Role of Non-Feminizing Estrogens in Brain Protection from Cerebral Ischemia: An Animal Model of Alzheimer's Disease Neuropathology

Bench to Bedside: Estrogen as a Case Study

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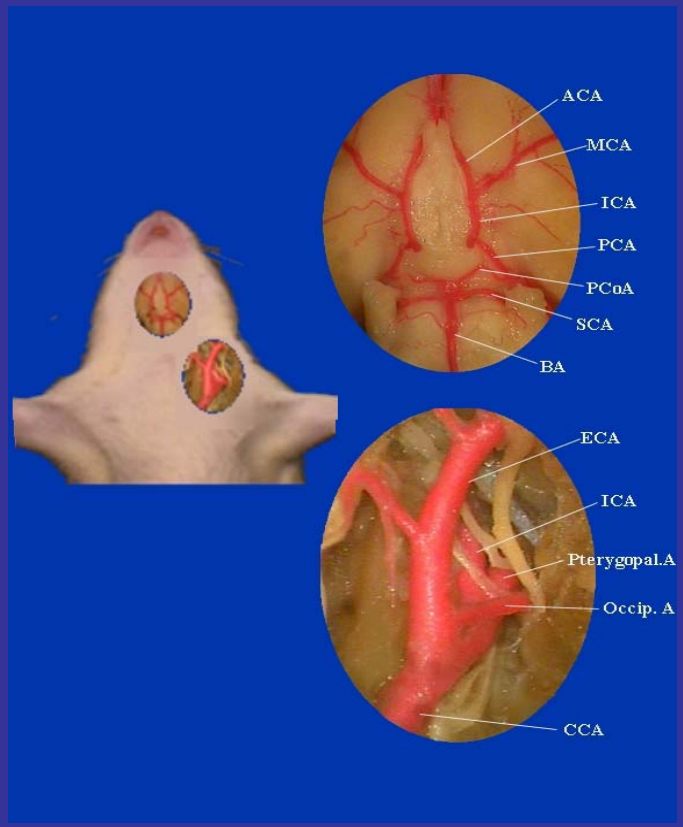
Estrogens are Potently Neuroprotective in Cerebral Ischemia

Middle Cerebral Artery Occlusion As a Stroke Model



Estrogens Shown to be Efficacious in Stroke

- MCA Occlusion

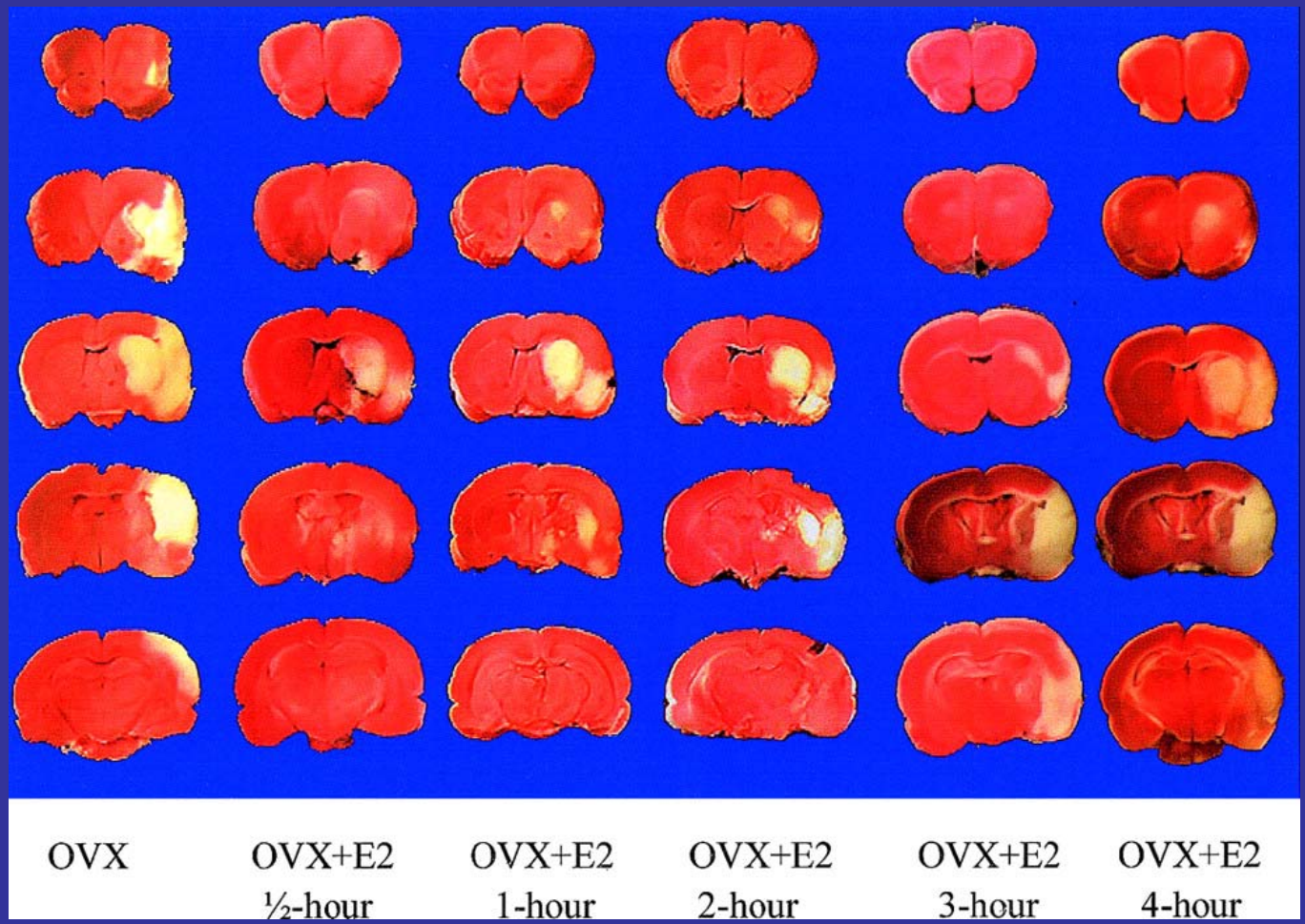
  17 β-Estradiol, 17 α-Estradiol, Ent-estradiol, Ent-17 Desoxyestradiol, 2 Adamantyl-estrone, 2 Adamantyl-4-methyl Estrone, Estrone, 10-Hydroxy-Estrone Quinol
- Global Ischemia

  17 β-Estradiol, 17 α-Estradiol
- Subarachnoid Hemorrhage

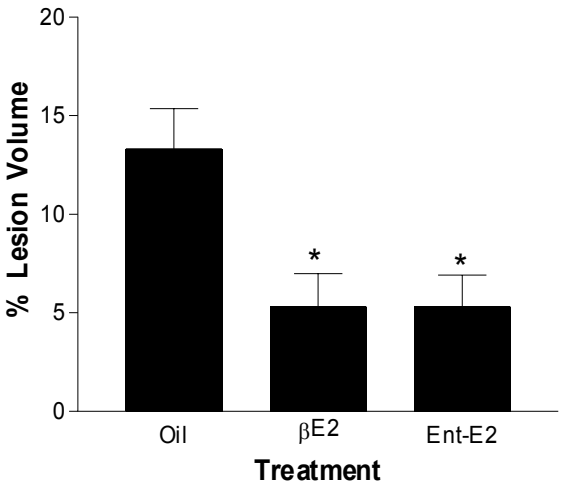
  17 β-Estradiol
- Spontaneous Hemorrhage in Stroke Prone Rats

