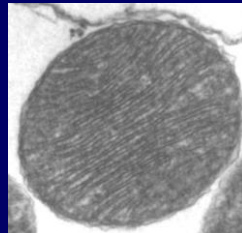


Diet, Energy Metabolism and Aging

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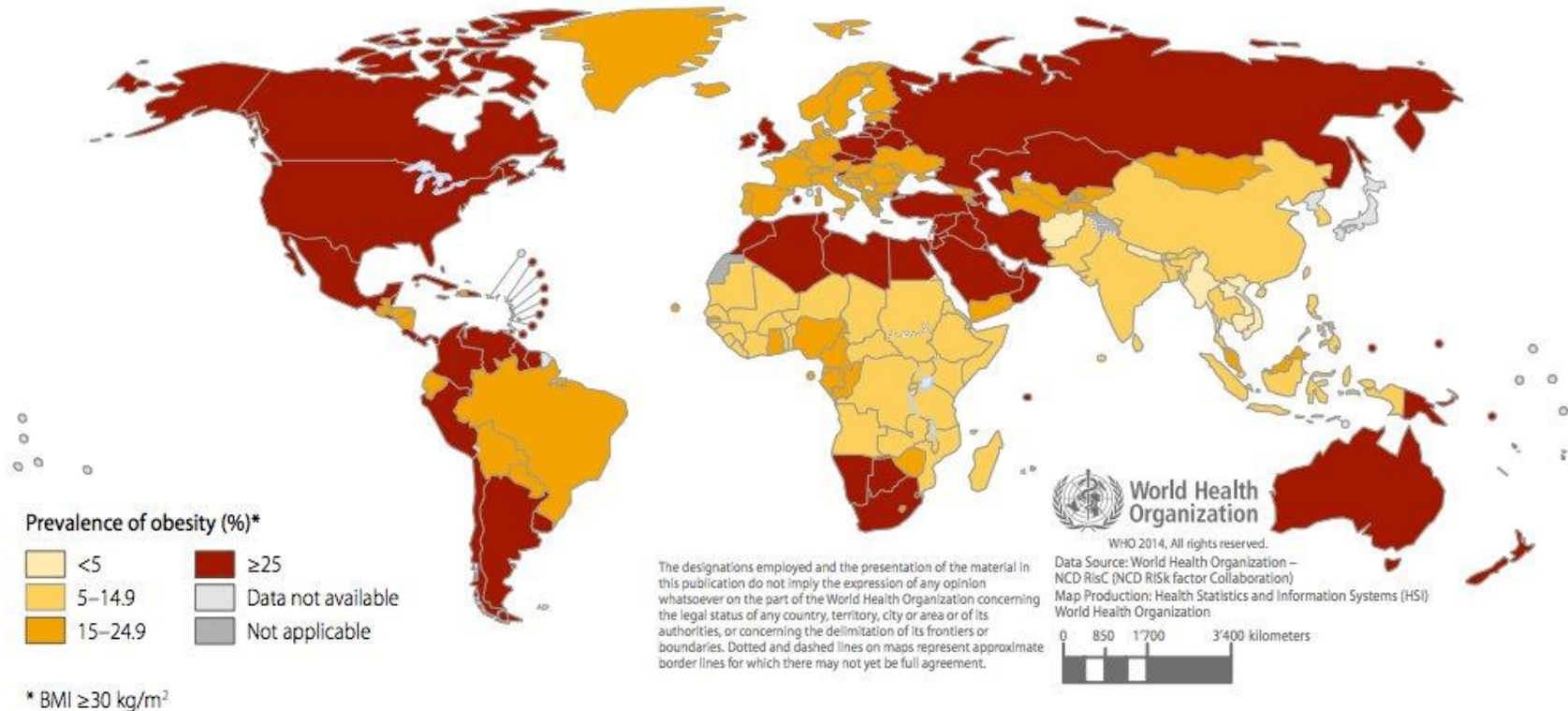
Longer, Healthier Lives



How Dr. Eric Kandel, Neuroscientist, Spends His Sundays, New York Times, May 5, 2017

Obesity x Healthspan

Age-standardized prevalence of obesity in women aged 18 years and over (BMI ≥ 30 kg/m²)



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)

Factor	Housing conditions		
	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
TNF α *	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.

