

Clinically approved daidzein enhances cholesterol homeostasis via ApoE to promote stroke recovery in mice



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Disclosure

Research Support

NIH-NHLBI

NIH NCRR

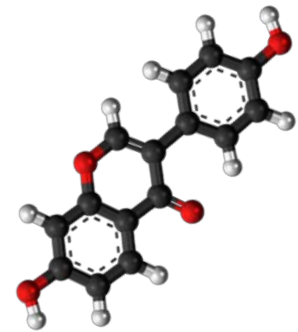
NINDS

Burke Foundation

Conflict of interest

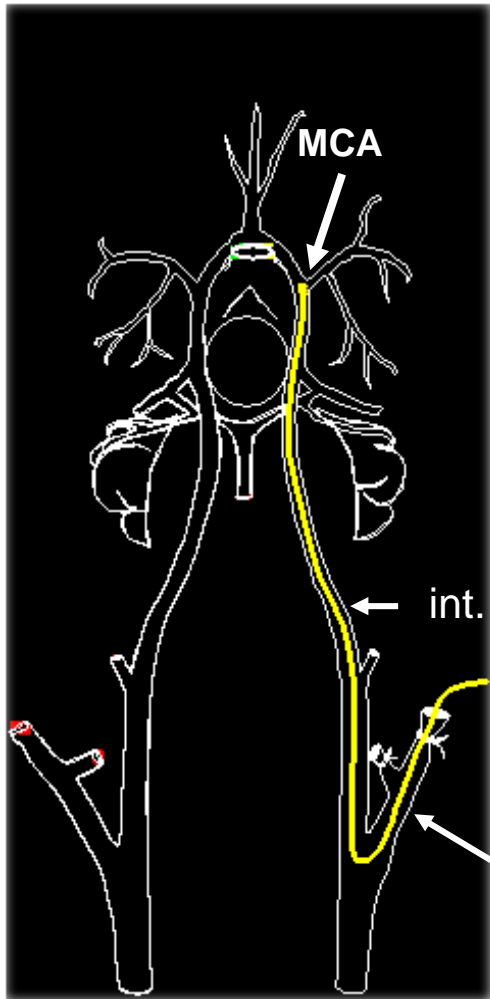
none

- Stroke is the leading cause of physiological disability in the world.
- No available FDA approved drug for stroke patients to enhance functional recovery.
- Synaptic plasticity and remodeling occur weeks after stroke:
 - restorative responses that occurs long after injury would be clinically relevant
- Ratan lab at Burke: FDA approved drug screening (HIF, Arg, P21) – Daidzein
- Daidzein is a major component of soy isoflavones.
 - Structure similarity to estrogen
 - Numerous health benefits
 - anti-inflammatory effect (*Dang and Lowik, 2004; Ricketts et al., 2005*)
 - promote mitochondrial biogenesis (*Rasbach and Schnellmann 2008*)
 - antidiabetic and hypolipidemic effects (*Mezei et al., 2003*)
 - vasodilatory effect (*Cao et al., 2006*).
 - promotes axon growth (*Wang et al., 2008*)
- In an animal model of optic nerve crush, *promote regeneration of axon* (*Ma et al., 2010*)

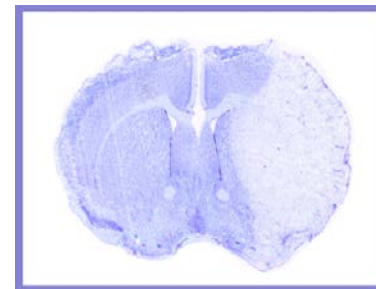
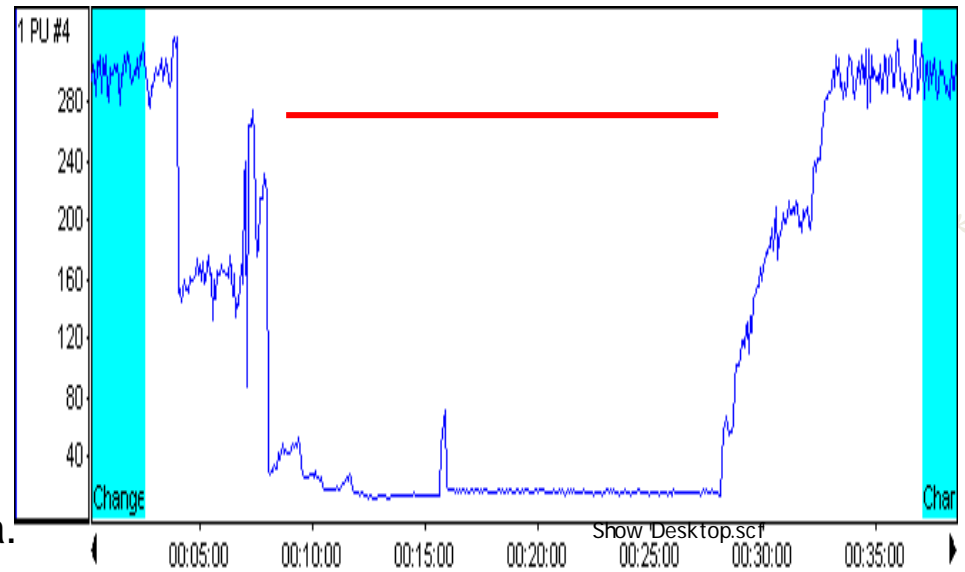