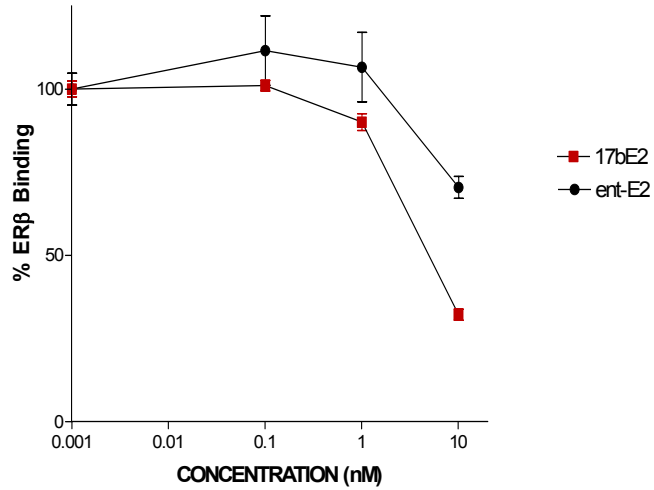
  17 β-Estradiol

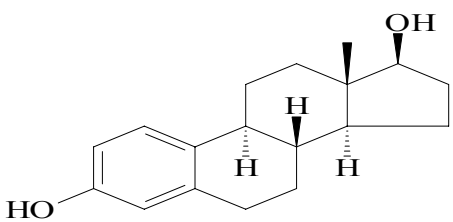
Lesion Volume with Post-Administration of Estradiol



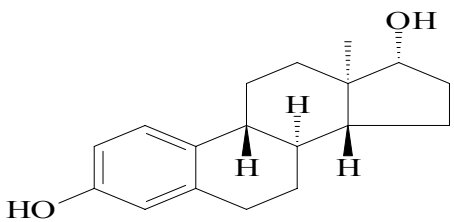
Ent-Estradiol is a Potent Neuroprotectant Against Middle Cerebral Artery Occlusion Infarcts



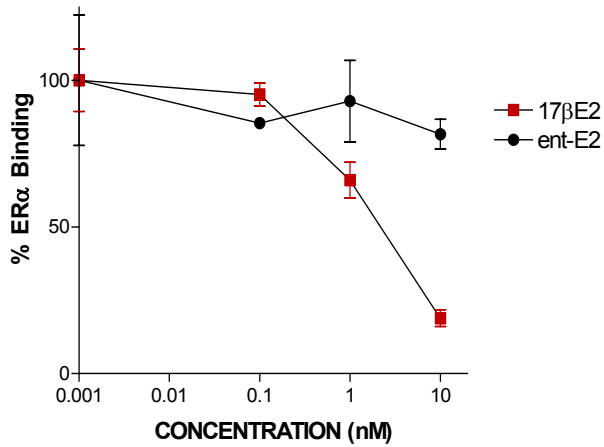




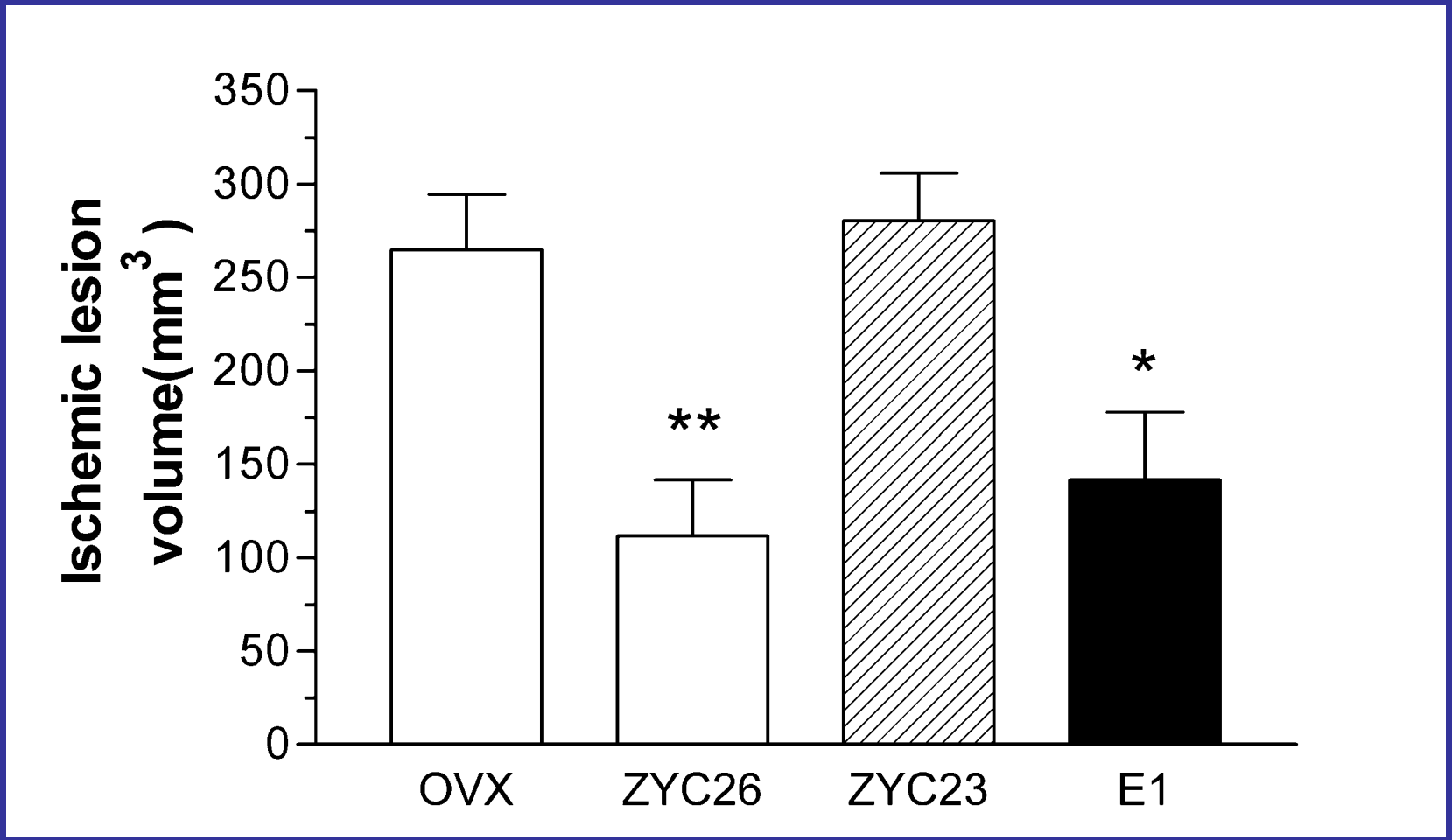
17β-estradiol



Ent-estradiol



Effects of E1, ZYC-23 and ZYC-26 on Infarct Volume Following Transient MCA Occlusion



Conclusions

- Estradiol and non-feminizing estrogen analogues are neuroprotective agents in rodent models for cerebral ischemia

- Specific structural modifications that enhance neuroprotective activity by as much as 100-fold, reduce ERβ and ERα.

