

# CASE PRESENTATION

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# Case Study

- ▶ Compound indicated for
  - Metabolic syndrome
  - Diabetes
- ▶ Dose-dependent, profound, transient hypoglycemia and hyperinsulinemia at high doses in all species
- ▶ Seizure activity in some animals, especially dogs
- ▶ Neuronal necrosis, mainly in rats
  - Temporal cortex
  - Thalamus
  - Caudate nuclei
  - Globus pallidus

*Pettersen et al., Tox path. 2014 Jun; 42(4):696-708*

# Case Study

## ▶ Peripheral neuropathy

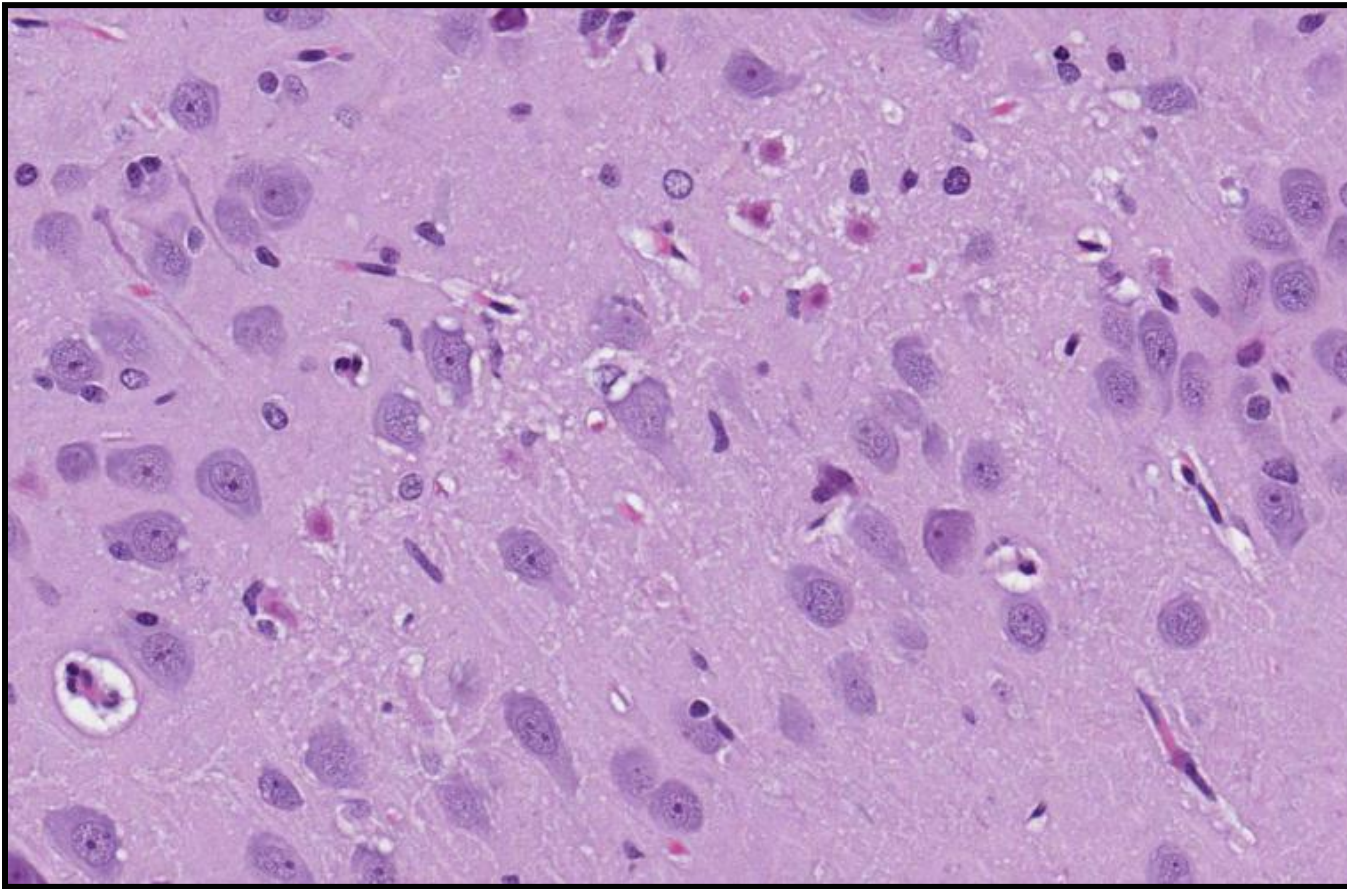
- Mice
- Rats
- Dogs
- NHPs

## ▶ Vasculopathy

- Dogs
- NHPs

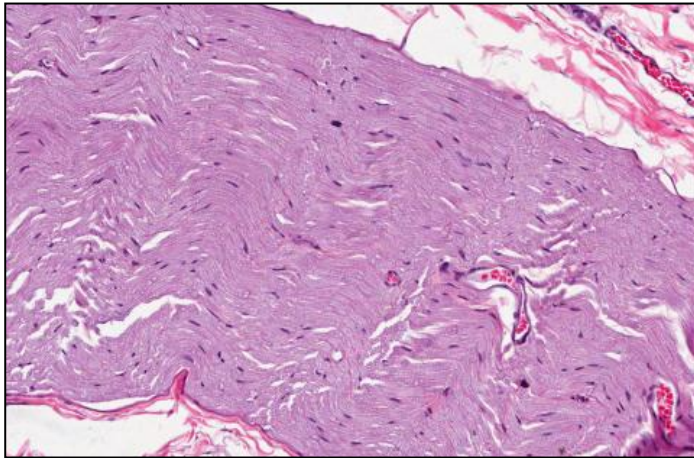
*Pettersen et al., Tox path. 2014 Jun; 42(4):696-708*

# Hippocampus, Brain, Rat - Neuronal Degeneration

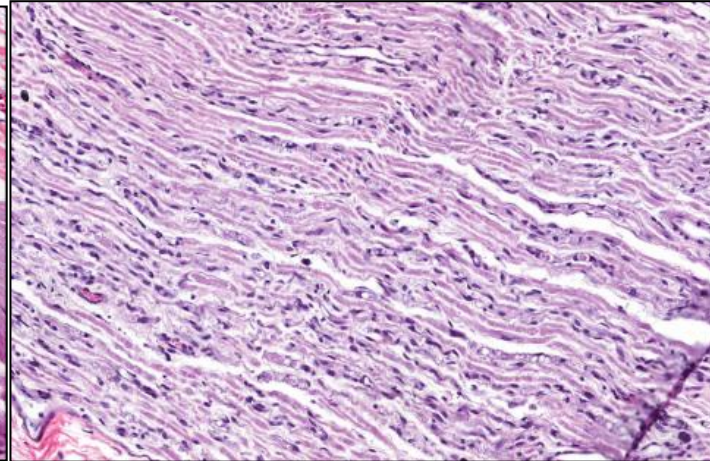


*Image Source - Covance*

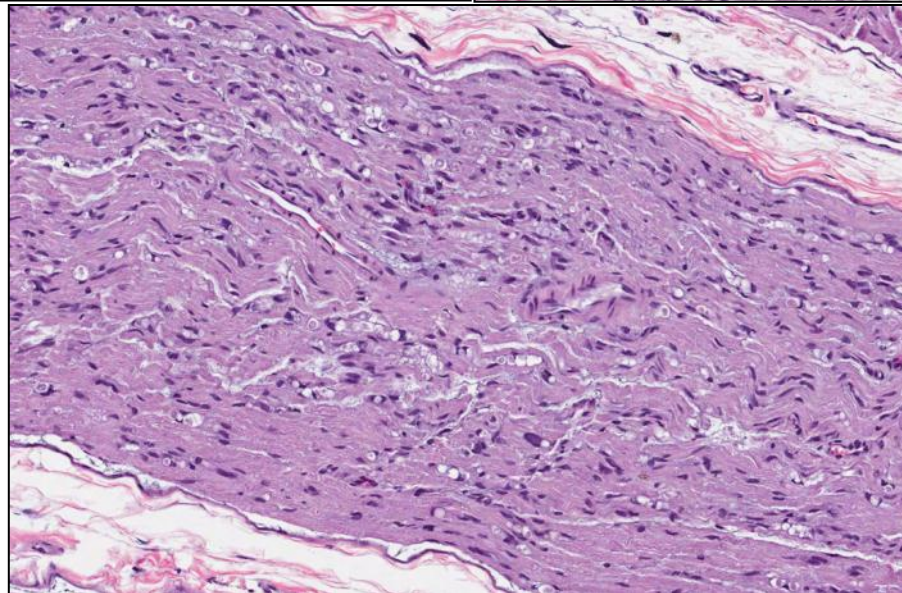
# Peripheral Nerves (Brachial Plexus) Rat - Axonal Degeneration



