Mitochondria, Diets and Aging

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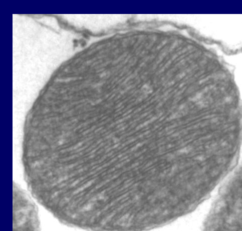
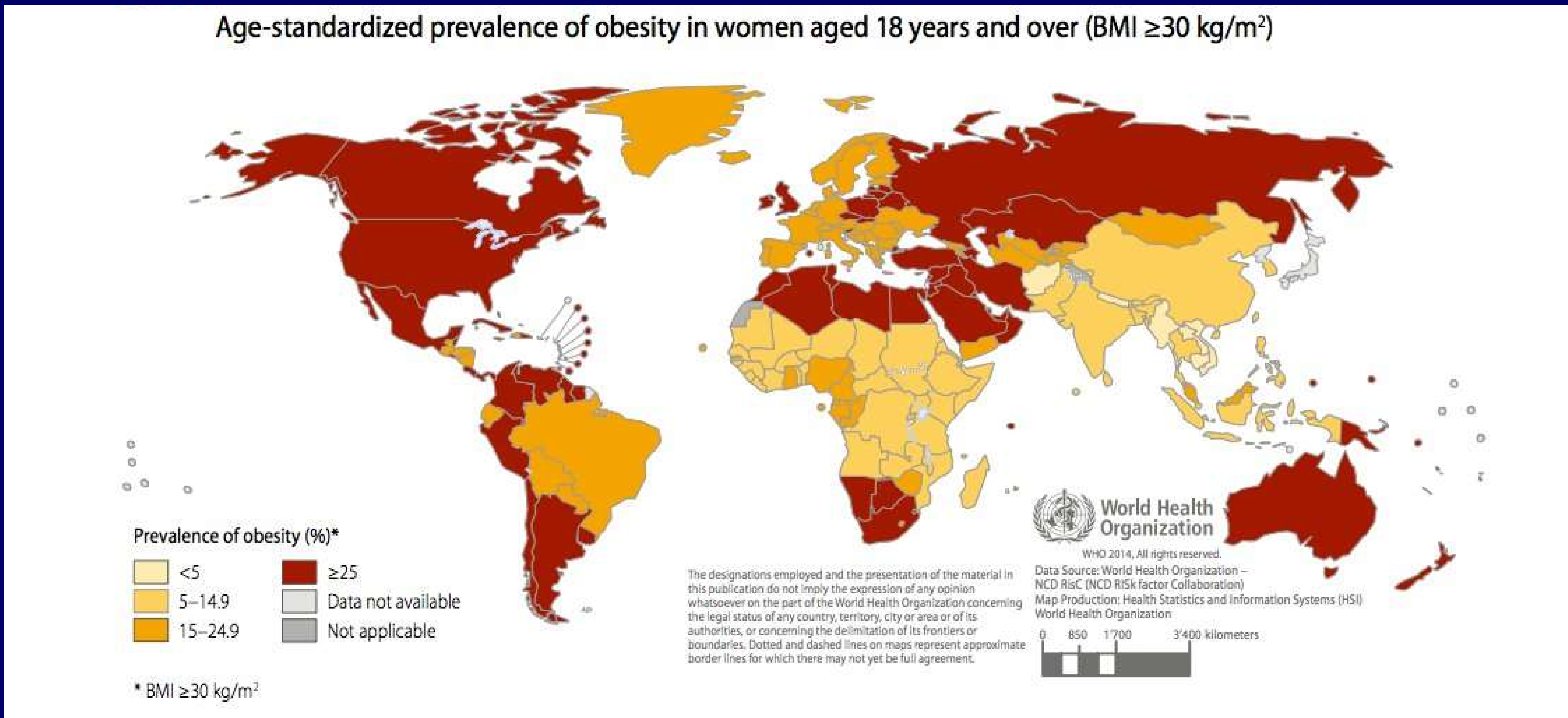


Obesity x Healthspan



World Health Organization, 2014

Laboratory Animals are Sedentary and Obese

Martin, B., Ji, S., Maudsley, S. and Mattson, MP (2010) “Control” laboratory rodents are metabolically morbid: Why it matters. Proc Natl Acad Sci U S A. 107: 6127–6133.

Table 1. Comparisons of physiological and metabolic factors in rats maintained under standard housing conditions (overfed and sedentary) and more natural conditions (reduced energy intake or running wheel exercise)

	Housing conditions		
Factor	Standard	Diet restriction	Exercise
Body weight	600–700 g	350–500 g	500–600 g
Total body fat	25–40%	5–20%	10–20%
Mean blood pressure	110–130 mm Hg	80–90 mm Hg	115–125 mm Hg
Resting heart rate	350–400 bpm	250–300 bpm	280–300 bpm
Plasma glucose	150–160 mg/dL	110–130 mg/dL	125–135 mg/dL
Plasma insulin	125–140 nmol/L	70–80 nmol/L	NA
Plasma leptin	8–12 ng/mL	2–6 ng/mL	NA
Plasma adiponectin	9–11 ng/mL	14–16 ng/mL	NA
Total cholesterol	140–170 mg/dL	70–100 mg/dL	130–140 mg/dL
LDL cholesterol	15–25 mg/dL	10–15 mg/dL	NA
TNFα*	6–7 pg/mL	3–4 pg/mL	NA
IL-6*	6.5–7.5 pg/mL	4.5–5.5 pg/mL	NA

Unless indicated otherwise, all data were from studies of male Sprague–Dawley rats. The information in this table is based on data in refs. 15, 16, 100, 101, and 102. bpm, beats per minute; NA, data not available.
*Data from male Dahl-SS rats.