Stroke as a Model for Alzheimer's Disease Neuropathology

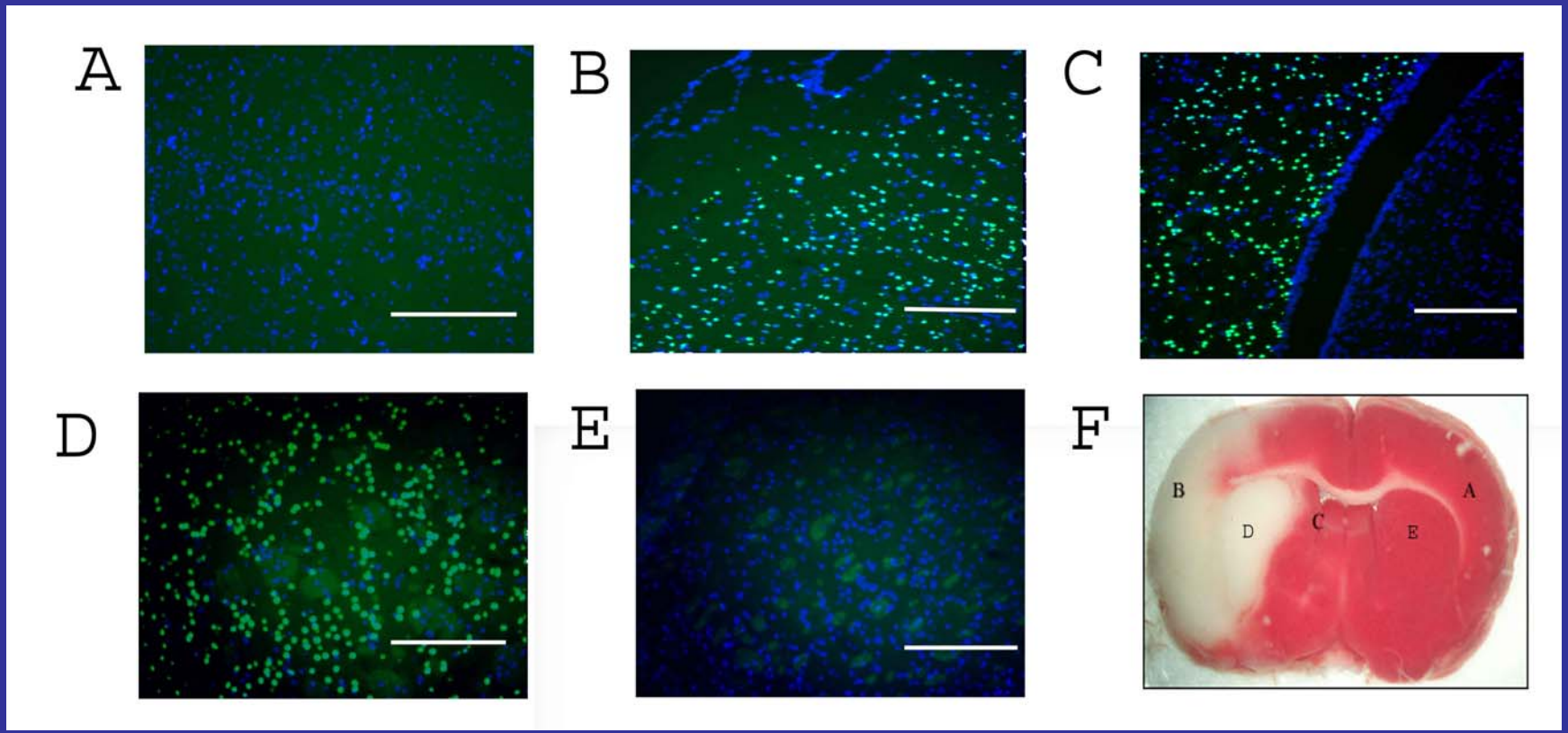
- The prevalence of dementia in ischemic stroke patients is nine-times higher than controls at 3 months (Tatemichi, Desmond et al. 1992) and 4-12 times higher than in controls at 4 years after a lacunar infarct (Loeb, Gandolfo et al. 1992).

- Many of these dementias developed progressively, and cerebral damage is believed to be the direct cause of cognitive decline in only half of these cases (Tatemichi, Paik et al. 1994).

Cerebral Ischemia in Rats as a Model for Alzheimer's Disease Neuropathology

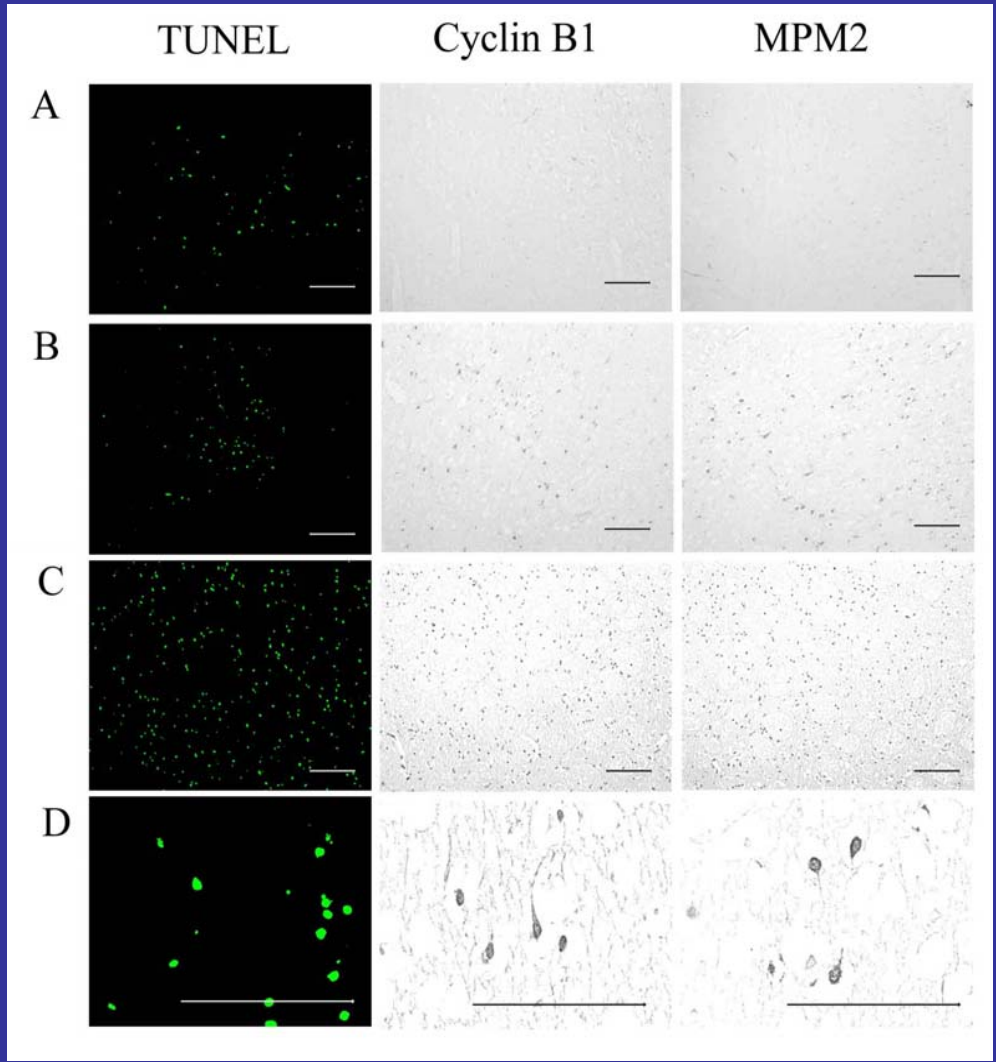
- Neuron Death
- Amyloid Production and Deposition
- Neurofibrillary Tangles
- Cell Cycle Reentry

