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

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Disclosure

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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 occur 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

I 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 for 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 the ischemic brain

Graph showing ApoE mRNA expression levels over time in contralateral and ipsilateral conditions. The graph includes statistical significance markers.
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

Body weight (% Pre)

Pre 1W 2W 3W 4W

Veh Dz

* *
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

Stride Length

Pre 1D 4D 1W 2W 3W 4W

Pre 1D 4D 1W 2W 3W 4W

Pre 1D 4D 1W 2W 3W 4W

Pre 1D 4D 1W 2W 3W 4W

Pre 1D 4D 1W 2W 3W 4W
Daidzein increases 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.

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