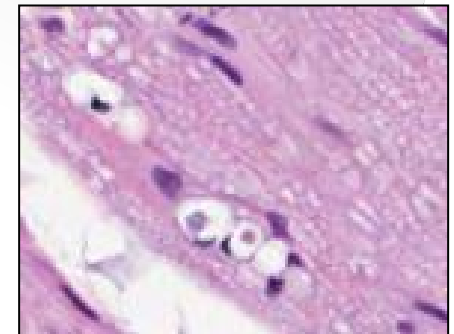
Control



High Dose



High Dose



*Image Source - Covance*

# Blood Glucose Measurements for Hypoglycemia Causing TAs

Helps to differentiate pharmacological effects from unintended off-target effects

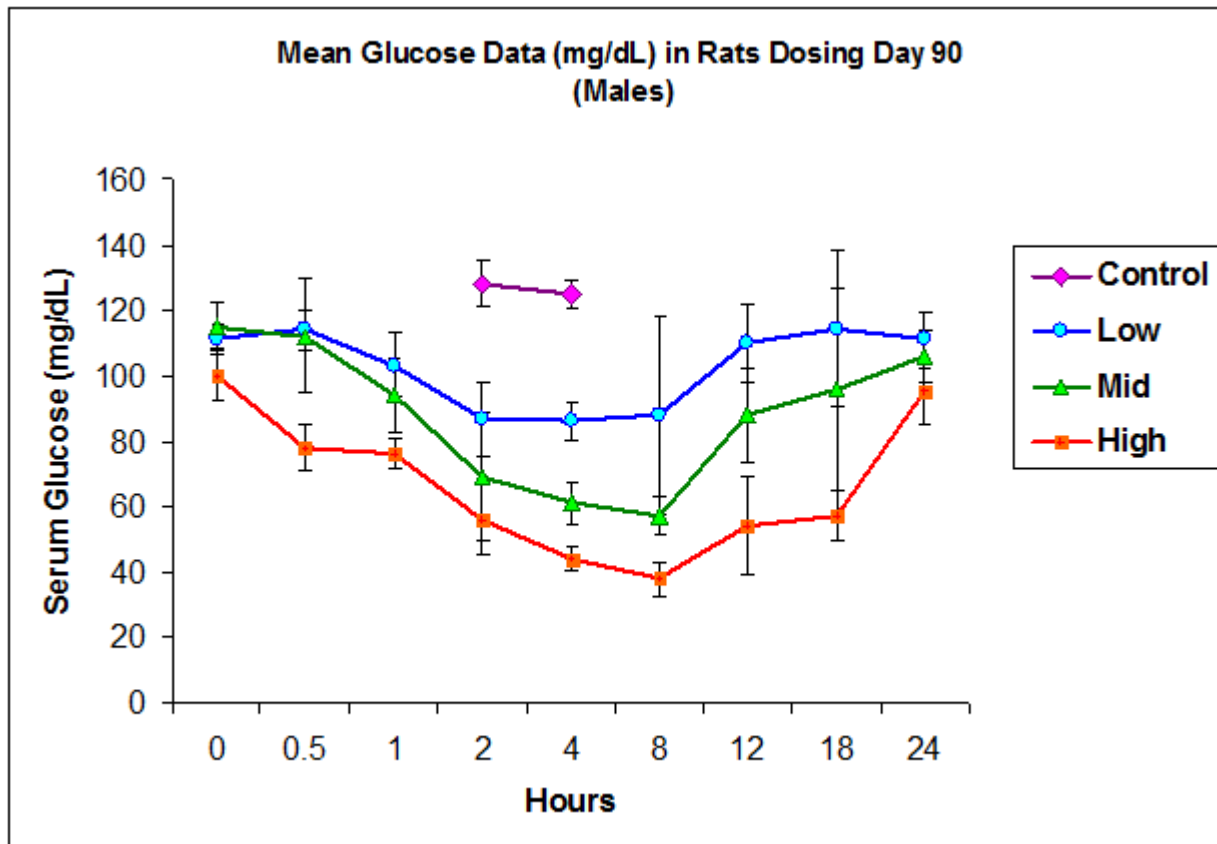
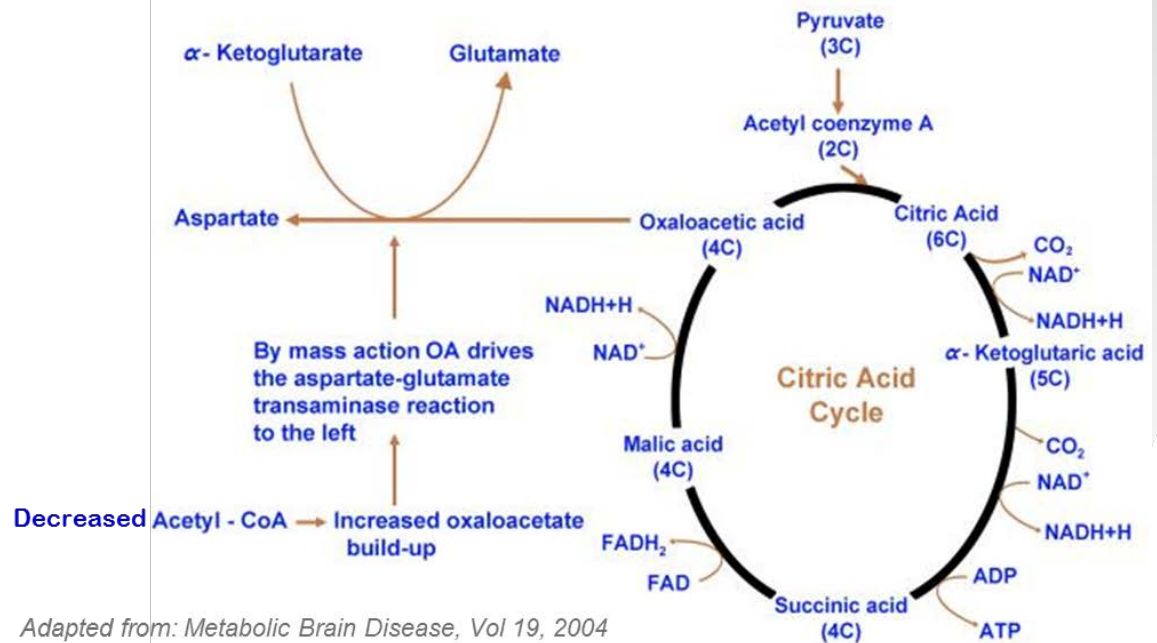