MCA Occlusion Induces Focal Apoptosis



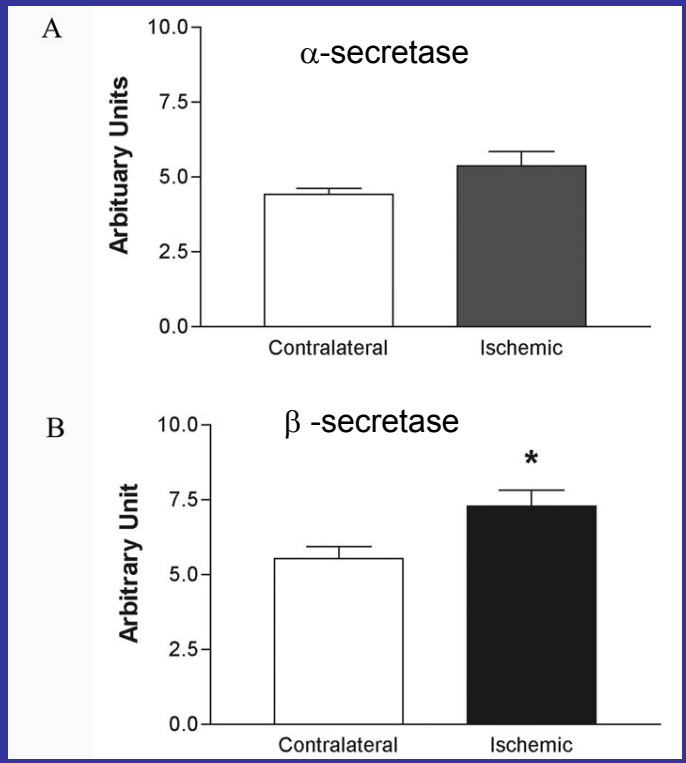
Blue : DAPI
Green: TUNEL

Association between Apoptosis and markers of cell cycle activation

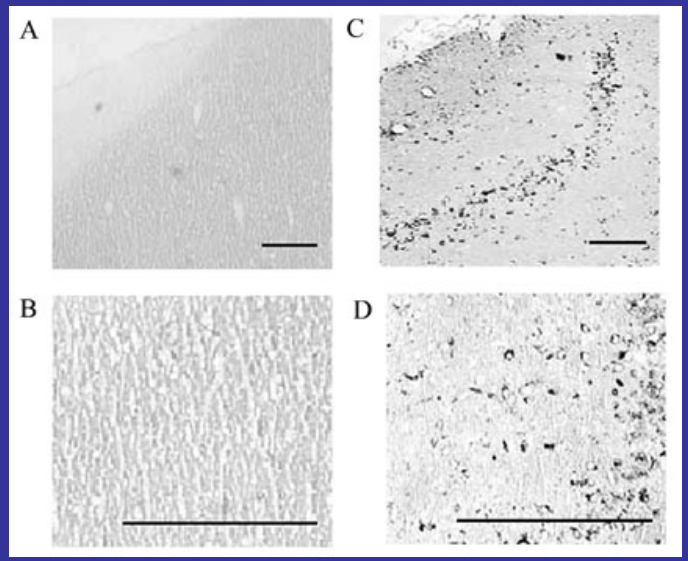


Stroke Activates BACE-1

Stroke Induces β -Secretase Activity

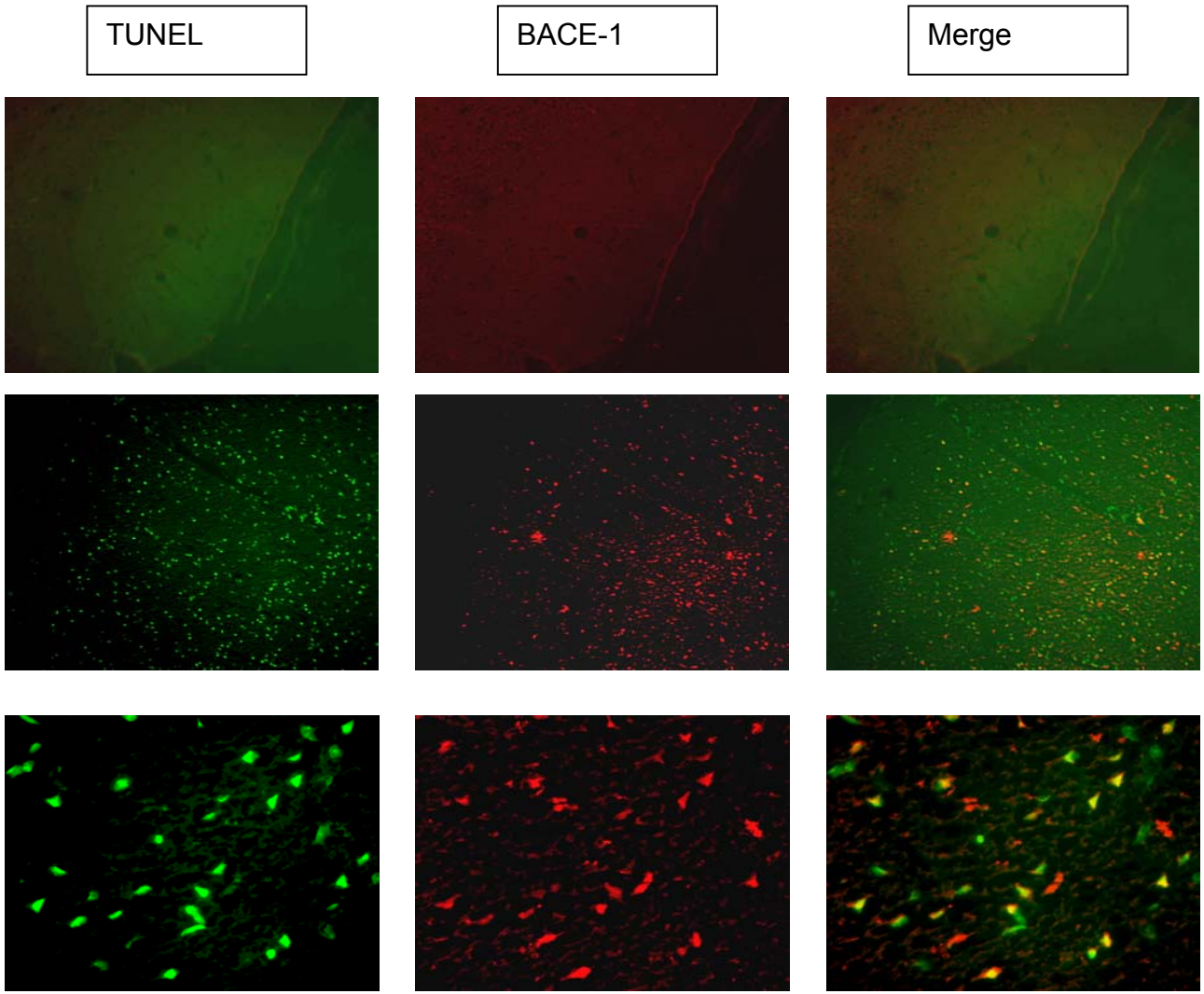


