II Seminario de Investigación Francisco Guillén

Hypoglycolytic neurons control memory and organismal fitness

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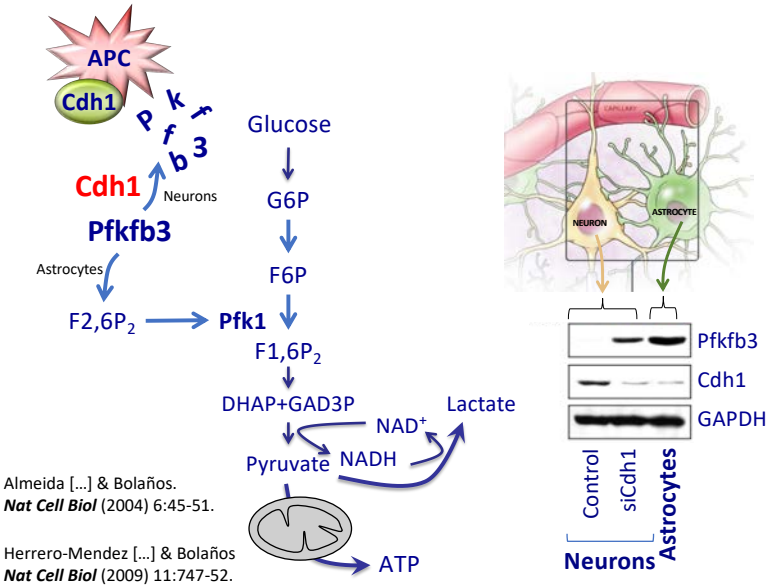
Webinar,
29st June 2022

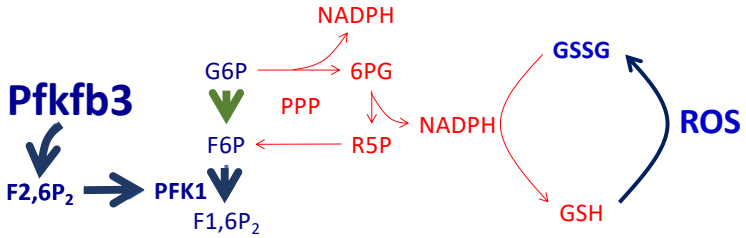
Glycolysis and Pfk1 *activity* in astrocytes are higher than in neurons
Because Pfkfb3 is continuously degraded in neurons



Almeida [...] & Bolaños.
Nat Cell Biol (2004) 6:45-51.

Herrero-Mendez [...] & Bolaños
Nat Cell Biol (2009) 11:747-52.

Pfkfb3 stabilization in neurons is associated with neurodamaging processes
Is Pfkfb3 a neuroprotective therapeutic target?



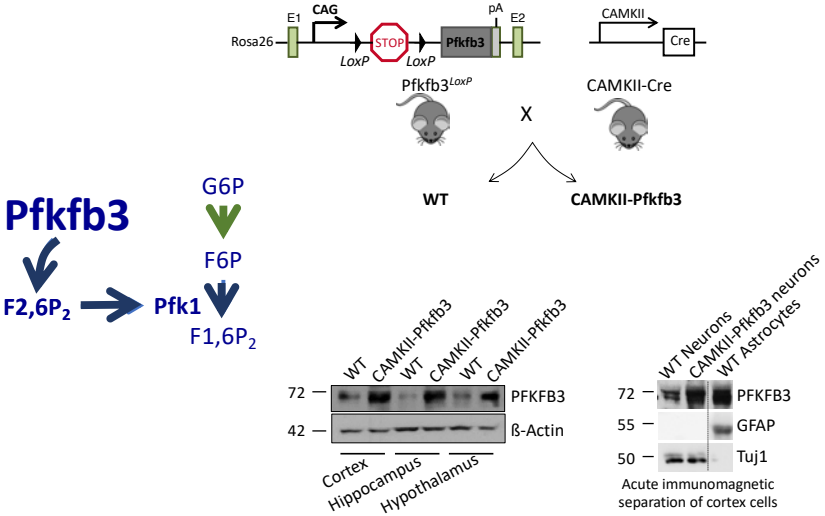
Redox stress

Herrero-Mendez [...] & Bolaños
Nat Cell Biol (2009) 11:747-52.

