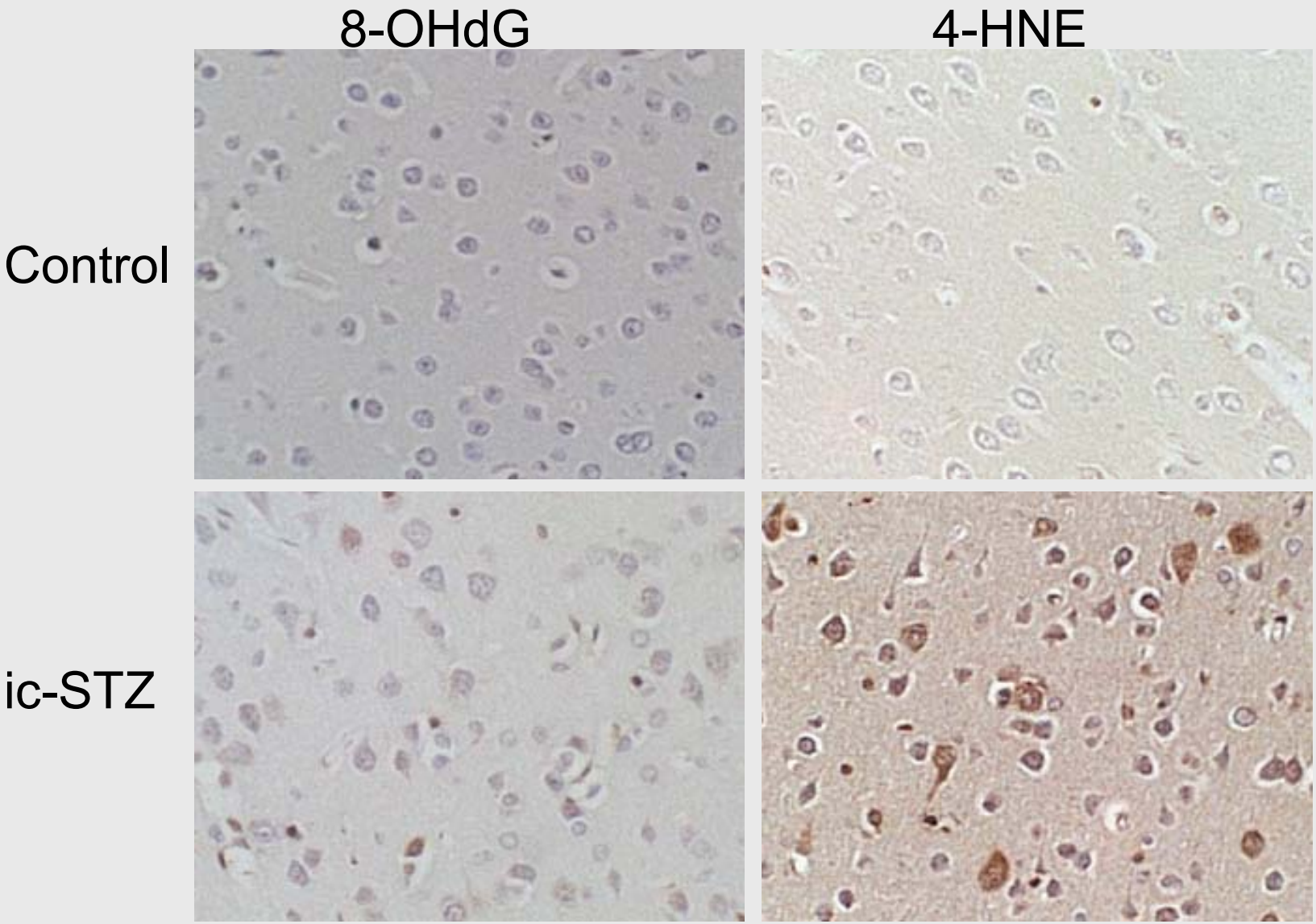




AD-Type Molecular Abnormalities in ic-STZ Model