BACE1 immunohistochemistry



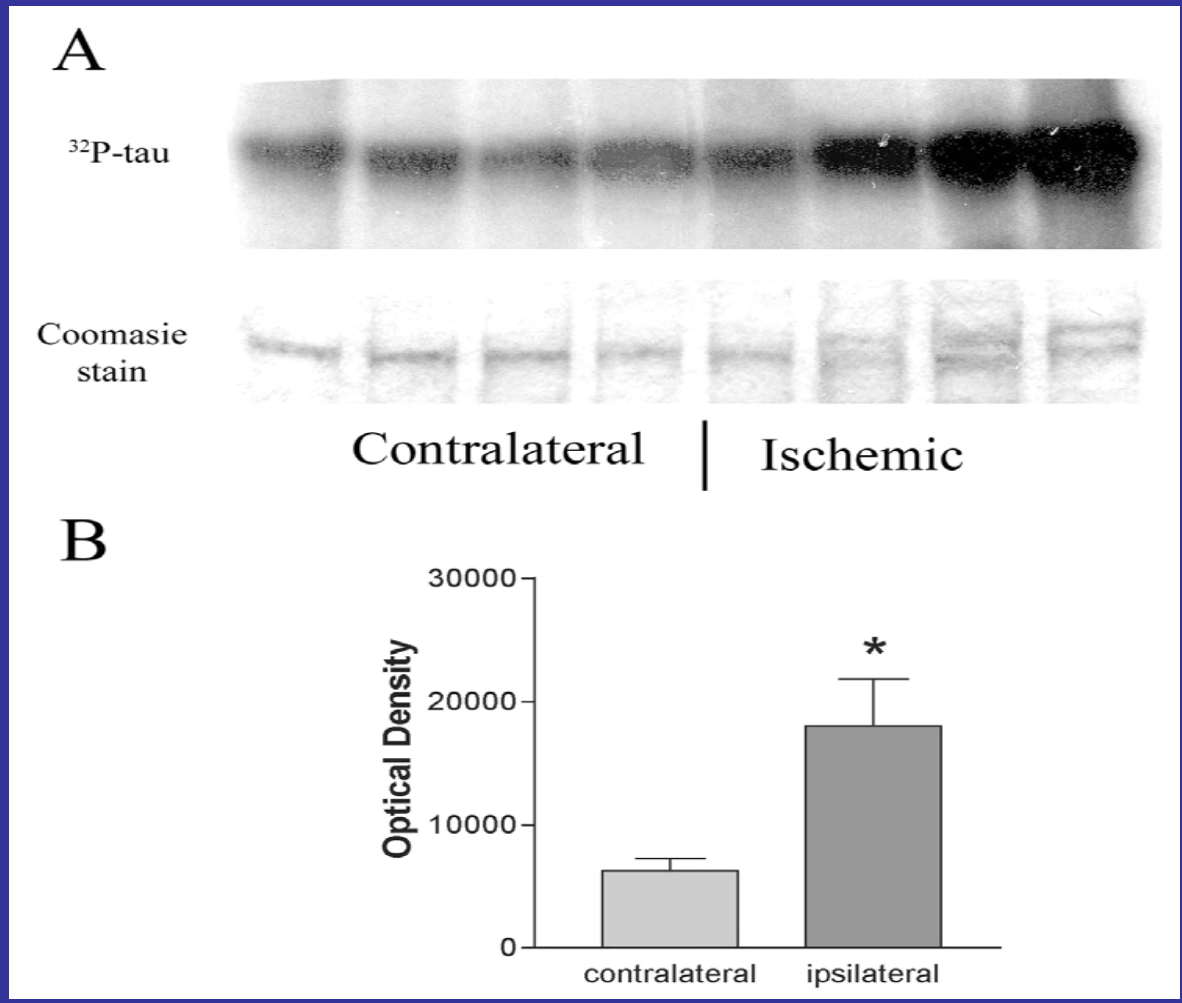
Contralateral Ipsilateral

Colocalization of BACE-1 and TUNEL in Stroke

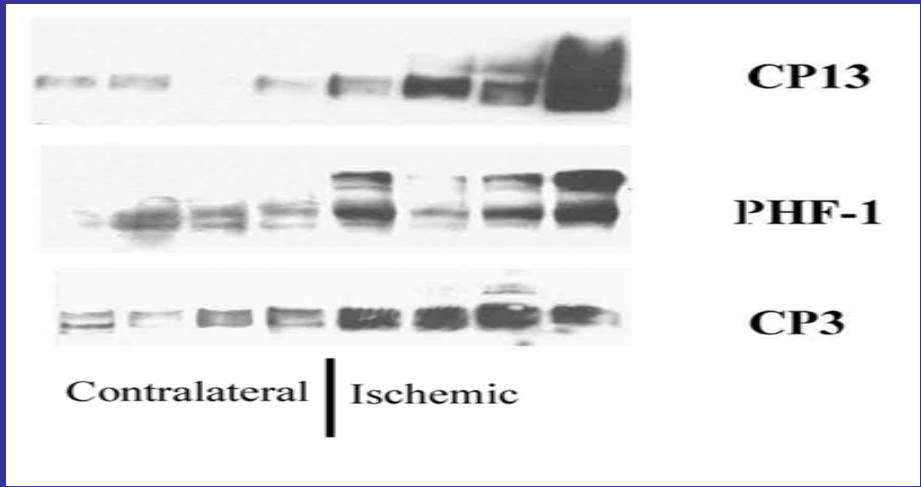


Stroke and Tau Hyperphosphorylation

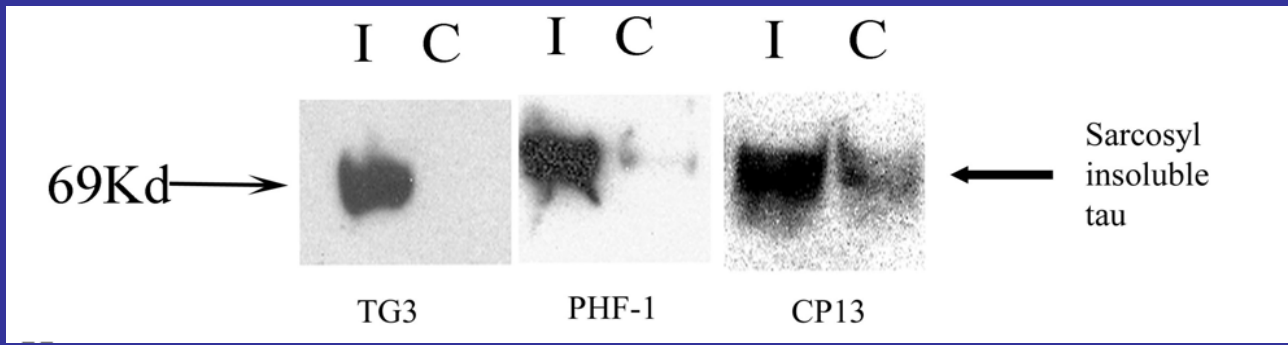
Transient Ischemia Induces Tau Hyperphosphorylation