Caloric Restriction

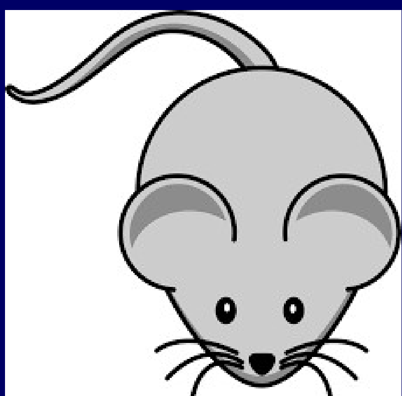
McCay et al. (1935) The effect of retarded growth upon the length of life span and upon the ultimate body size. J Nutr 10: 63-79.

CR = Undernutrition without malnutrition

Does CR change β-cell physiology?

Experimental Model

CR x AL
Rats



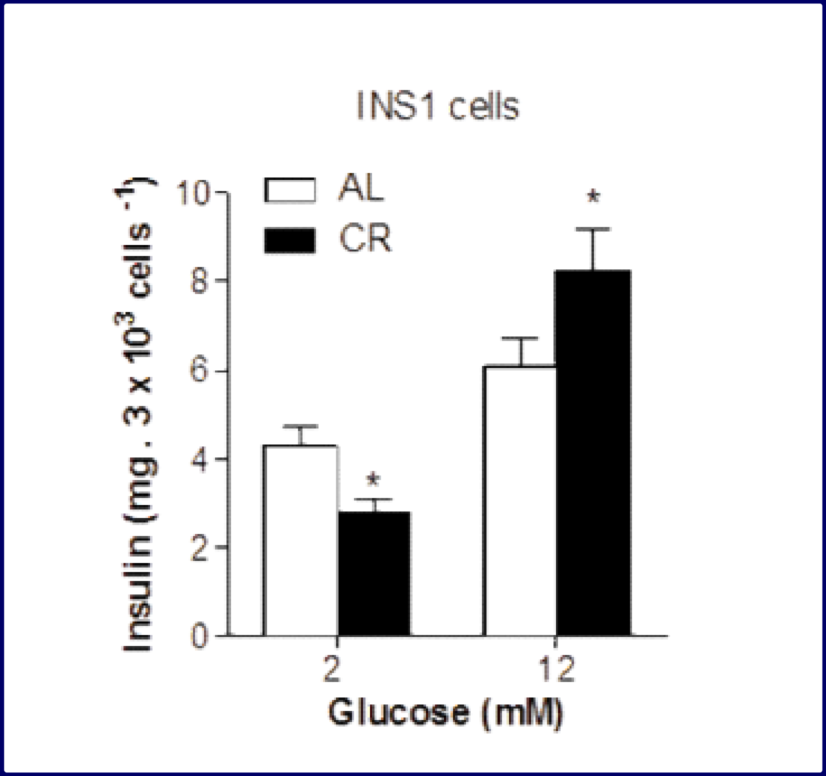
Serum

Cultured
INS1 or Mouse Islets

Insulin
secretion

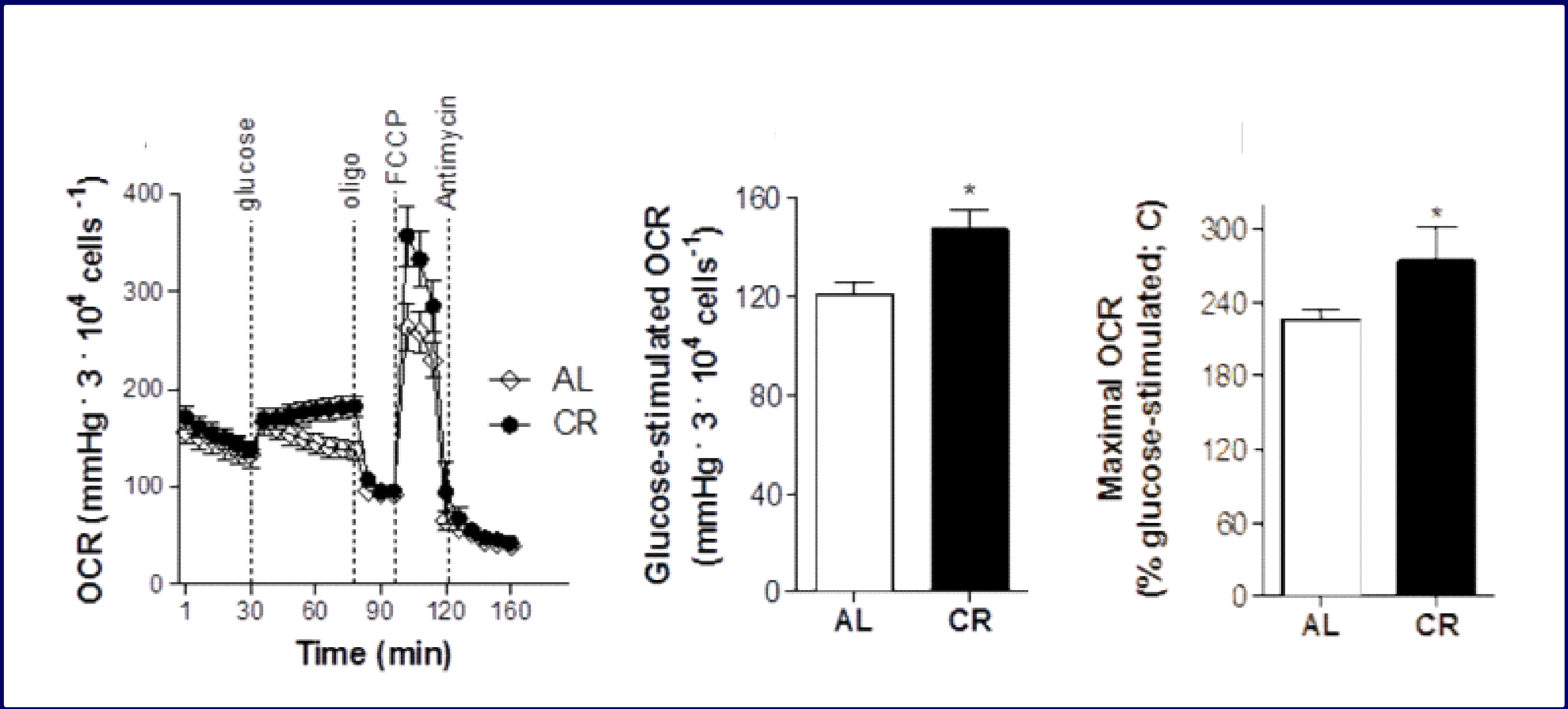
Mitochondrial
physiology

CR Serum Increases Insulin Release



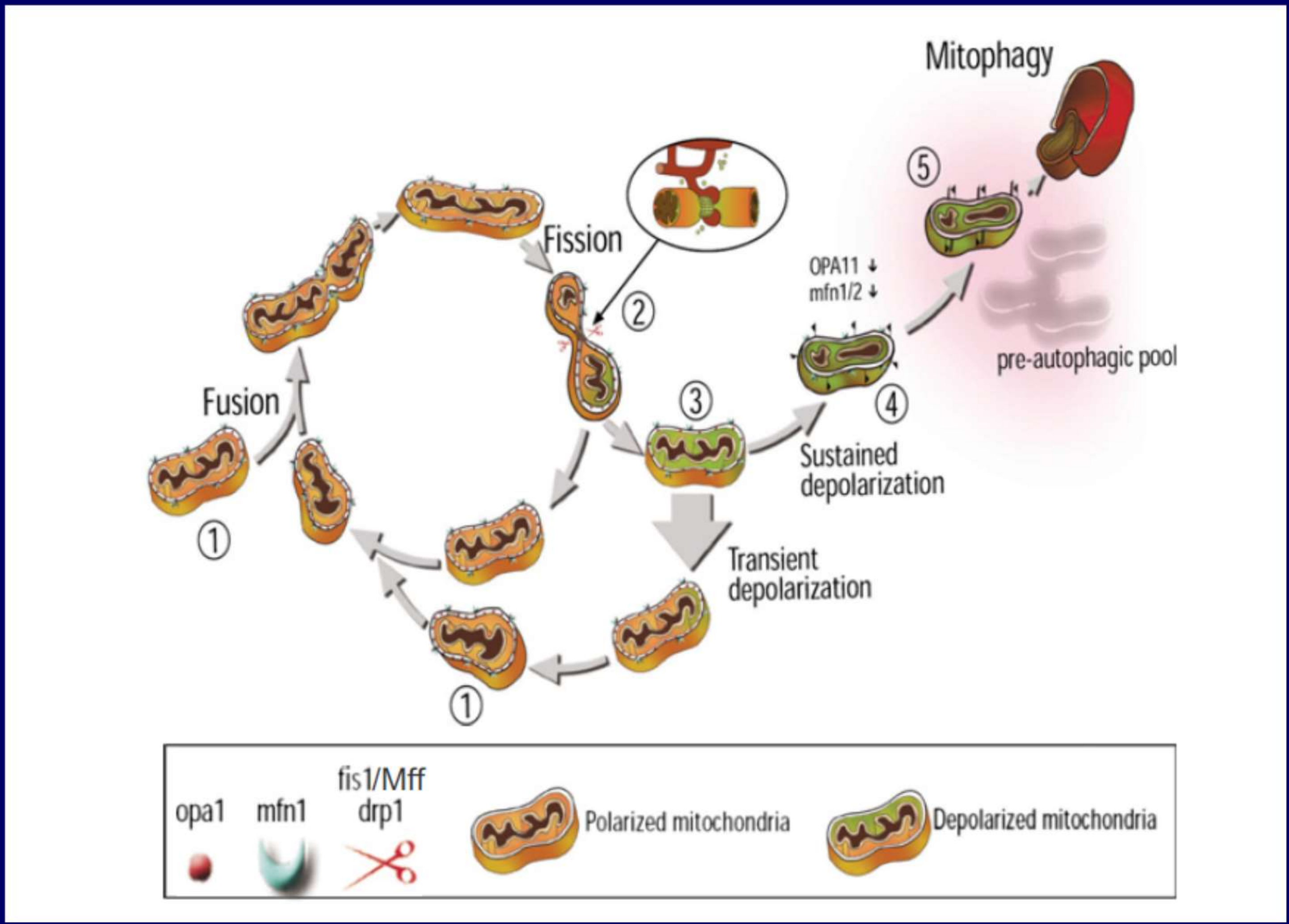
Cerqueira *et al*., FEBS J 283:822-33