Rodriguez-Rodriguez P [...] & Bolaños JP
Cell Death Differ. (2012) 19:1582-9

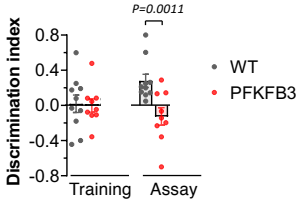
PPP = Pentose-Phosphate Pathway

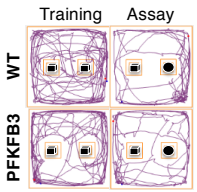
Neuron-specific Pfkfb3-overexpressing transgenic mice

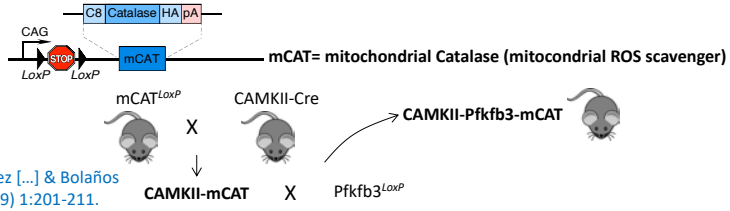


Cognitive Impairment in *Pfkfb3* knock-in mice
Short-term memory phenotype. **Rescue** with **mCAT**

Novel Object Recognition Test



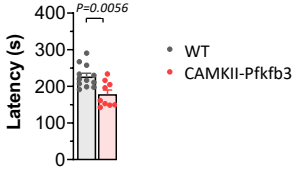


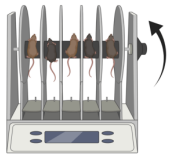


Vicente-Gutierrez [...] & Bolaños
Nat Metab (2019) 1:201-211.

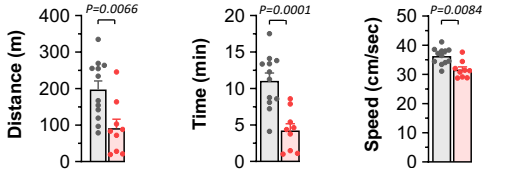
Low **motor activity, poor endurance and Slowness**
in *Pfkfb3* knock-in mice. **Rescue** with **mCAT**

Rotarod Test
(Physical activity level)

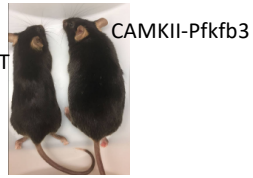


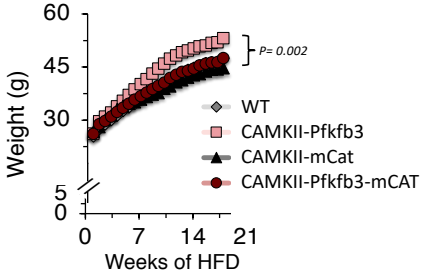


Treadmill Test
(Endurance and Velocity)

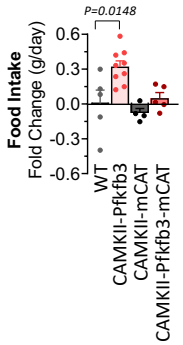


Food Intake and **Glucose tolerance** in
Neuron-specific Pfkfb3-overexpressing transgenic mice