Immunoblotting of total and sarcosyl-insoluble brain extracts

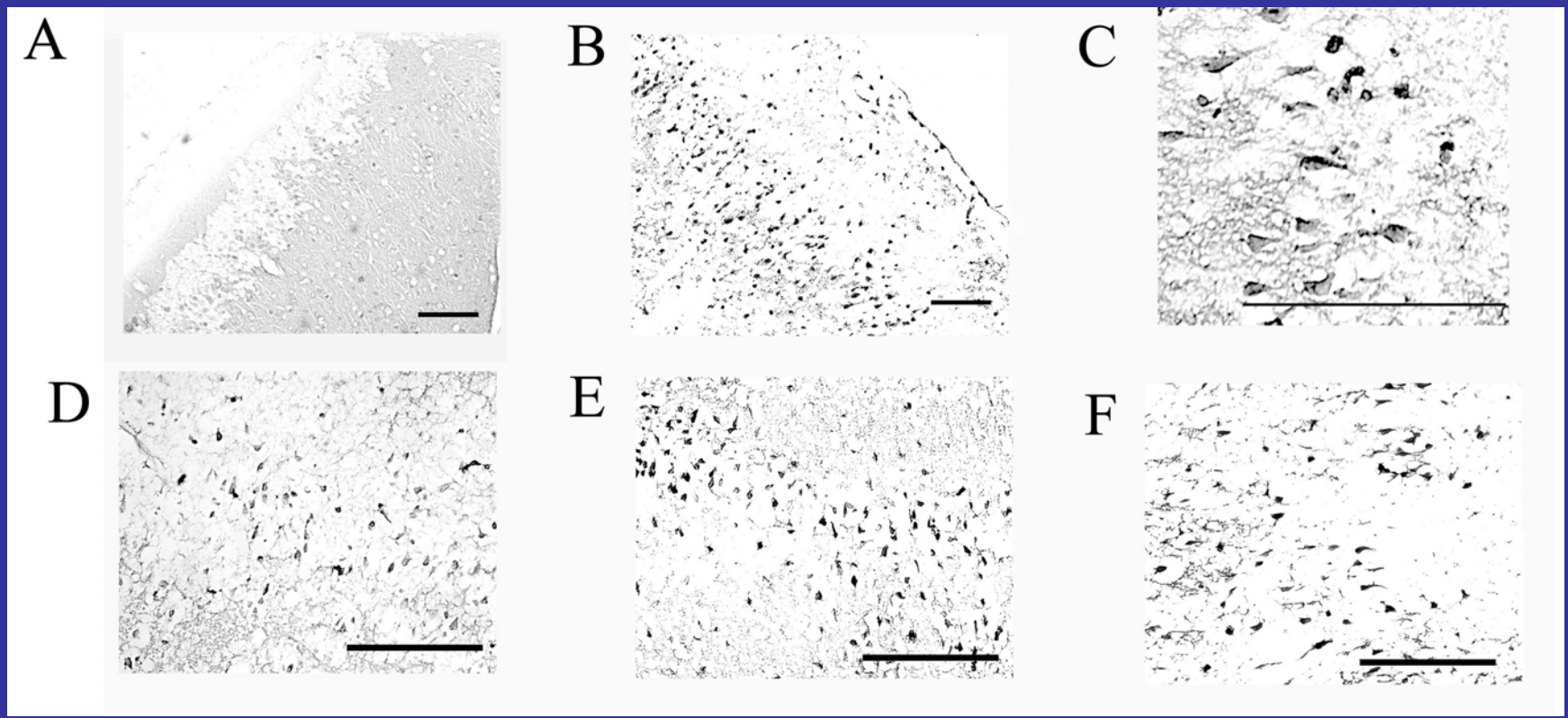


Brain extracts



Immunohistochemistry with Phospho-tau epitopes

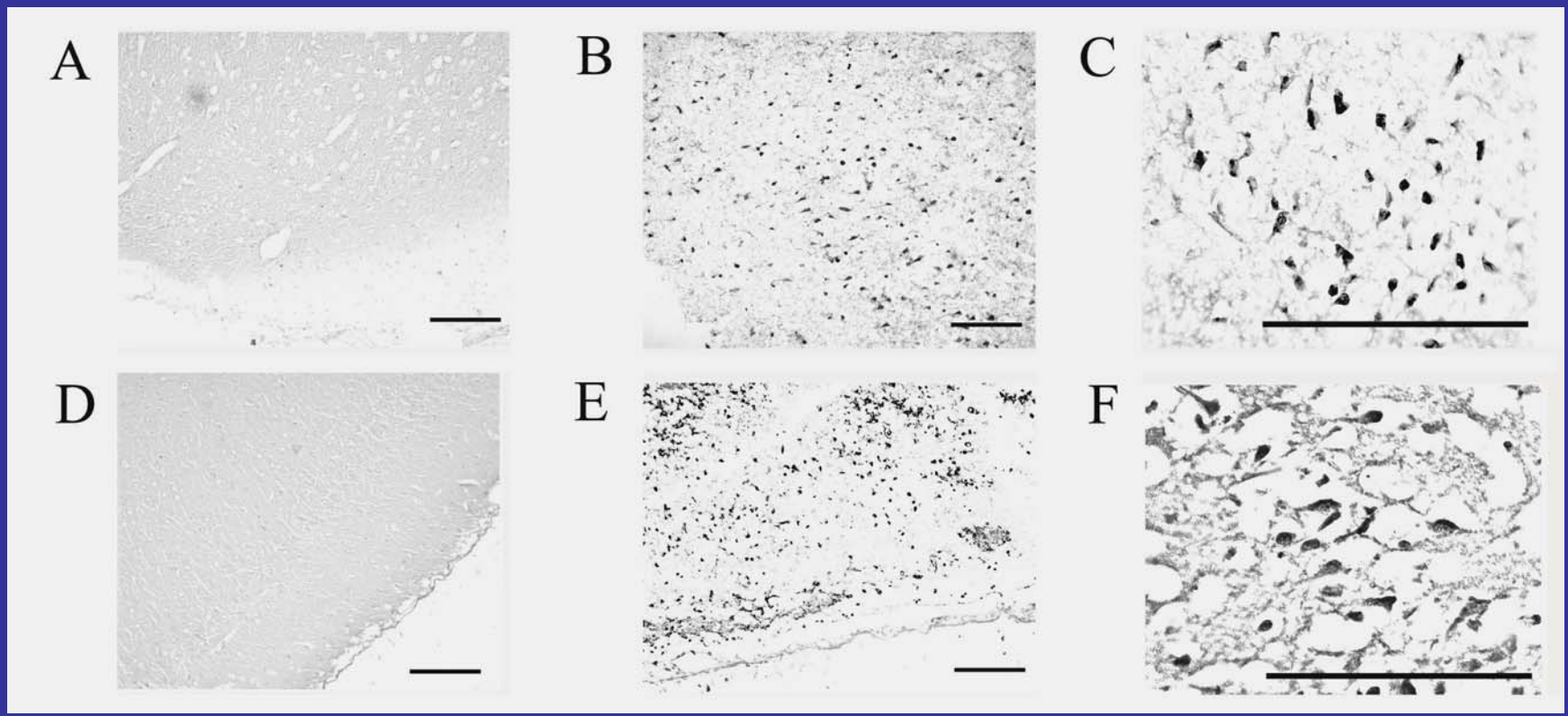
PHF-1 PHF-1 PHF-1



CP 3 CP 9 CP 13

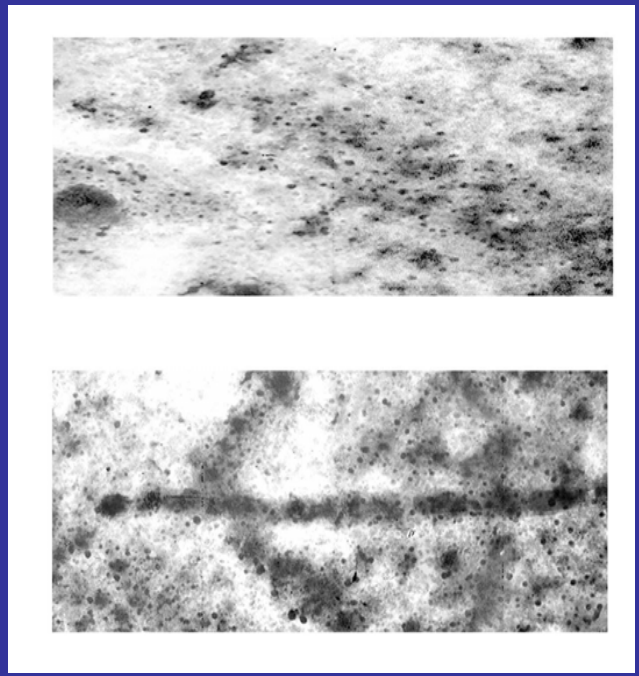
Immunohistochemistry for Confirmational Epitopes

TG3 TG3 TG3



MC1 MC1 MC1

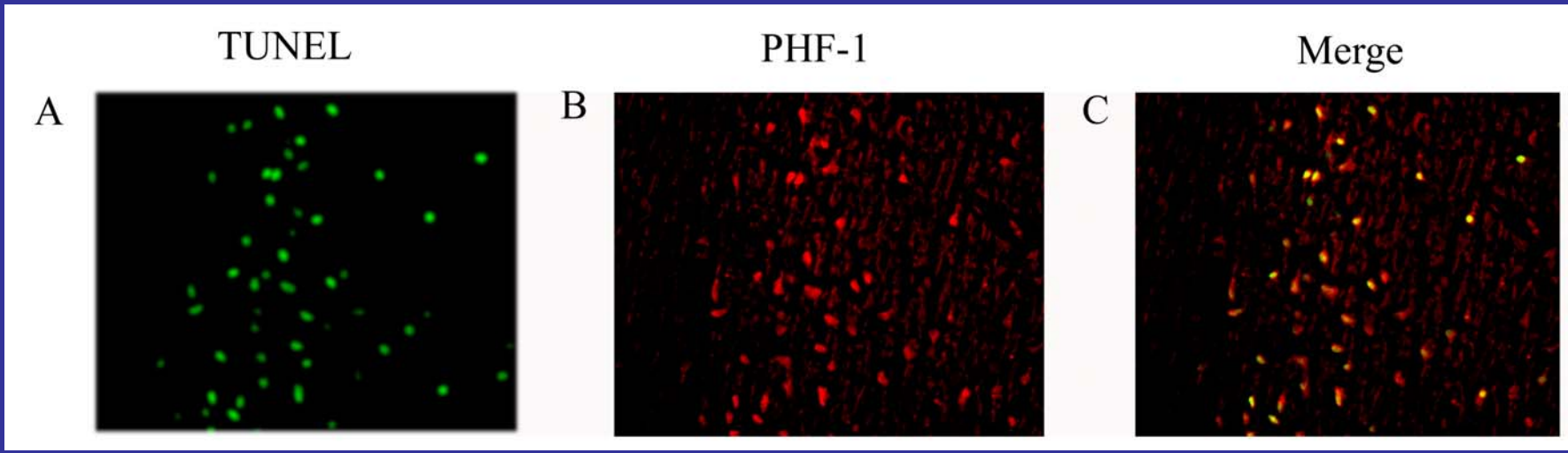
Electronic microscopy analysis of Sarcosyl-insoluble extracts