Effects of daidzein in acute neuroprotection and functional recovery

Middle Cerebral Artery Occlusion (MCAO) in mice



CBF measurement
by laser Doppler flowmetry



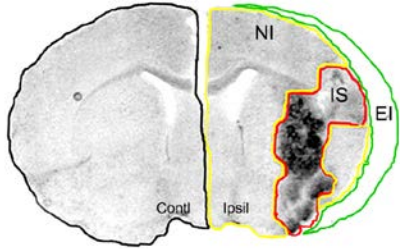
3 days after MCAO

Daidzein does not reduce stroke-induced brain injury

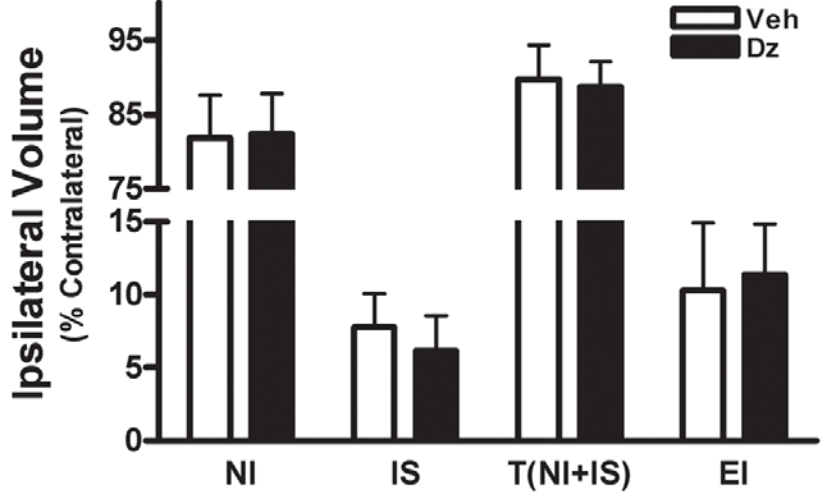
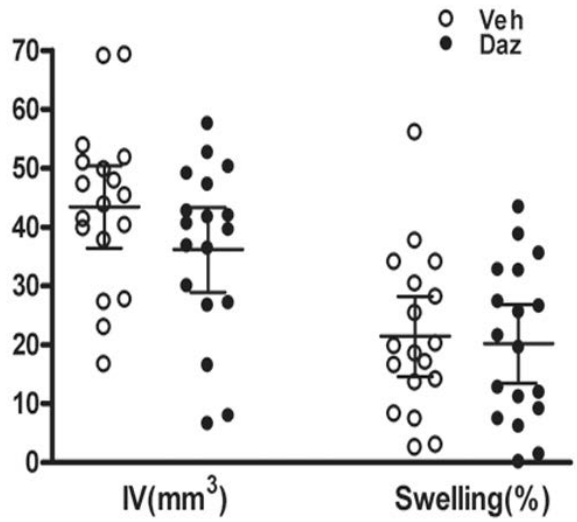
3 days after MCAO



1 month after MCAO

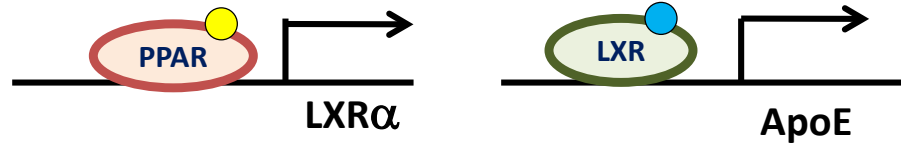


NI: non-injured tissue
 IS: injured scar tissue
 EI: estimate infarct volume



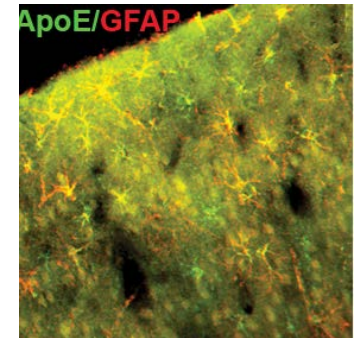
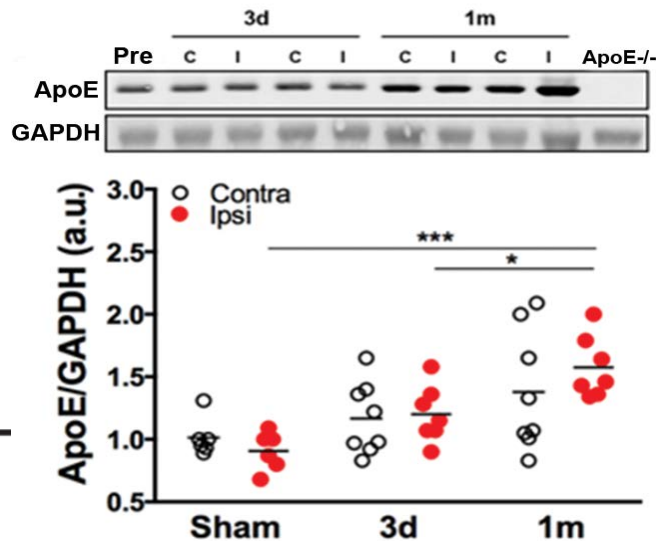
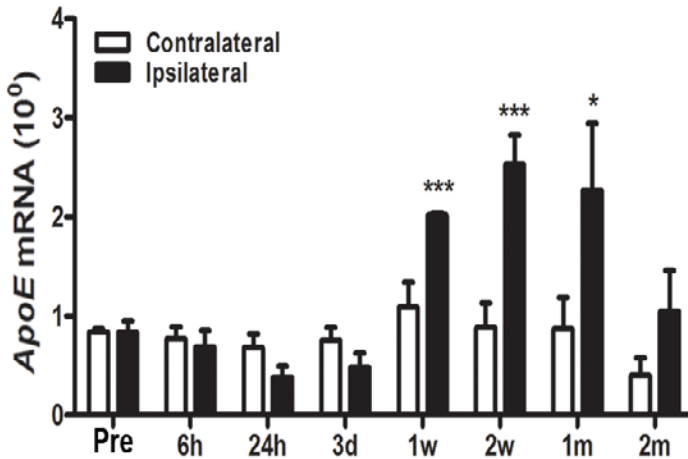
ApoE expression increases in the post-ischemic brain