Image Source - Covance

# Mechanism of Neurodegeneration and Peripheral Neuropathy

- ▶ Hypoglycemia induced increased aspartate causes neurodegeneration - Excitotoxicity
- ▶ No clear pathogenesis for axonal degeneration:
  - Reduced or absent energy substrates
  - Impairment of energy consuming anterograde axonal transport
  - So, maintenance of distal part of axon may be compromised (Diabetes, Vol 36)



# Are These Findings Adverse?

- ▶ Neuronal and axonal degeneration are always considered ADVERSE findings
  - Reversibility of axonal degeneration does not make it NON-ADVERSE

# Are These Findings Adverse?

- ▶ To investigate whether these ADVERSE effects were secondary to exaggerated pharmacology (persistent and profound hypoglycemia) in euglycemic rats
  - Zucker diabetic fatty rats (hyperglycemic and insulin resistant) were used as they better represent hyperglycemic and diabetic patients than normal euglycemic rats, dogs and NHPs
    - TA did not cause hypoglycemia, clinical signs of hypoglycemia or any of the histopathologic ADVERSE effects observed in euglycemic animals

*Tirmenstein et al. (2015). Tox Path, 43: 825-837.*

# Are These Findings Adverse?

- ▶ Based on glucodynamic data (blood glucose measurements) and absence of findings in Zucker rats
  - Toxicity in euglycemic animals considered secondary to exaggerated pharmacology
- ▶ The TA went to the clinical trials

*Tirmenstein et al. (2015). Tox Path, 43: 825-837.*

# Thank You!

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