CR Serum Increases Mitochondrial Respiration



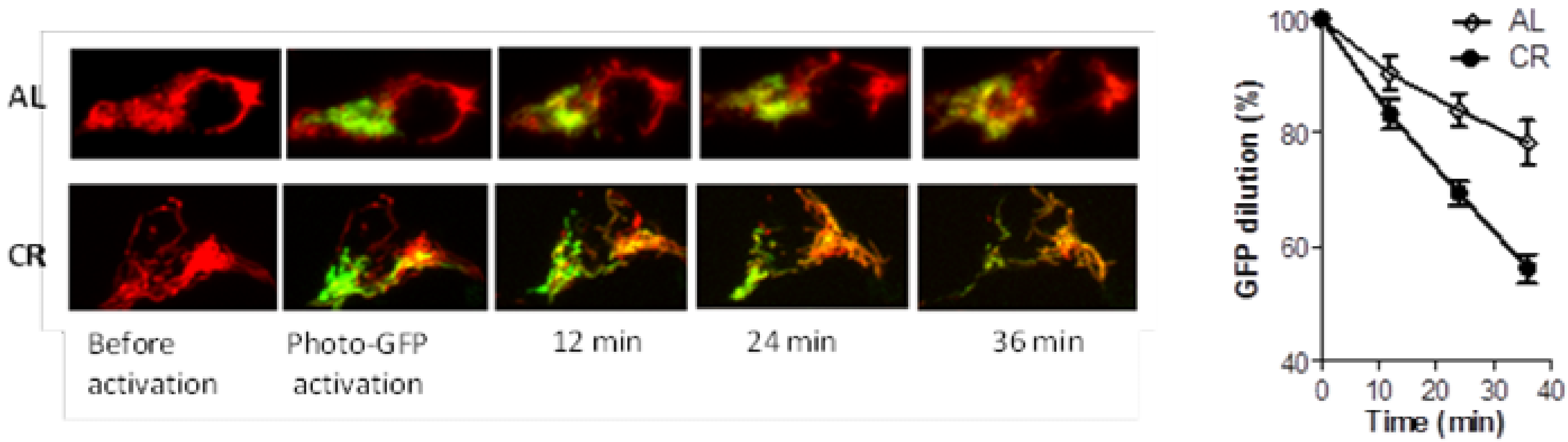
Cerqueira *et al.*, FEBS J 283:822-33

Mitochondria are Dynamic Organelles



Stiles and Shirihai Clinical Endocrinol. Met. 26:725-738

CR Serum Increases Mitochondrial Dynamics



Cerqueira *et al.*, FEBS J 283:822-33