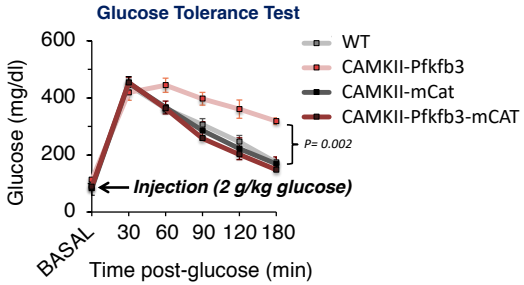




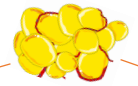
Food intake



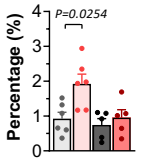
Glucose Tolerance Test

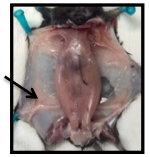


Higher adiposity in neuron-specific
Pfkfb3 knock-in mice

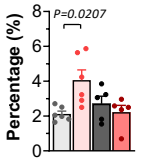


Subcutaneous Fat

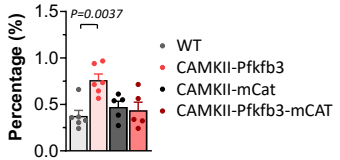


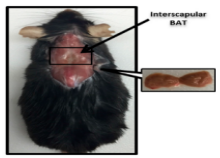


White Adipose Tissue

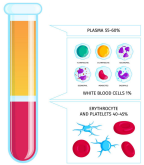


Brown Adipose Tissue

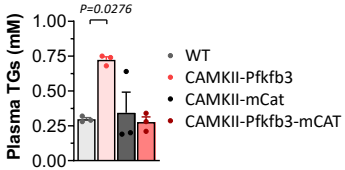


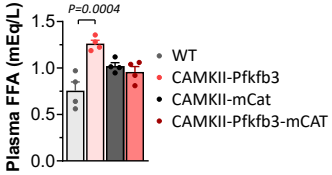


Blood markers in neuron-specific *Pfkfb3* knock-in mice. **Metabolic Syndrome (MS)**

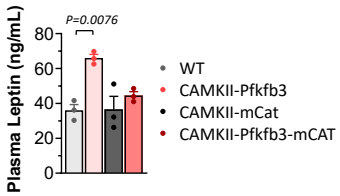


Dyslipidemia

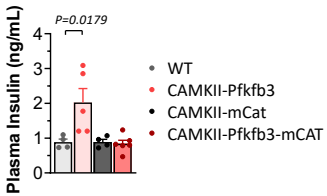




Hyperleptinemia

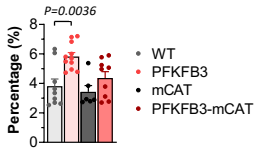


Hyperinsulinemia



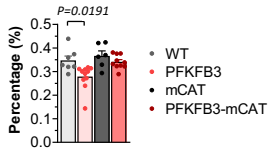
Hepatomegaly and **Sarcopenia** in neuron-specific *Pfkfb3* knock-in mice. **Metabolic Syndrome (MS)**

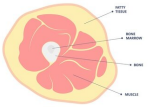
Liver



Enlarged liver

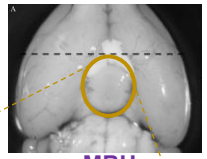
Gastrocnemius



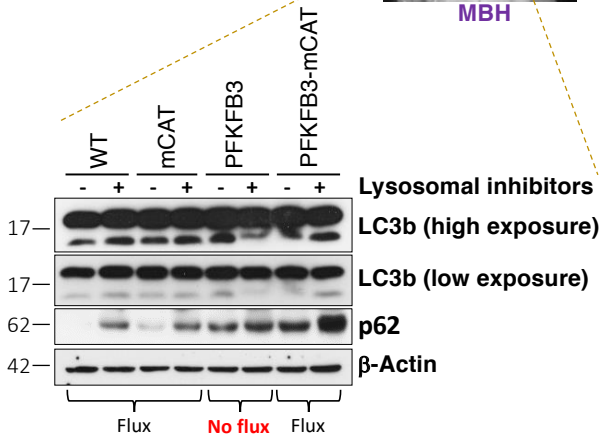


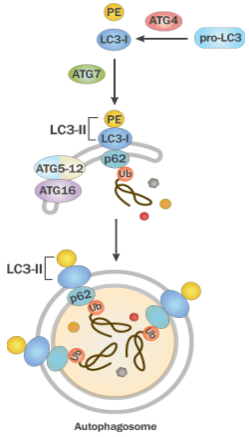
Sarcopenia→ Loss muscle mass and weakness