- Daidzein is a known PPAR agonist
LXR and ApoE transcription

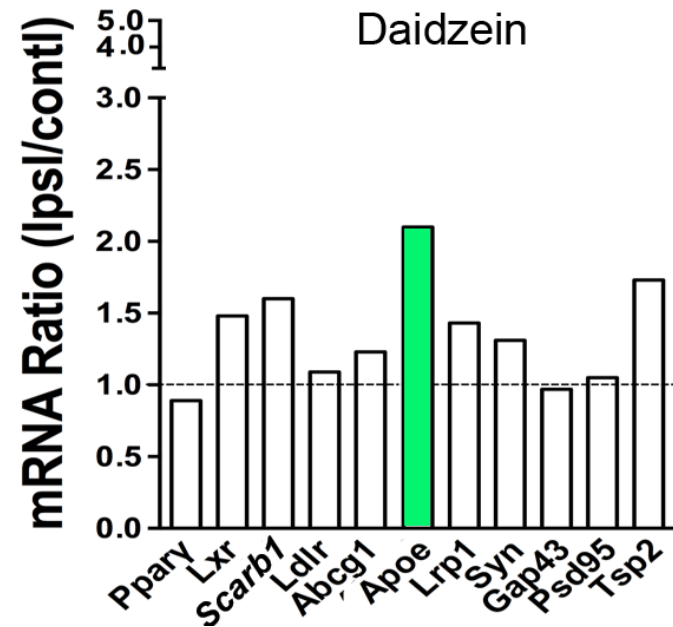
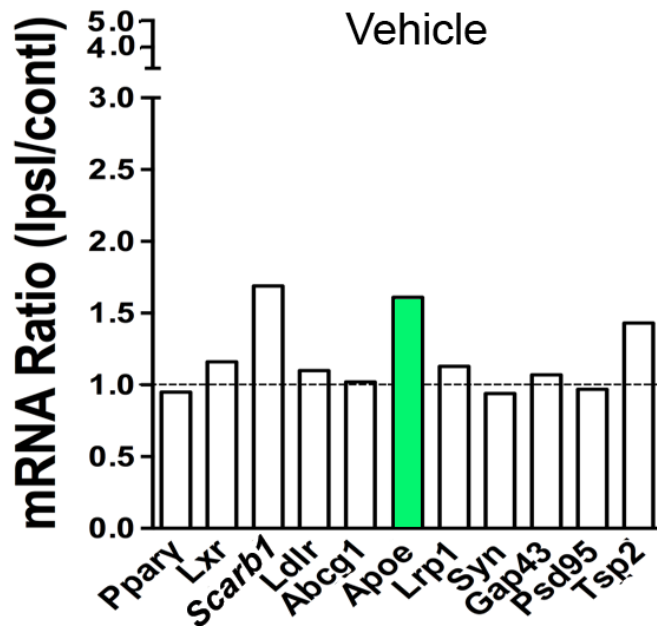


- ApoE
 - Cholesterol is a critical substrate for synaptic plasticity
 - ApoE is the most abundant cholesterol transporter in the brain
 - It controls cellular cholesterol efflux