CR Serum + β-Cells

↓

↑ Mitochondrial Fusion — Mfn-2

↓

↑ Mitochondrial Dynamics

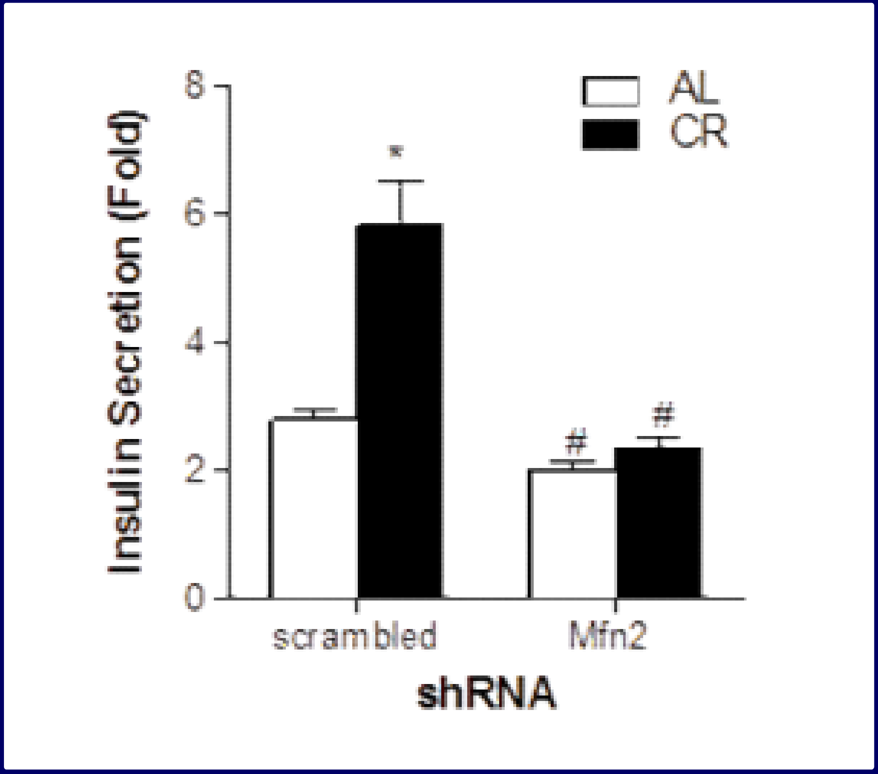
↓

↑ Respiratory Response to Glucose

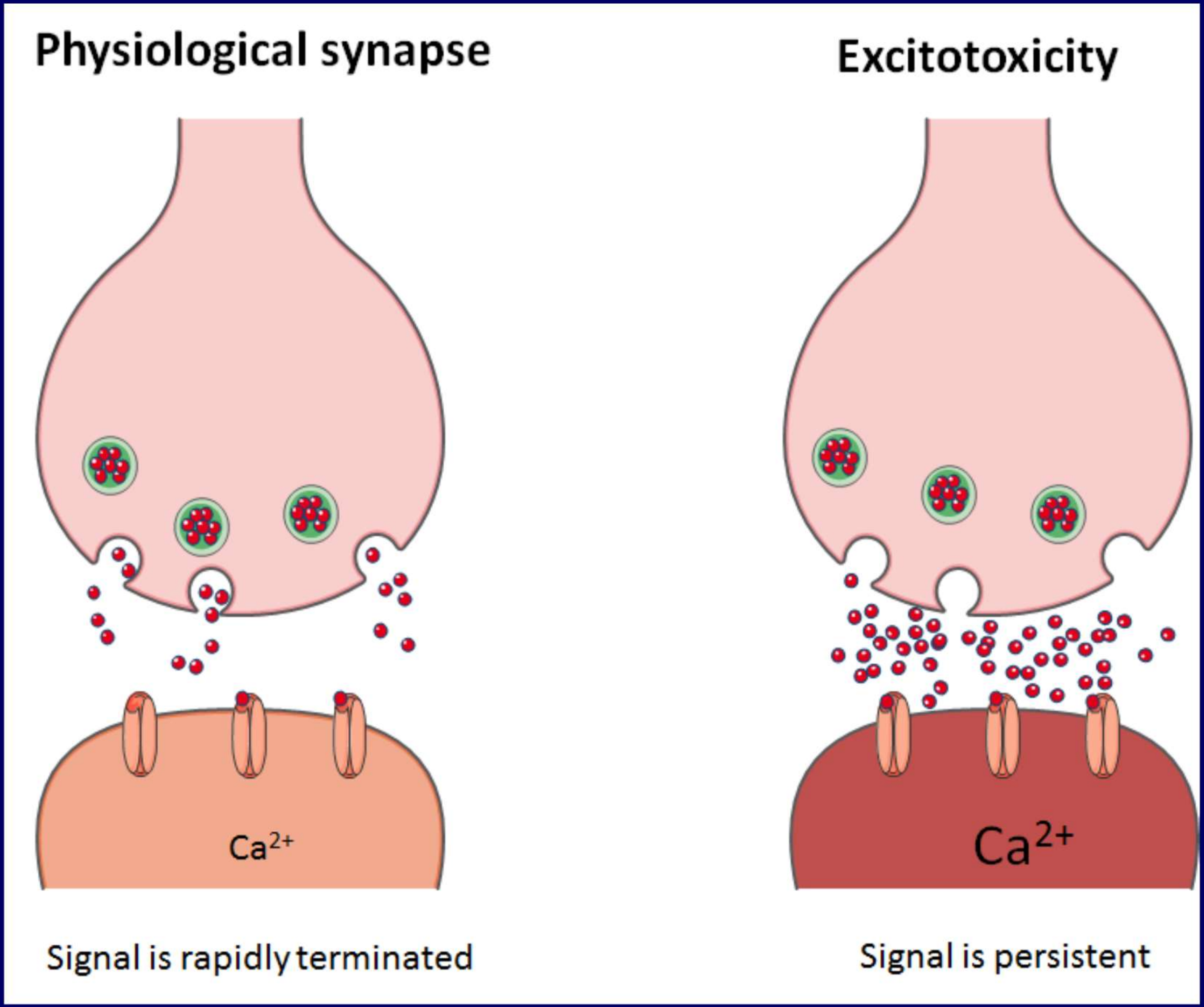
↓

↑ Insulin Release

Mfn-2 shRNA Reverses the Effects of CR Serum

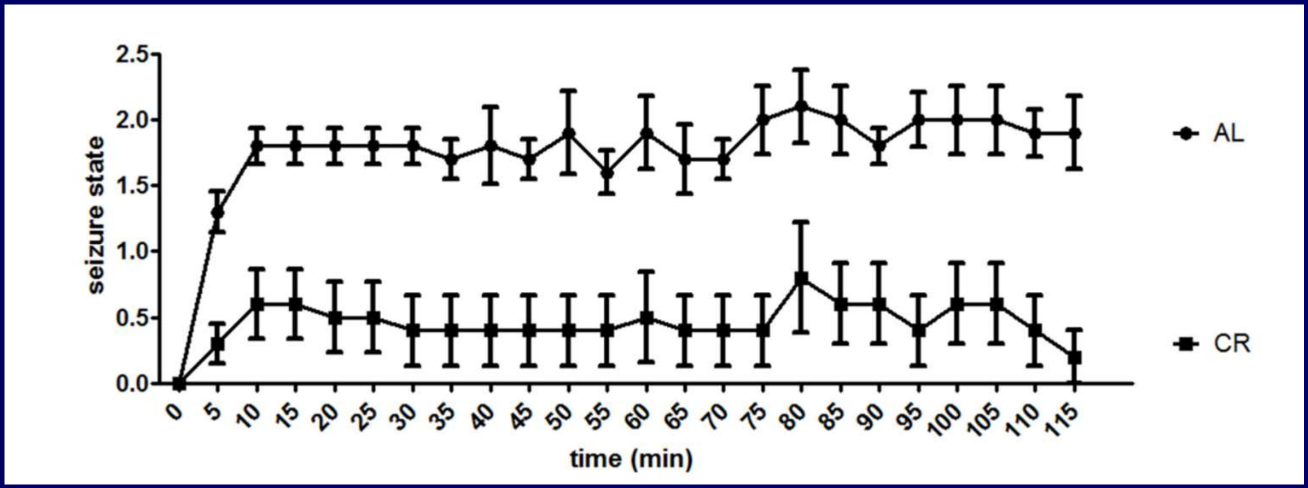