Contralateral

Ipsilateral

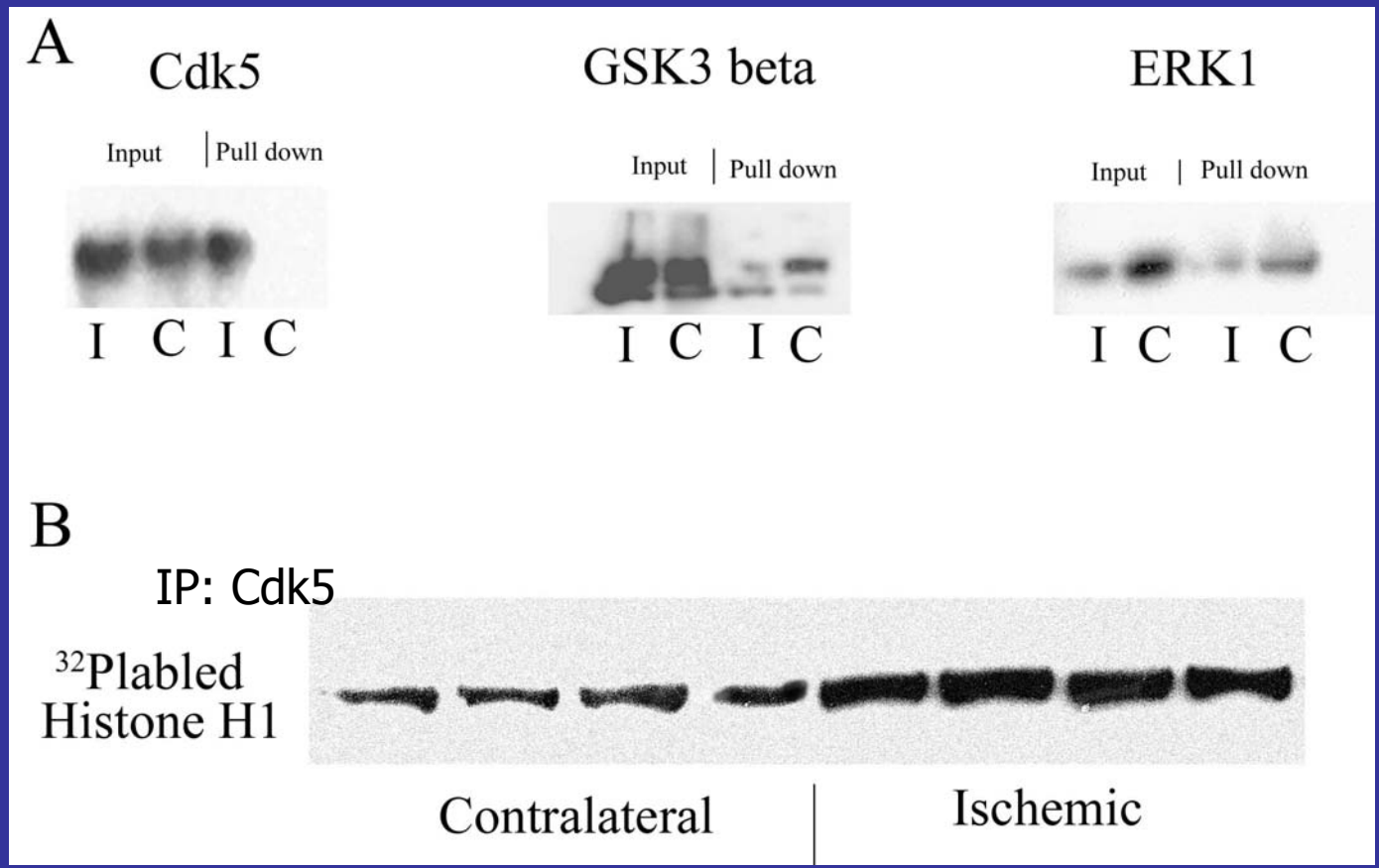
Colocalization of PHF-1 with TUNEL



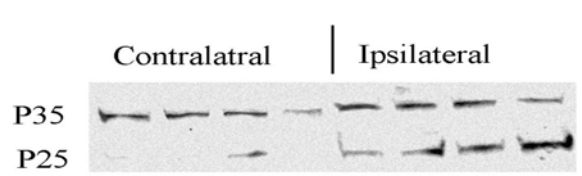
Introduction: Cdk5

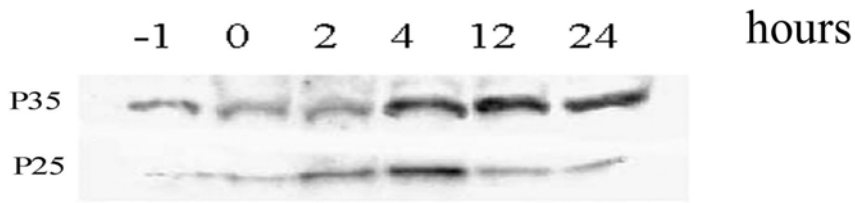
- A distinct member of cyclin-dependent kinase family
- Activation requires no cyclins but needs co-activators, P35/P39 or their cleaved product P25/P29
- Active exclusively in neurons
- Not responsible for cell division, but for synaptic formation and, neuronal migration, and other neuro-plastic activities

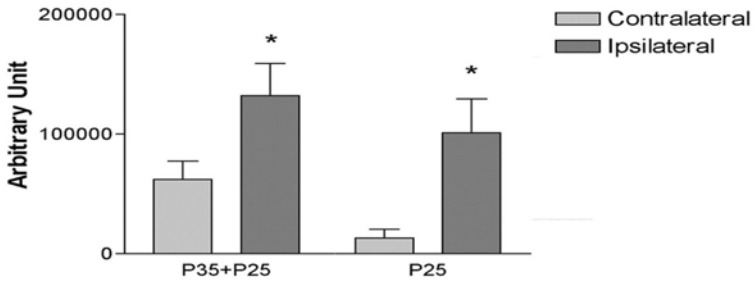
Tau associates with Cdk5 in an activation-dependent manner