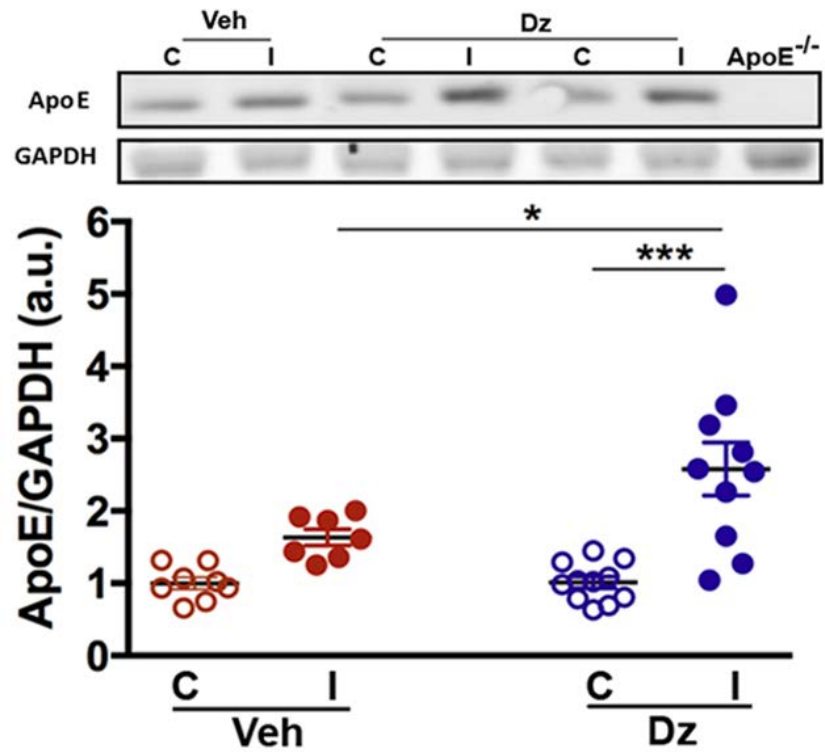
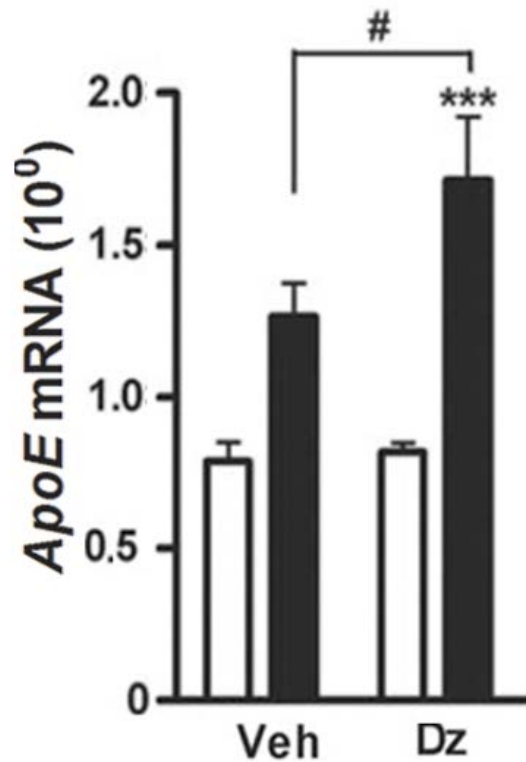
ApoE expression in ischemic brain