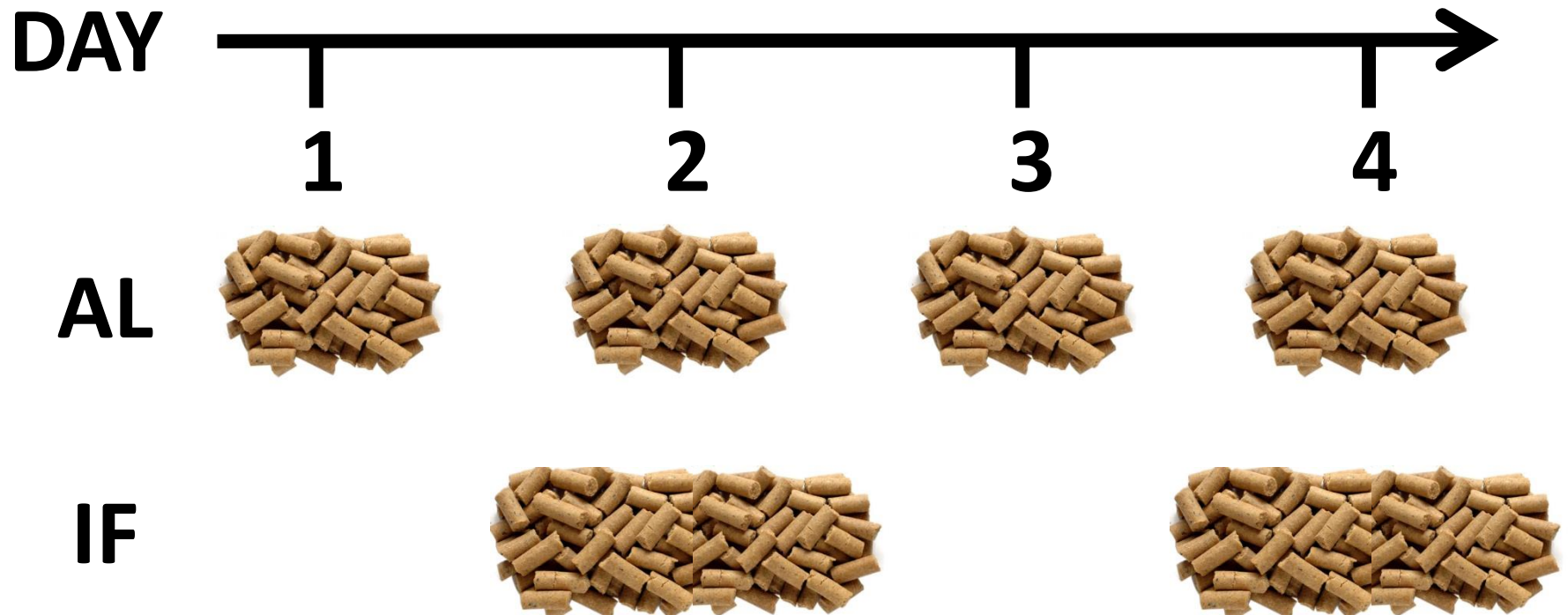
Caloric Restriction

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

Intermittent Fasting (IF) x *Ad Libitum* (AL)



Intermittent Fasting X Caloric Restriction

- Weight loss (muscle)
- Fat production/degradation cycles
- Normal leptin signaling
- Largely enhanced hunger
- Increased AGRP and NPY
- Weight loss (fat)
- Prevention of fat production
- Normal leptin signaling
- Normal hunger
- Normal orexigenesis

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.

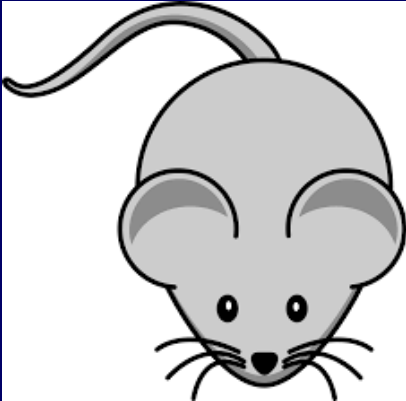


CR = Undernutrition without malnutrition

Does CR change β -cell physiology?