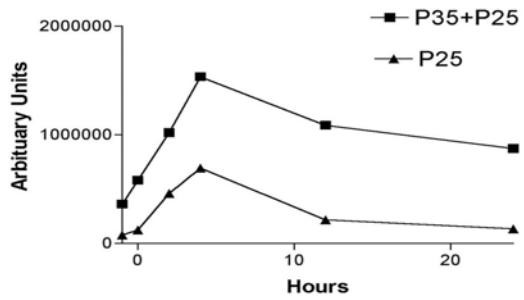


Stroke induces the cleavage and accumulation of P35

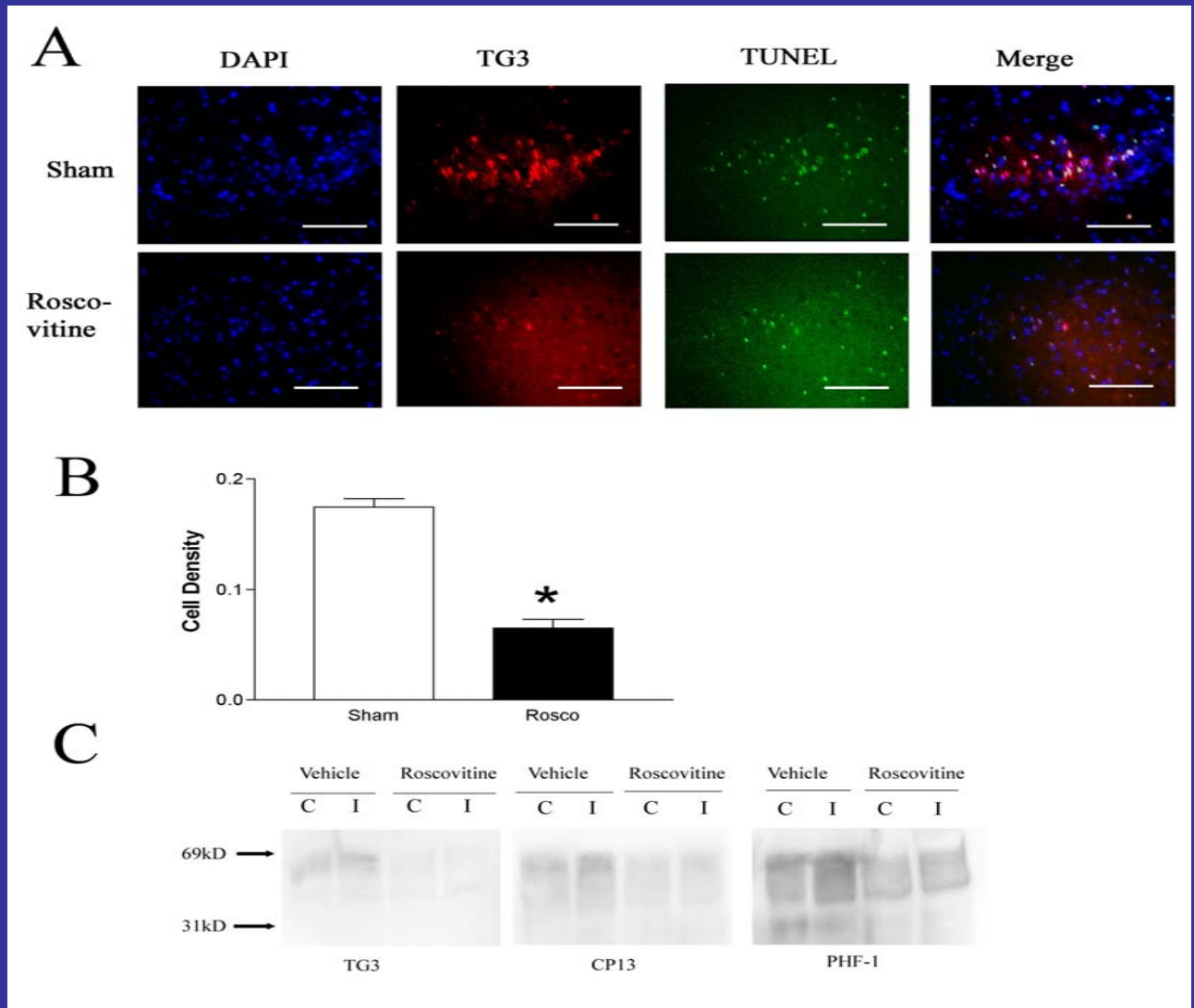


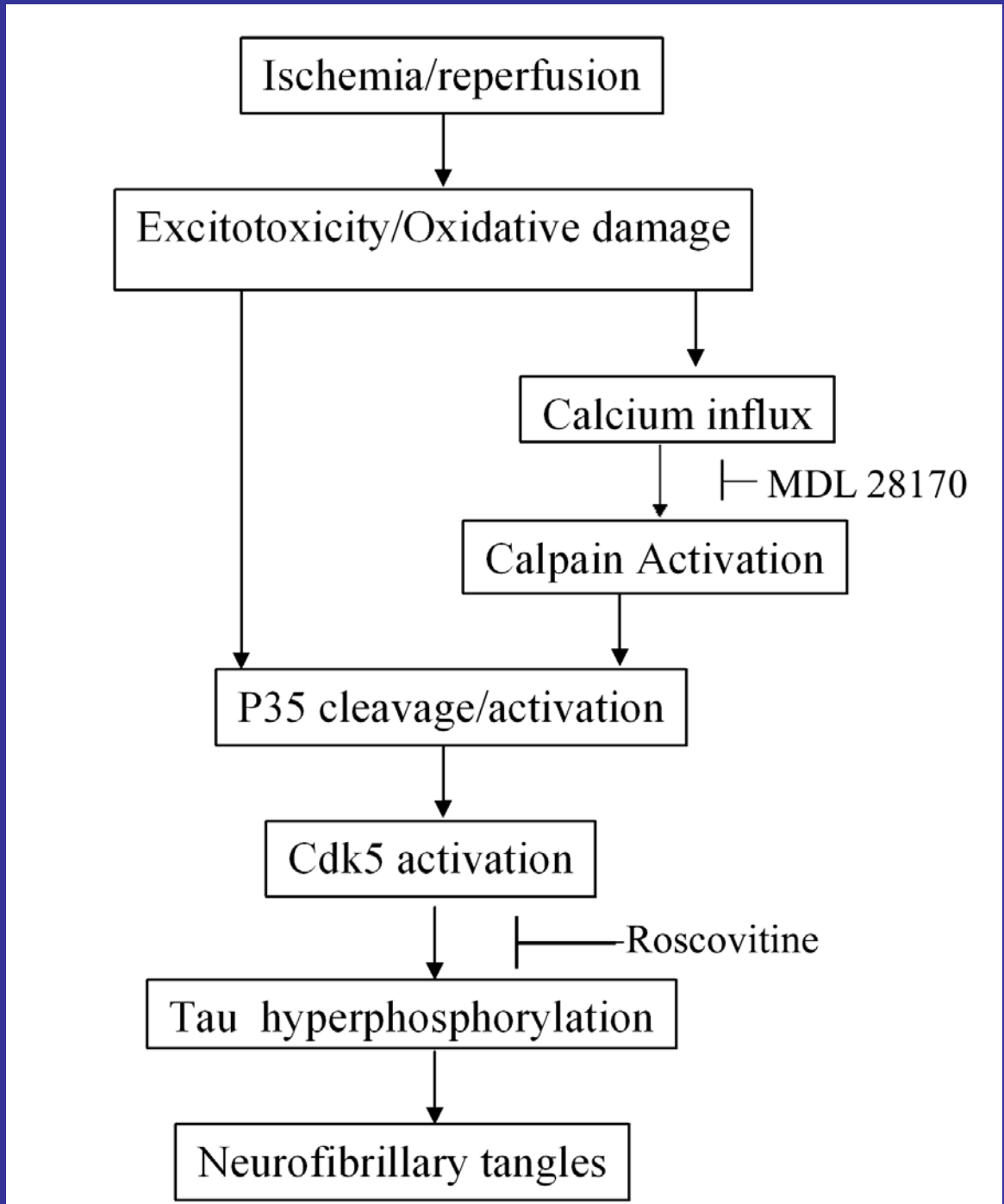




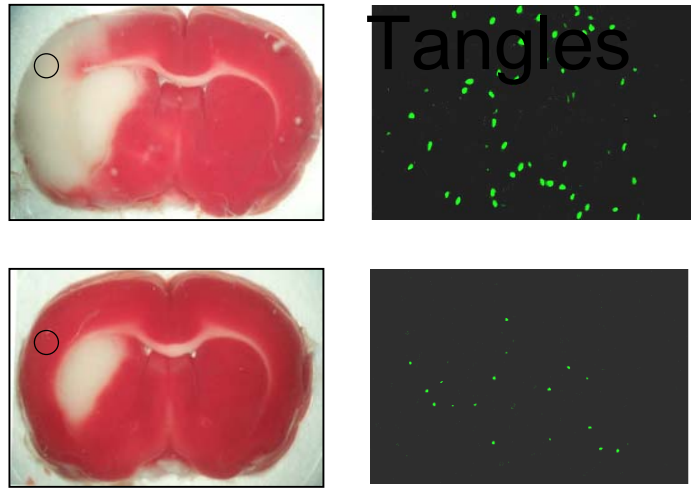


Inhibition of Cdk5 reduces tau hyperphosphorylation




Ischemia/reperfusion
Excitotoxicity/Oxidative damage
Calcium influx
MDL 28170
Calpain Activation
P35 cleavage/activation
Cdk5 activation
Roscovitine
Tau hyperphosphorylation
Neurofibrillary tangles

Estrogen Protection from Apoptosis, Aberrant Cell Cycle Protein Activation and Neurofibillary



Summary

- Stroke increases BACE-1 activity and Aβ production.
- Stroke induces tau hyperphosphrylation.
- Hyperphosphorylated tau shows AD specific conformational changes.
- Evidence for the presence of hyperphosphrylated tau in an aggregated form.
- Signs of mitotic event in neurons.
- These neuropathologies colocalize with apoptosis.
- All of these stroke-induced changes are ameliorated by acute estrogen treatment.

Acknowledgements

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