Effect of daidzein on stroke-induced gene expression at 1M

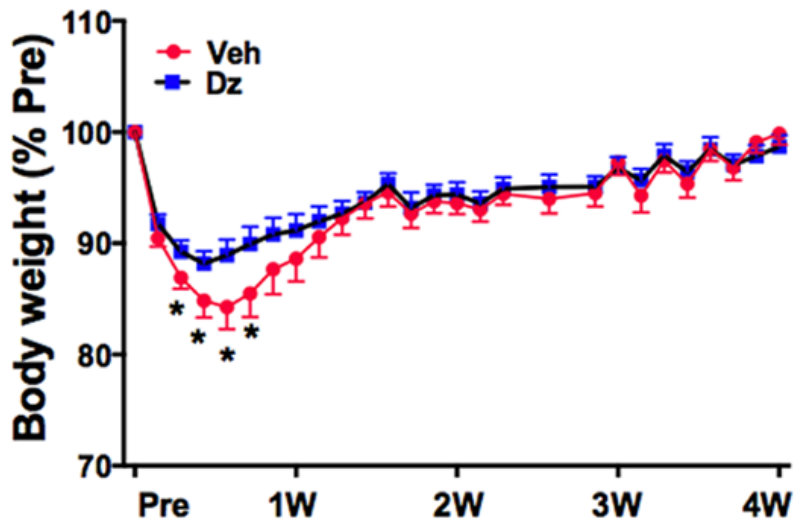


Daidzein increased ApoE expression in 1M post-stroke brain

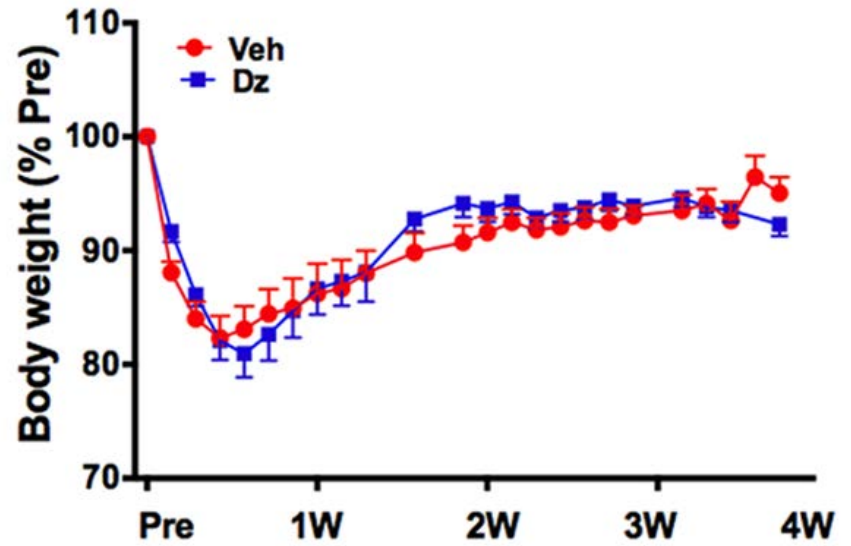


Daidzein's effect on post-stroke BW loss

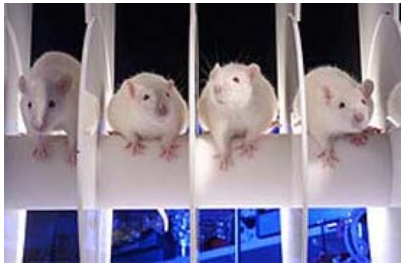
C57



ApoE KO

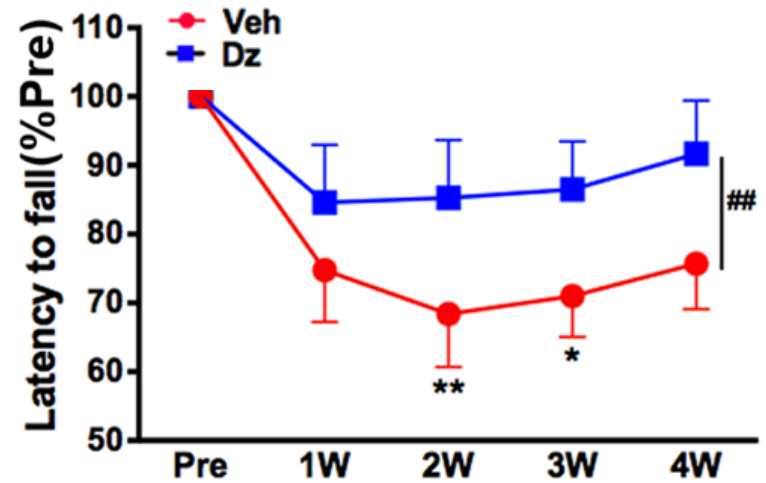


Daidzein's effect on motor function

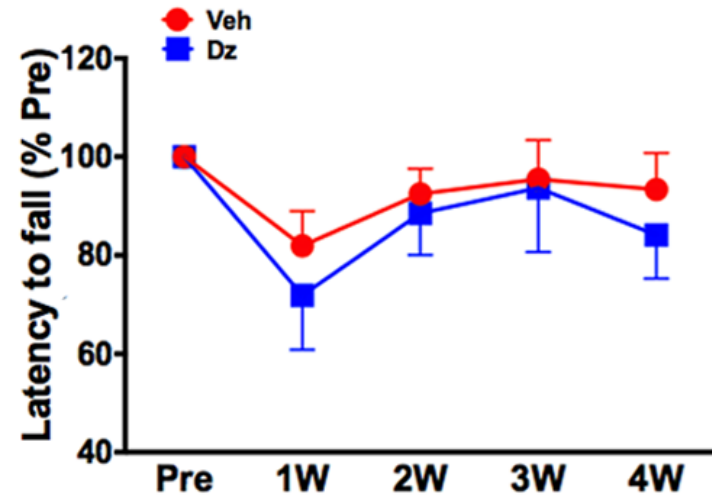


Rotarod Test

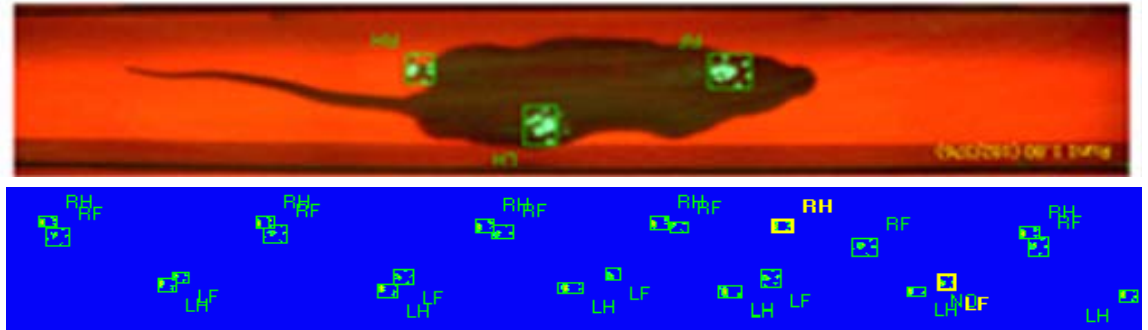
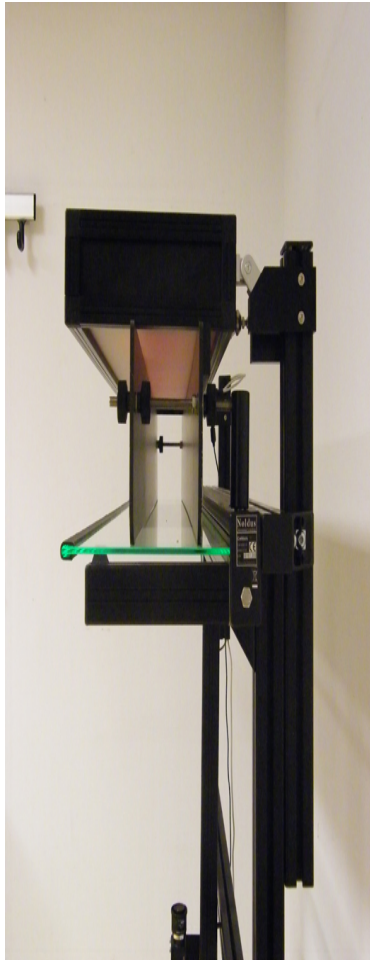
C57