Experimental Model

CR x AL
Rats



Serum



Cultured
INS1 or Mouse Islets



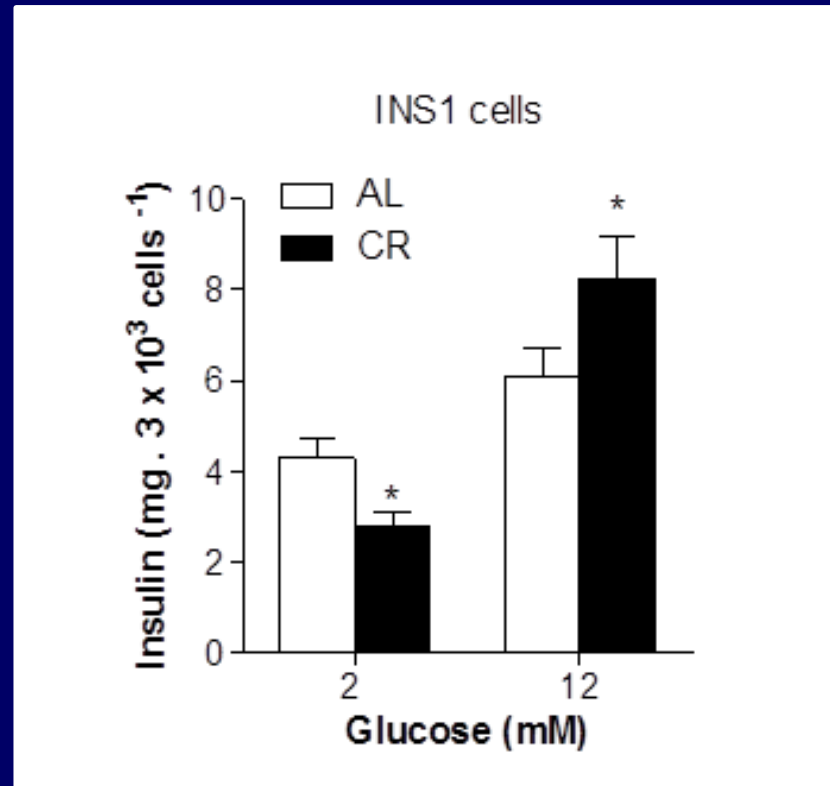