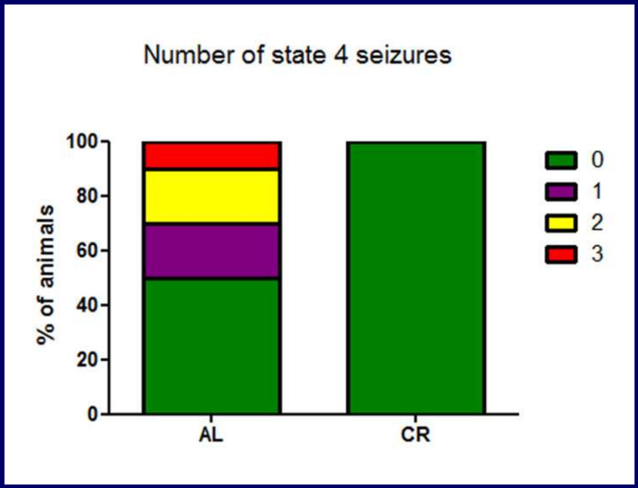
Does CR protect the brain and prevent excitotoxicity?



Physiological synapse
Excitotoxicity
Ca2+
Ca2+
Signal is rapidly terminated
Signal is persistent

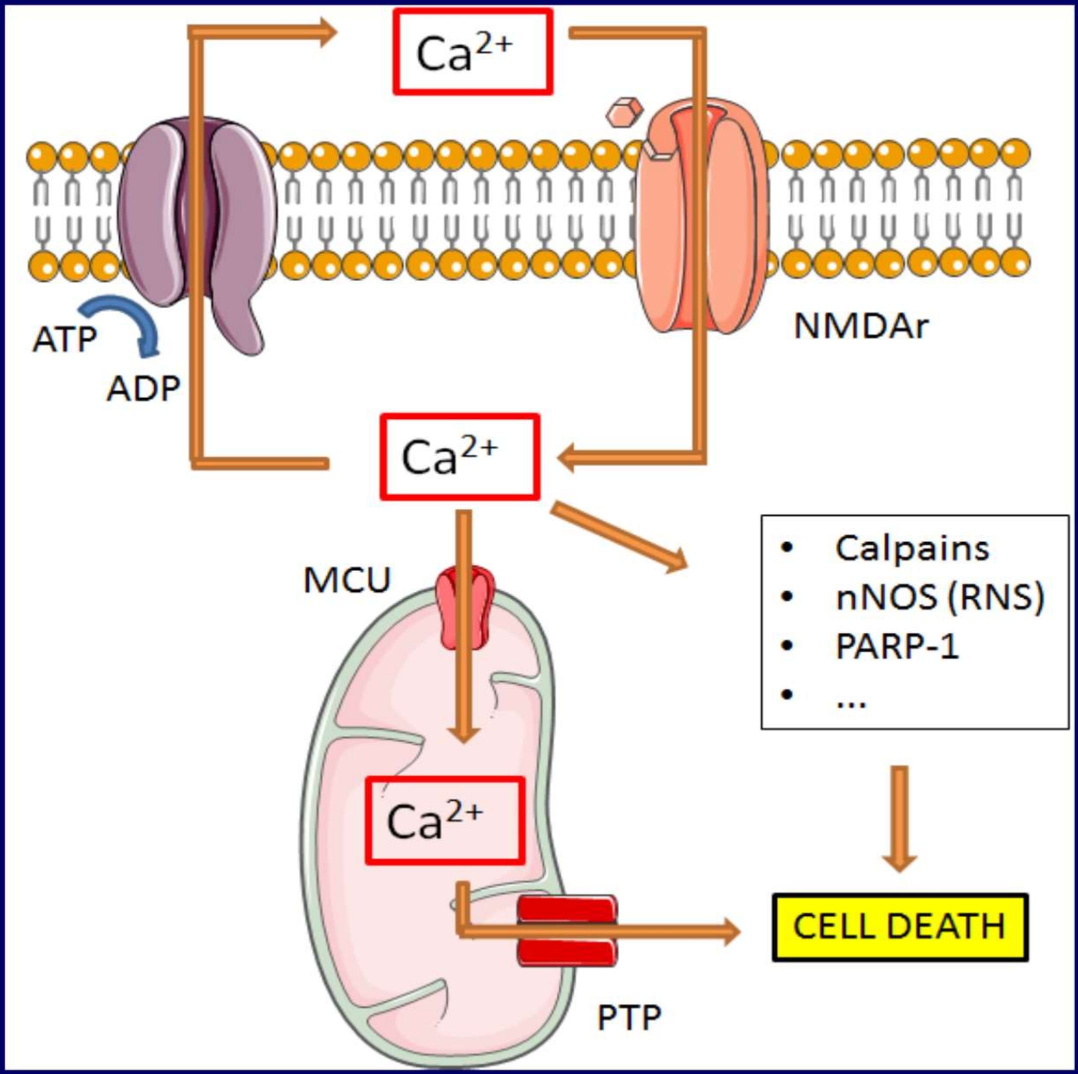
CR Prevents Kainic Acid-Induced Seizures