ApoE KO



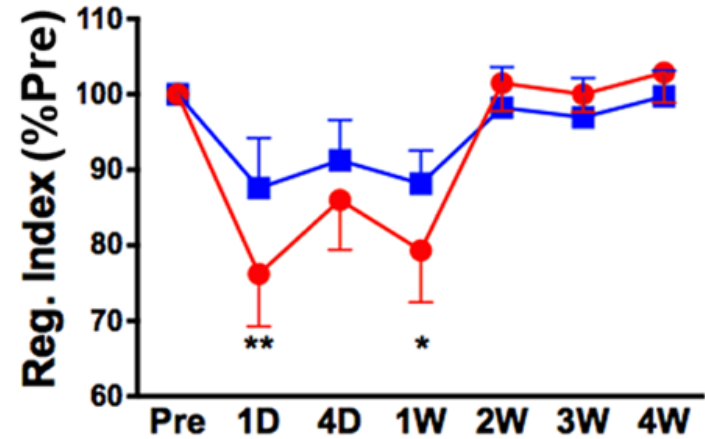
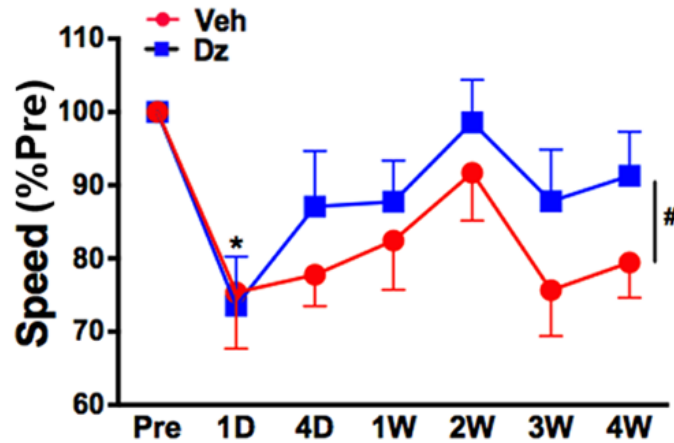
Catwalk Gait Analysis



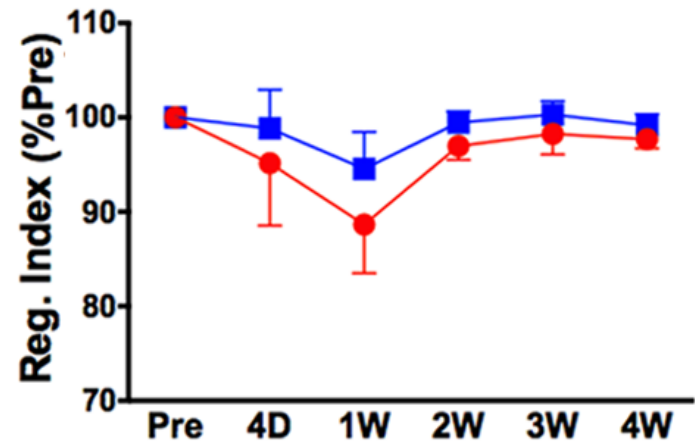
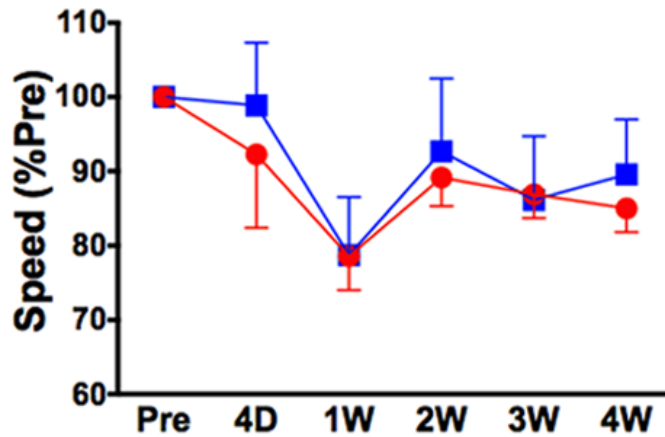
1. Overall gait
 - Walk Speed
 - Regularity index
2. Spatial parameters based on individual paw
 - Stride lengths
 - Swing Speed
 - Max contact area
 - Mean intensity