Insulin
secretion

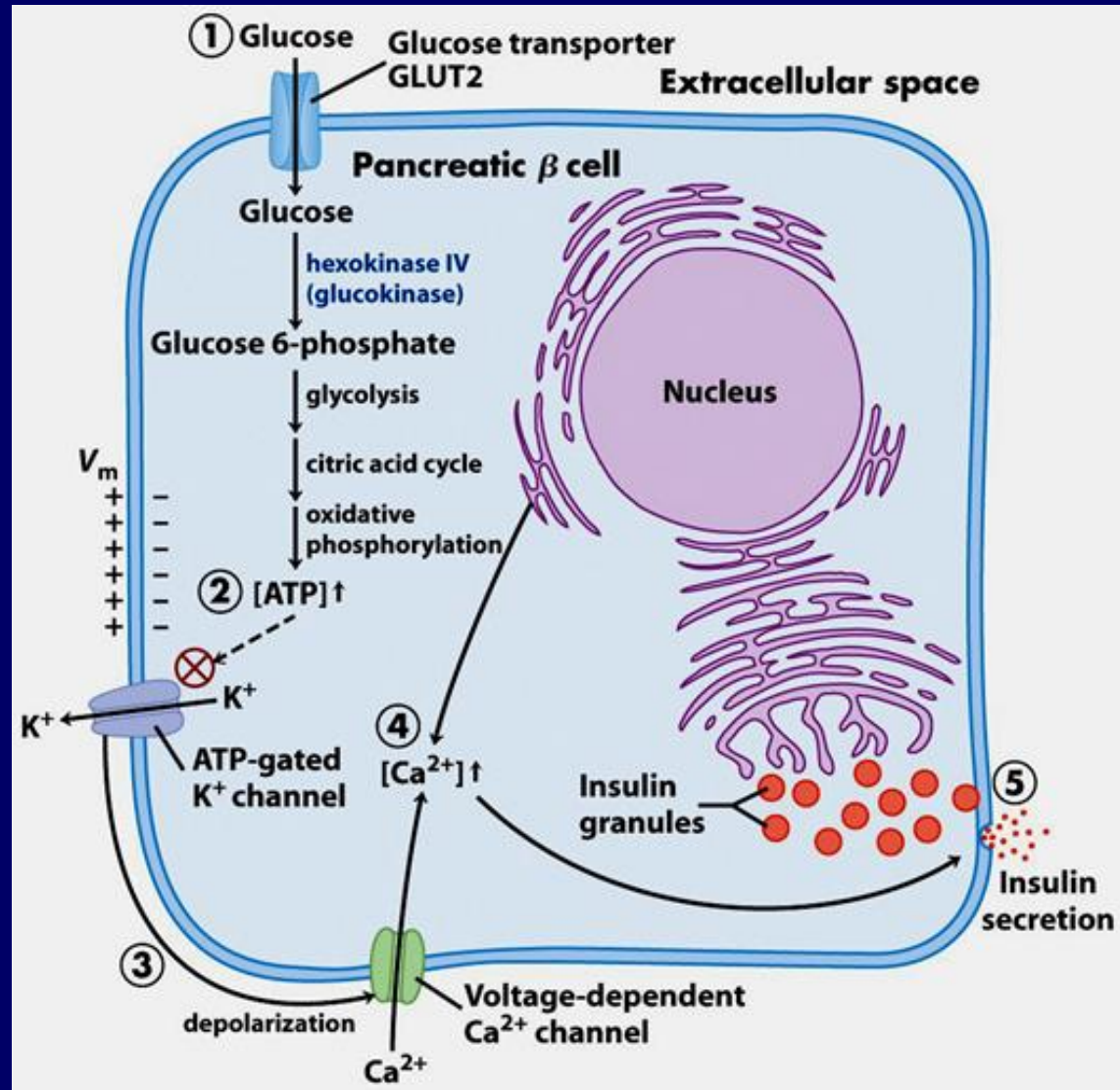


Mitochondrial
physiology