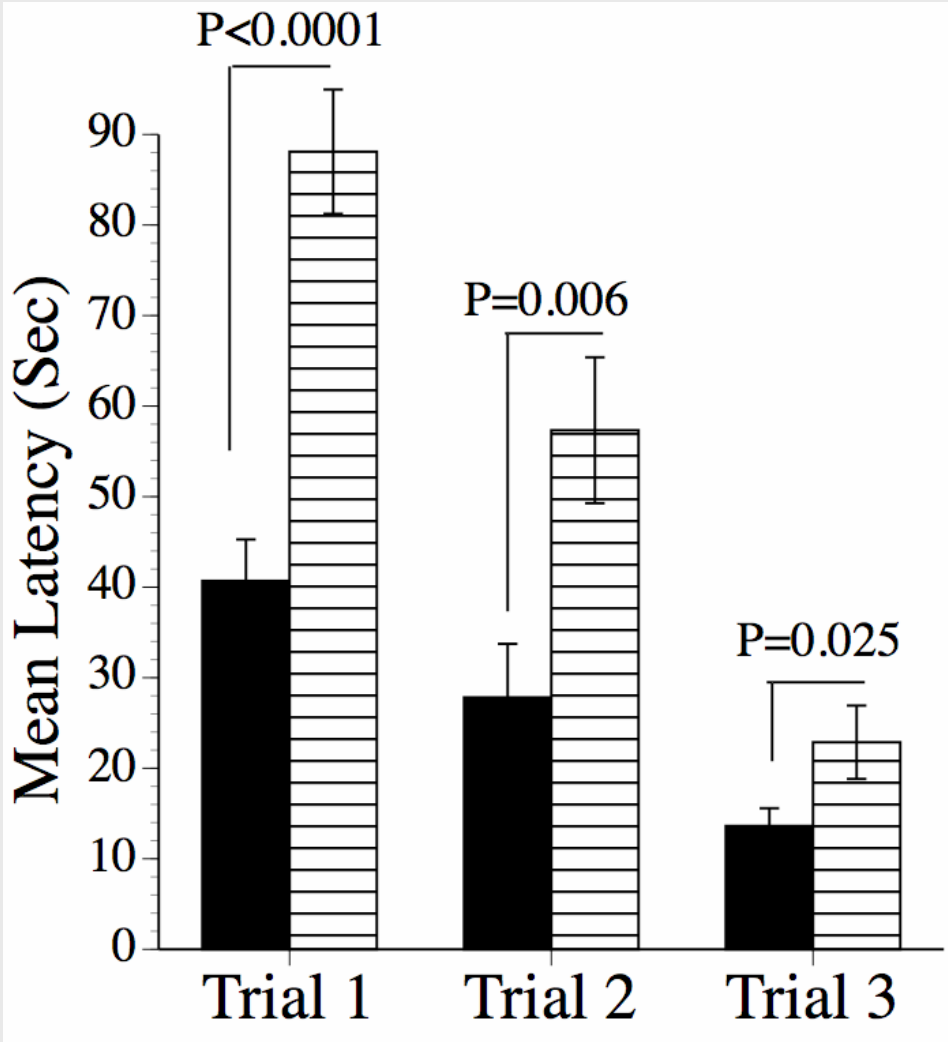


Increased DNA Damage/Oxidative Stress in ic-STZ Model

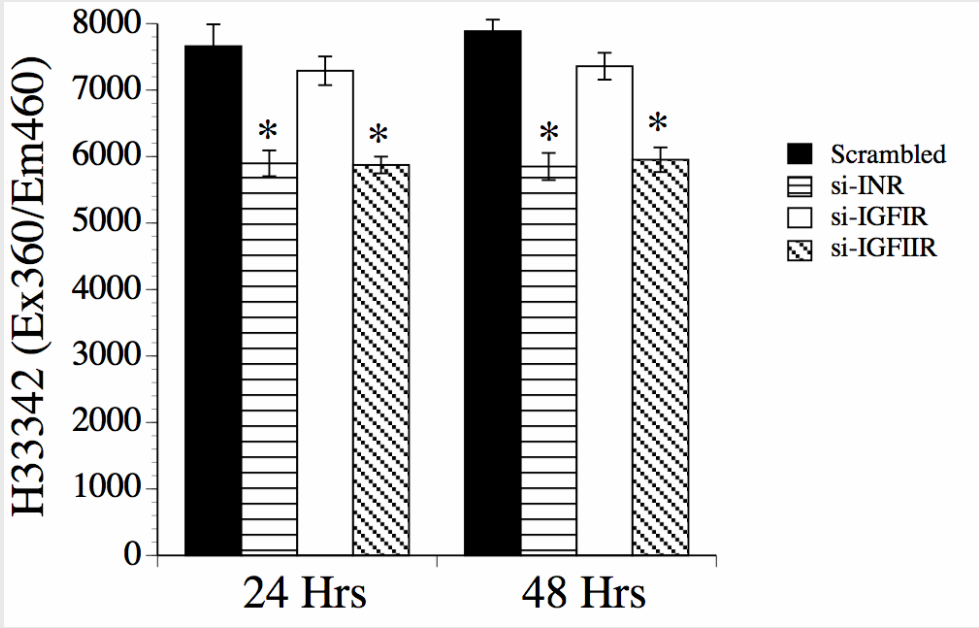