Impaired autophagy in MBH from neuron-specific *Pfkfb3* knock-in mice

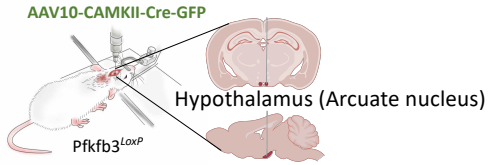


MBH

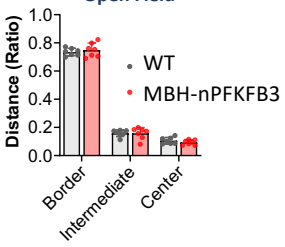


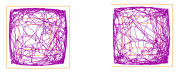


MBH-neuron-specific Pfkfb3-overexpressing transgenic mice



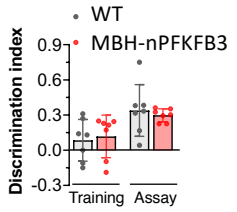
Open Field

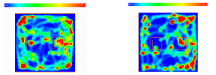




WT MBH-nPFKFB3

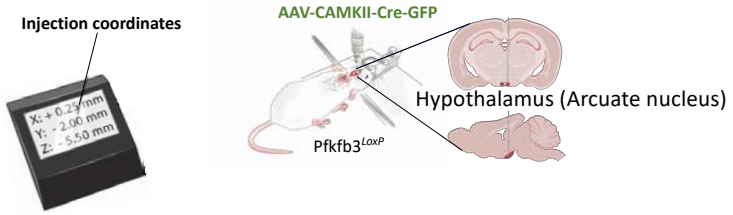
Novel Object Recognition Test



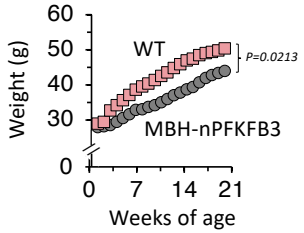


WT MBH-nPFKFB3

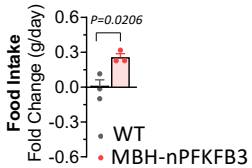
MBH-neuron-specific Pfkfb3-overexpressing transgenic mice



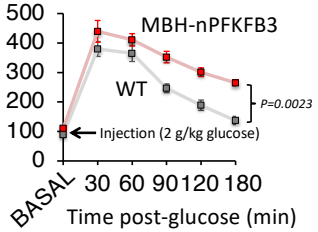
Weight



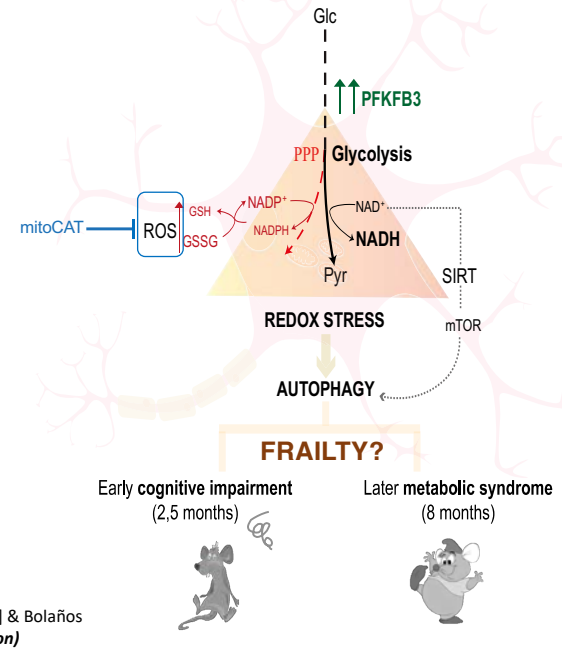
Food intake



Glucose Tolerance Test



Complete History



Jimenez-Blasco [...] & Bolaños
(in preparation)

Created by Paula Alonso

Conclusions

1. **Glycolysis** is tightly controlled in **neurons** due to continuous proteosomal **PFKFB3 protein degradation**. However, neuronal OXPHOS efficiency is high.

2. Increased **neuronal PFKFB3** causes **aberrant glycolytic activation**, increased **redox stress** and reduced **autophagy**, determining **cognitive impairment** and **metabolic syndrome**.

3. These data strongly suggest that the occurrence of a **low glycolytic activity** in **neurons** is a **natural mechanism** aimed to sustain **organismal welfare.**