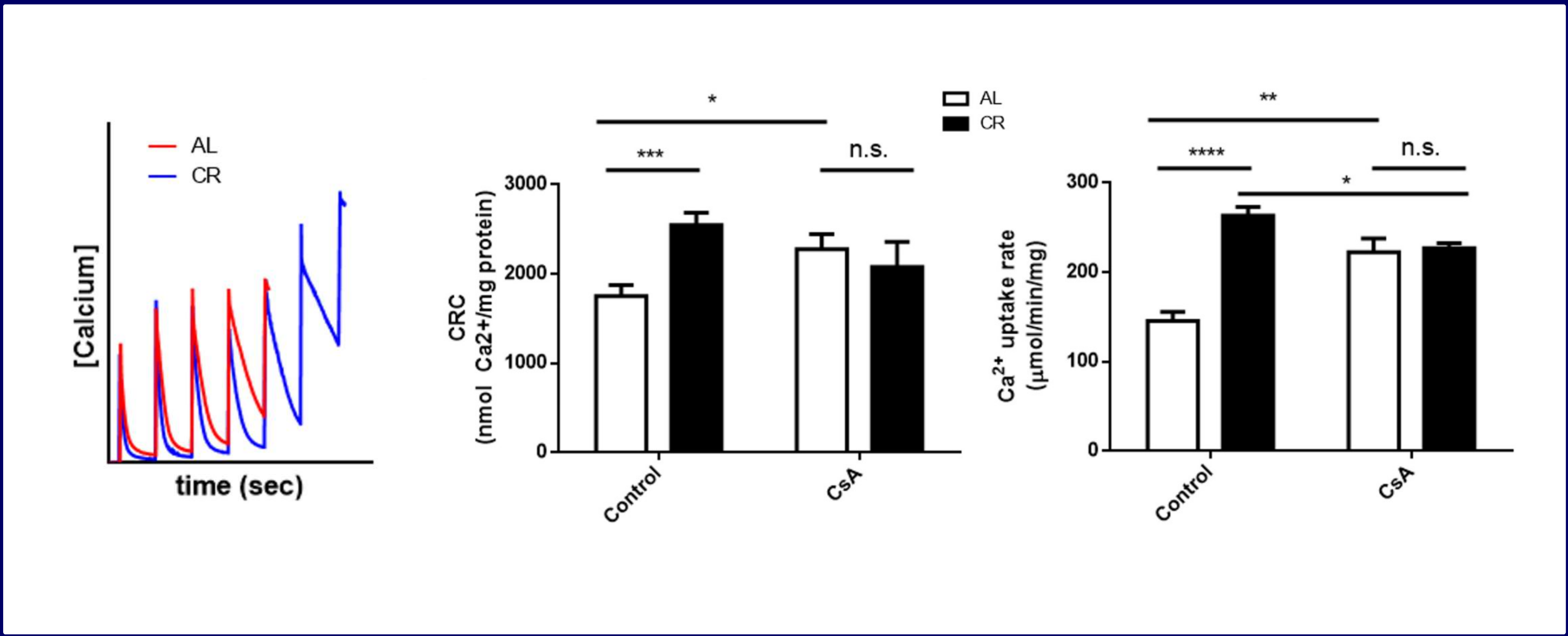


Amigo *et al*., Aging Cell 16:73-81

Mitochondria and Excitotoxicity



CR Increases Mitochondrial Ca^{2+} Uptake



Amigo *et al*., Aging Cell 16:73-81

CR

↓

↑ Sirt3 levels

↓

↓ Acetylation

↓

↓ Cyclophilin D Activity

↓

↓ Mitochondrial Permeability Transition

↓

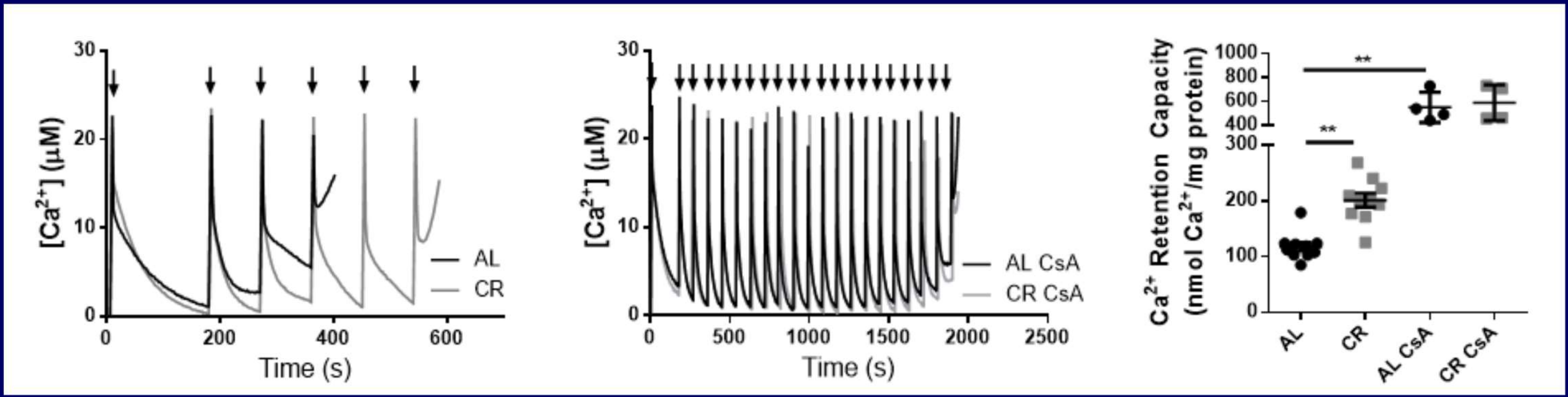
↑ Mitochondrial Ca^{2+} Uptake

↓

↓ Excitotoxicity

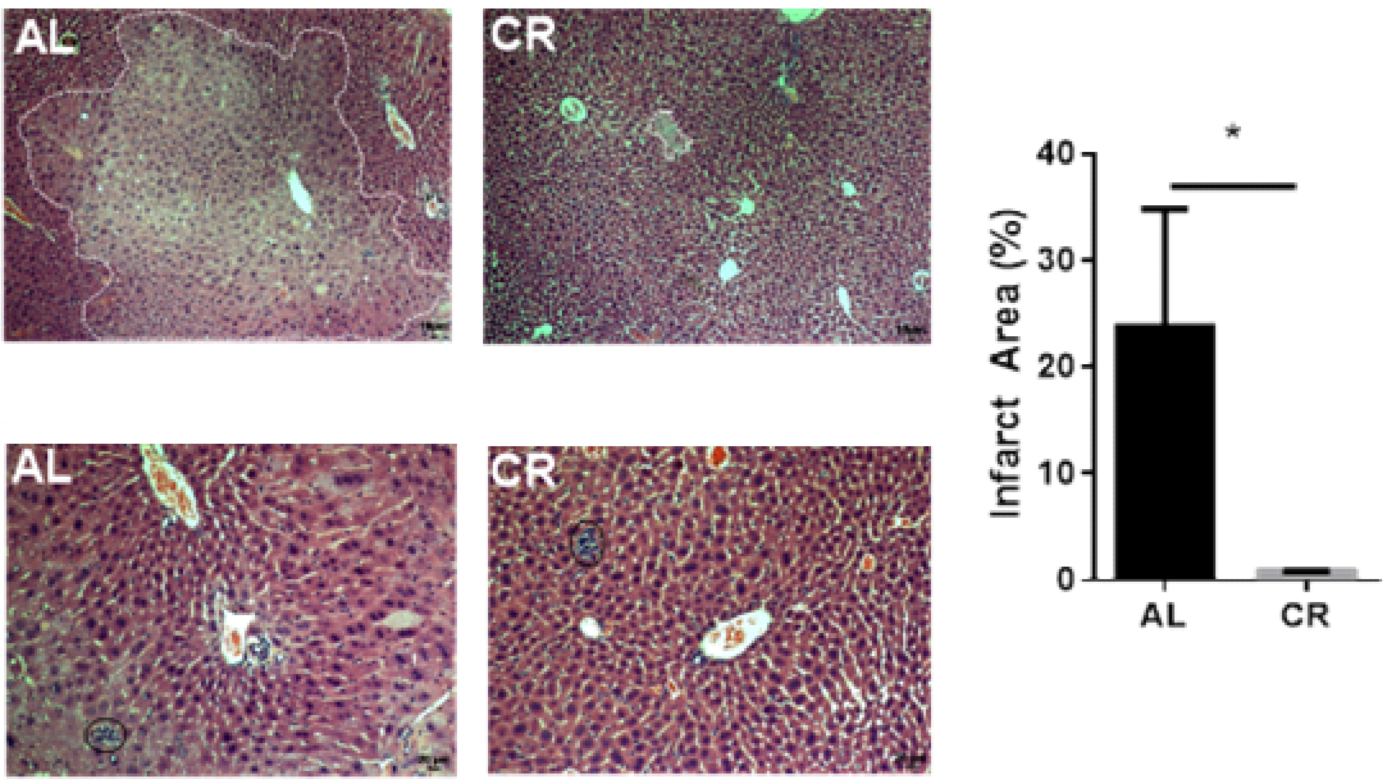
What about the liver?

CR Increases Liver Mitochondrial Ca^{2+} Uptake



Menezes *et al.*, Free Rad Biol & Med 110:219-227

CR Strongly Protects Against Liver Ischemia



Menezes *et al*., Free Rad Biol & Med 110:219-227

Calorie Restriction is Protective: Mitochondrial Mechanisms

β-cells:	Increased mitochondrial fusion and dynamics Maintains adequate insulin secretion
Brian:	Prevents excitotoxic damage Increases mitochondrial Ca^{2+} uptake
Liver:	Increases mitochondrial Ca^{2+} uptake Prevents ischemic damage

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