Daidzein's effect on overall gaits

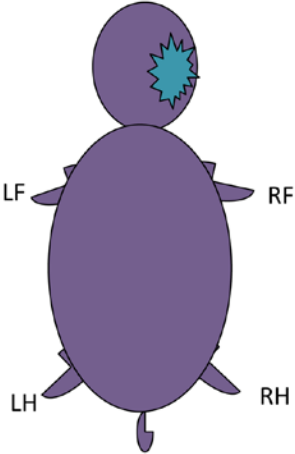
C57



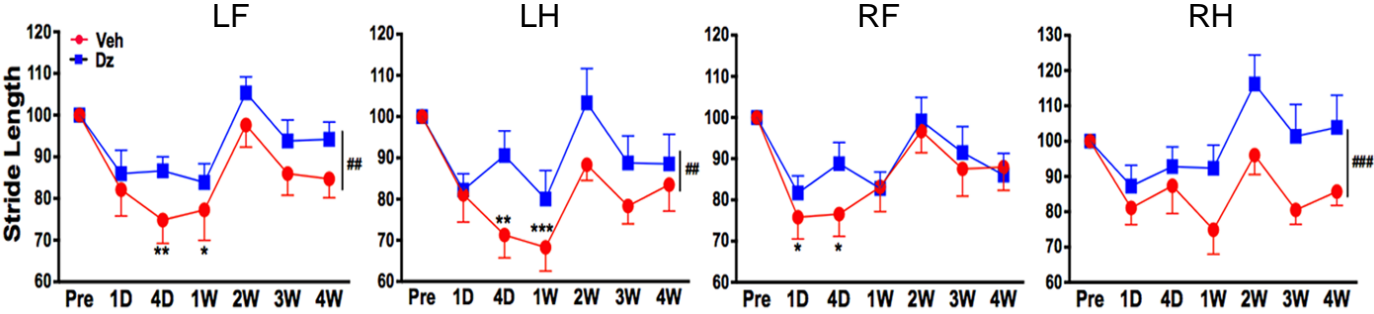
ApoE KO



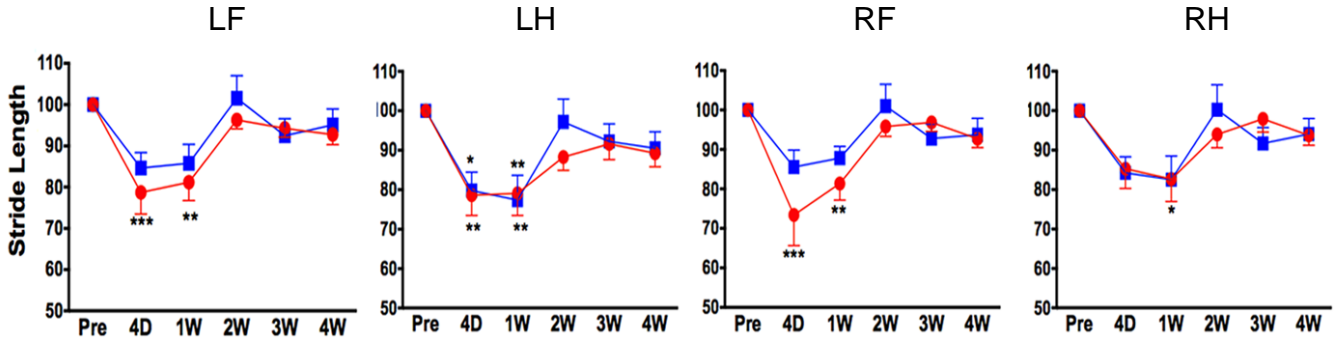
Daidzein's effect on stride length in each limb



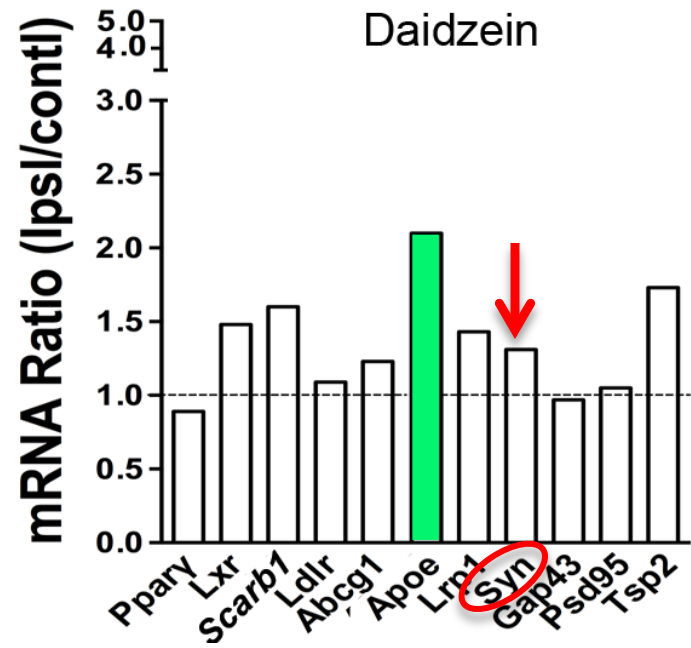
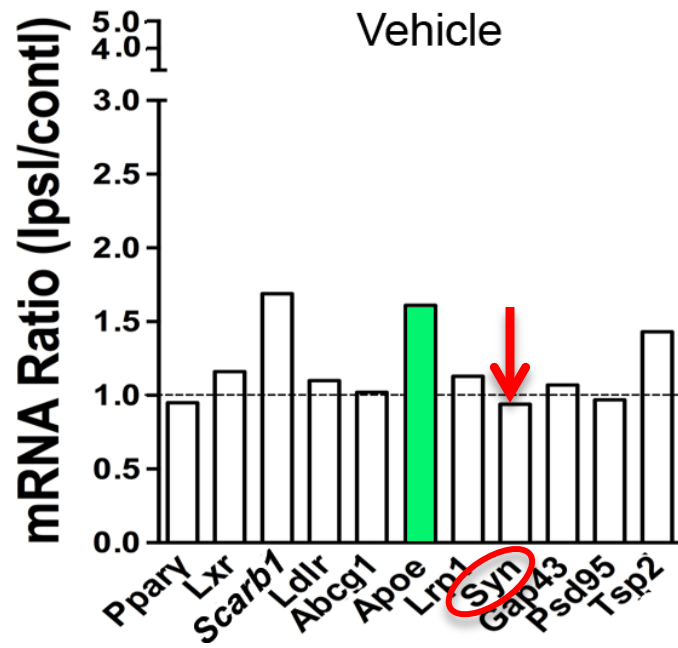
C57