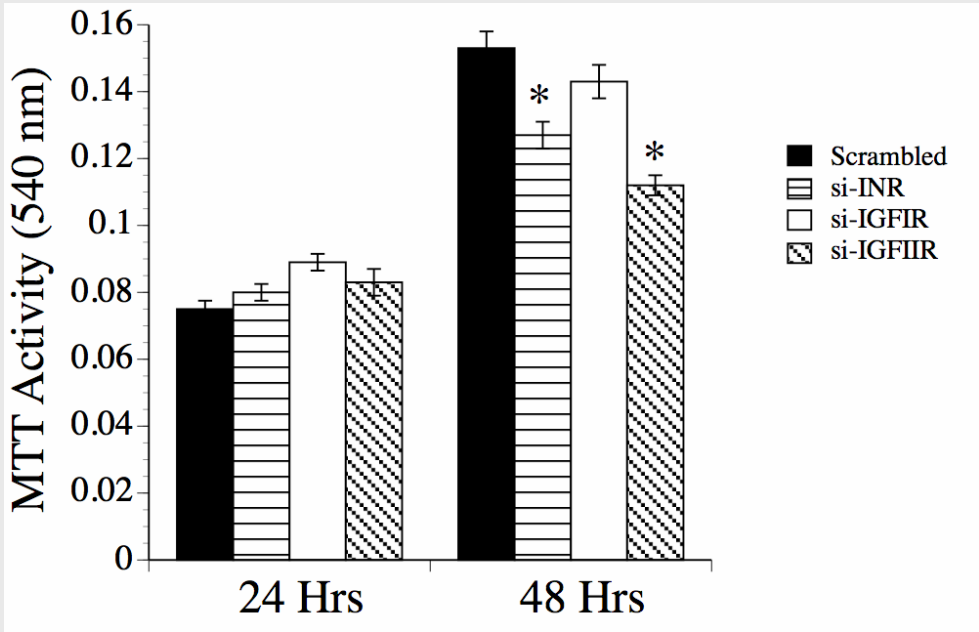
Impaired Learning/Memory in Experimental Type 3 Diabetes

Morris Water Maze

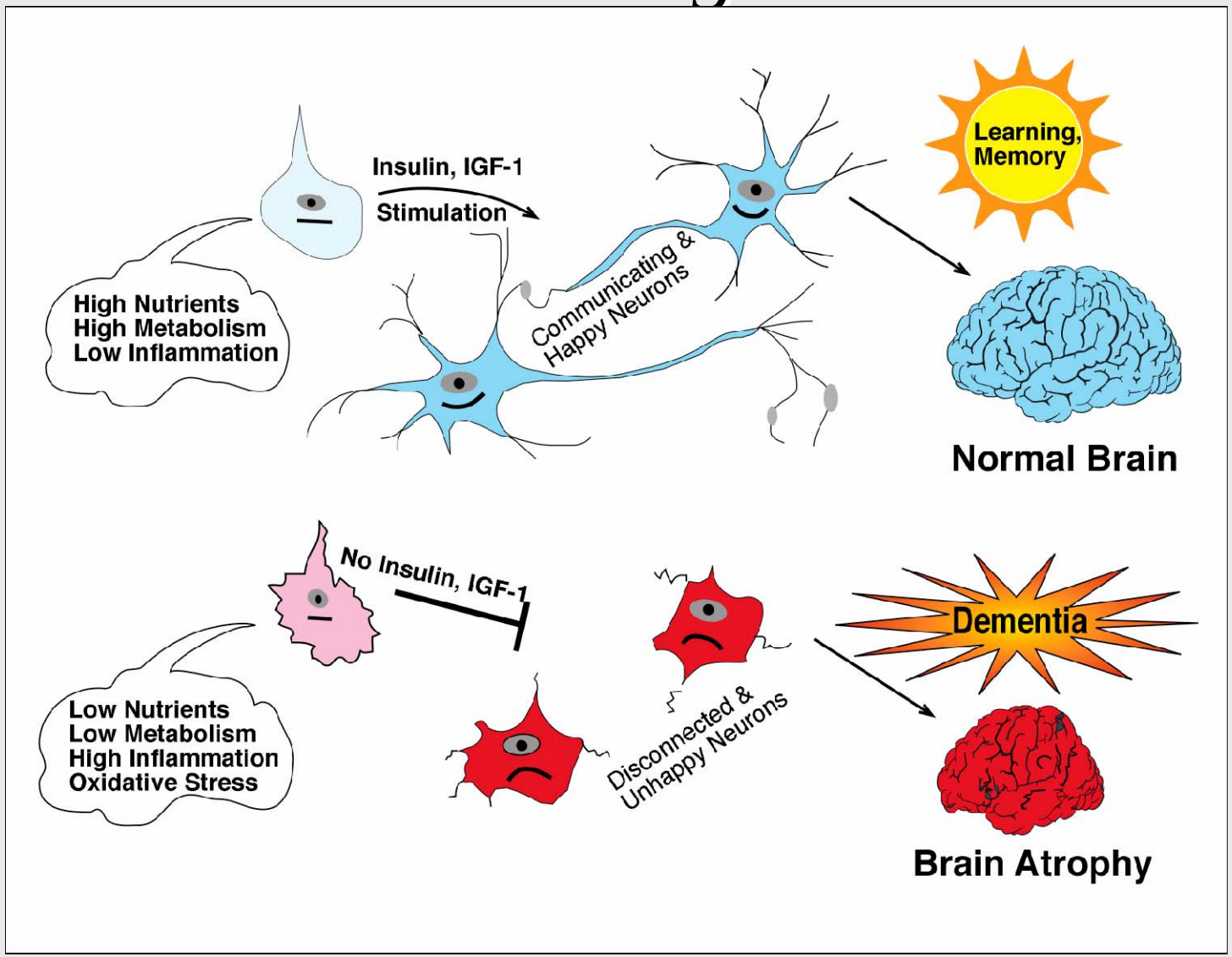


Effects of Insulin & IGF Receptor Depletion on Neuronal Viability and Mitochondrial Function





Hypothetical Scheme: Mechanisms of Neurodegeneration in AD



Future Directions

- Utilize in vivo model to:
  - Screen for novel therapeutic compounds to restore insulin/IGF responsiveness
  - Develop methods to detect insulin/IGF-II depletion and resistance in the CNS
- Identify genes that mediate insulin resistance and insulin gene depletion in the CNS

Credits

- Eric Steen
- Enrique Rivera
- Nataniel Lester-Coll
- Ming Tong
- Alison Goldin
- Noah Fulmer
- Stephanie Soscia
- Ariel Cohen
- Jack R. Wands
- NIAAA, NCI (NIA-funded brain banks)