ApoE KO

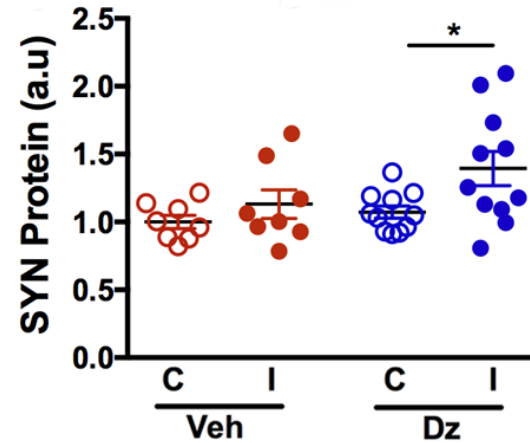
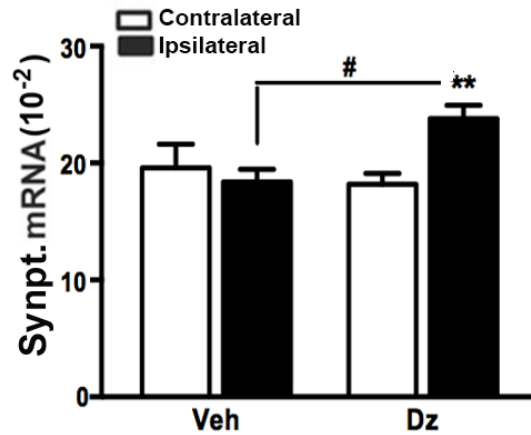


Daidzein increase synaptophysin expression at 1M

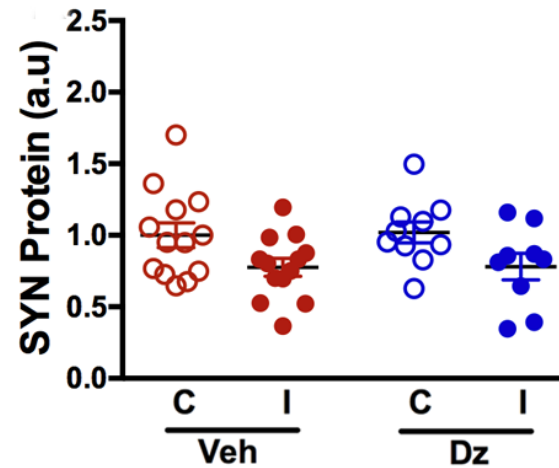
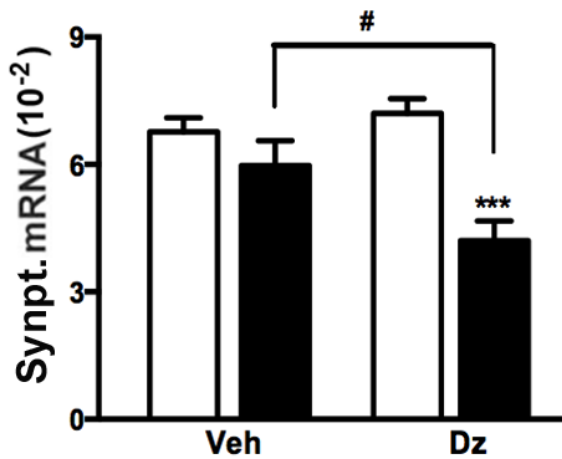


Daidzein increased synaptophysin expression in C57 mice

C57



ApoE KO



Daidzein treatment following stroke in C57 mice

- no effect on reducing infarct size
- Increased ApoE expression at 1 m post-ischemia
 - predominantly in astrocytes
- attenuated stroke-induced body weight loss during acute period (3-5 days post)
- promoted motor/gait function during recovery phase
- increased synaptophysin expression

However, Daidzein treatment in ApoE KO mice reverse functional benefits and synaptophysin expression

- ✓ *the study suggest the importance of daidzein-induced ApoE up-regulation in fostering stroke recovery.*
- ✓ *daidzein-induced functional benefits in the absence of neuroprotection suggest the presence of non-overlapping mechanisms underlying recovery processes versus acute pathology.*
- ✓ *With its known safety in humans, early and chronic use of daidzein aimed at augmenting ApoE may serve as a novel, translatable strategy to stroke recovery functional recovery in stroke patients without adverse acute effect.*

Special thanks.....

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