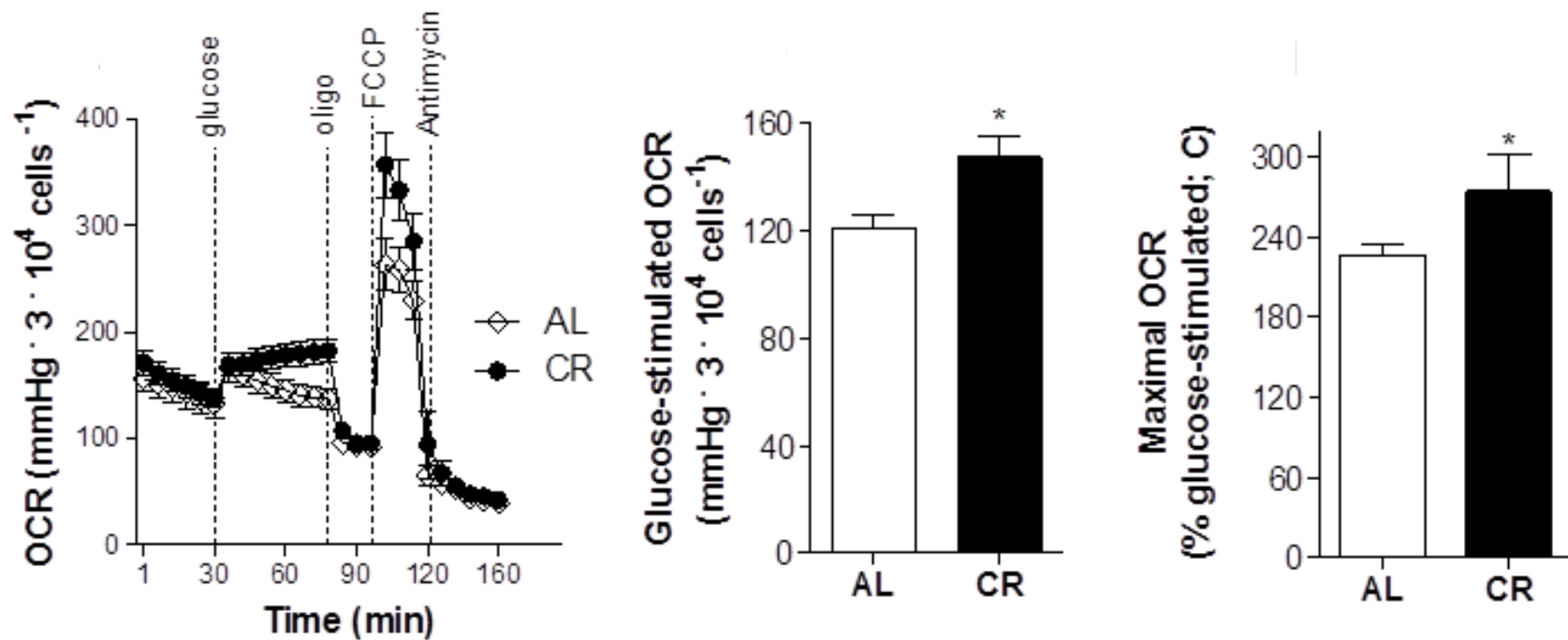


CR Serum Increases Insulin Release

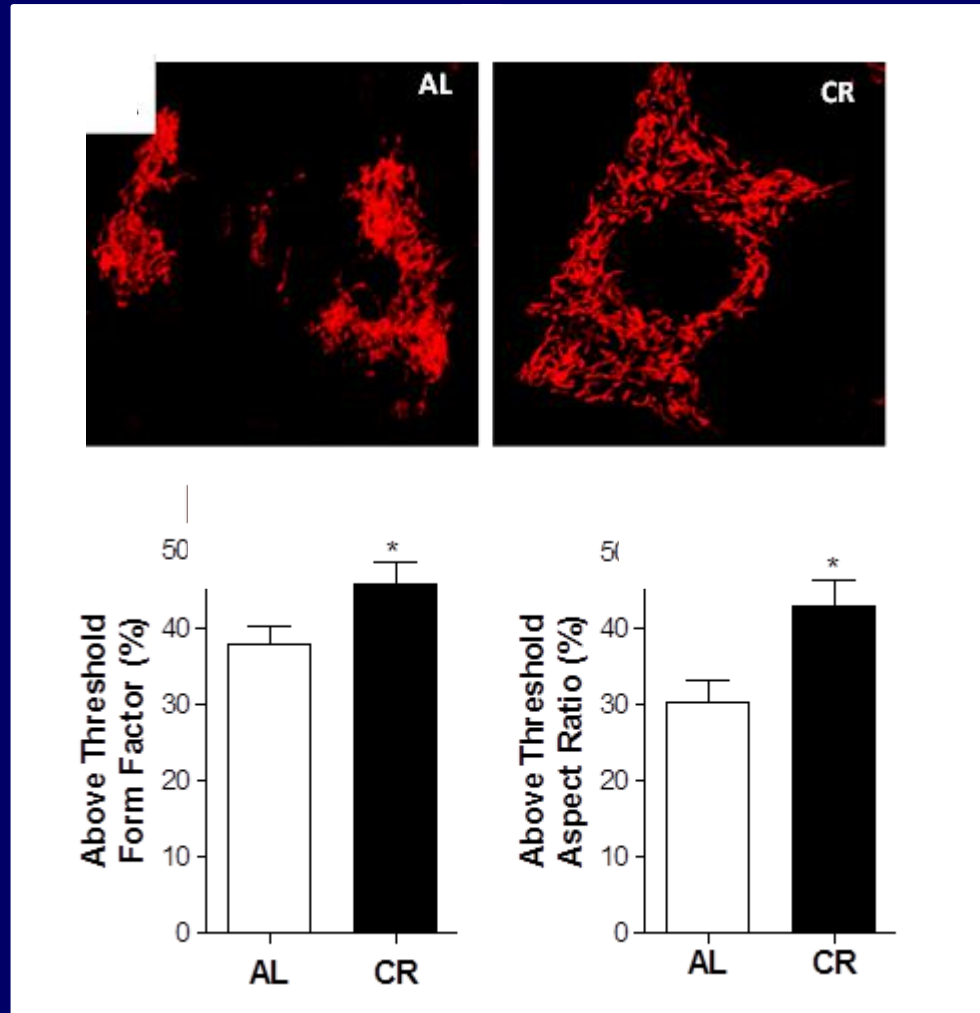




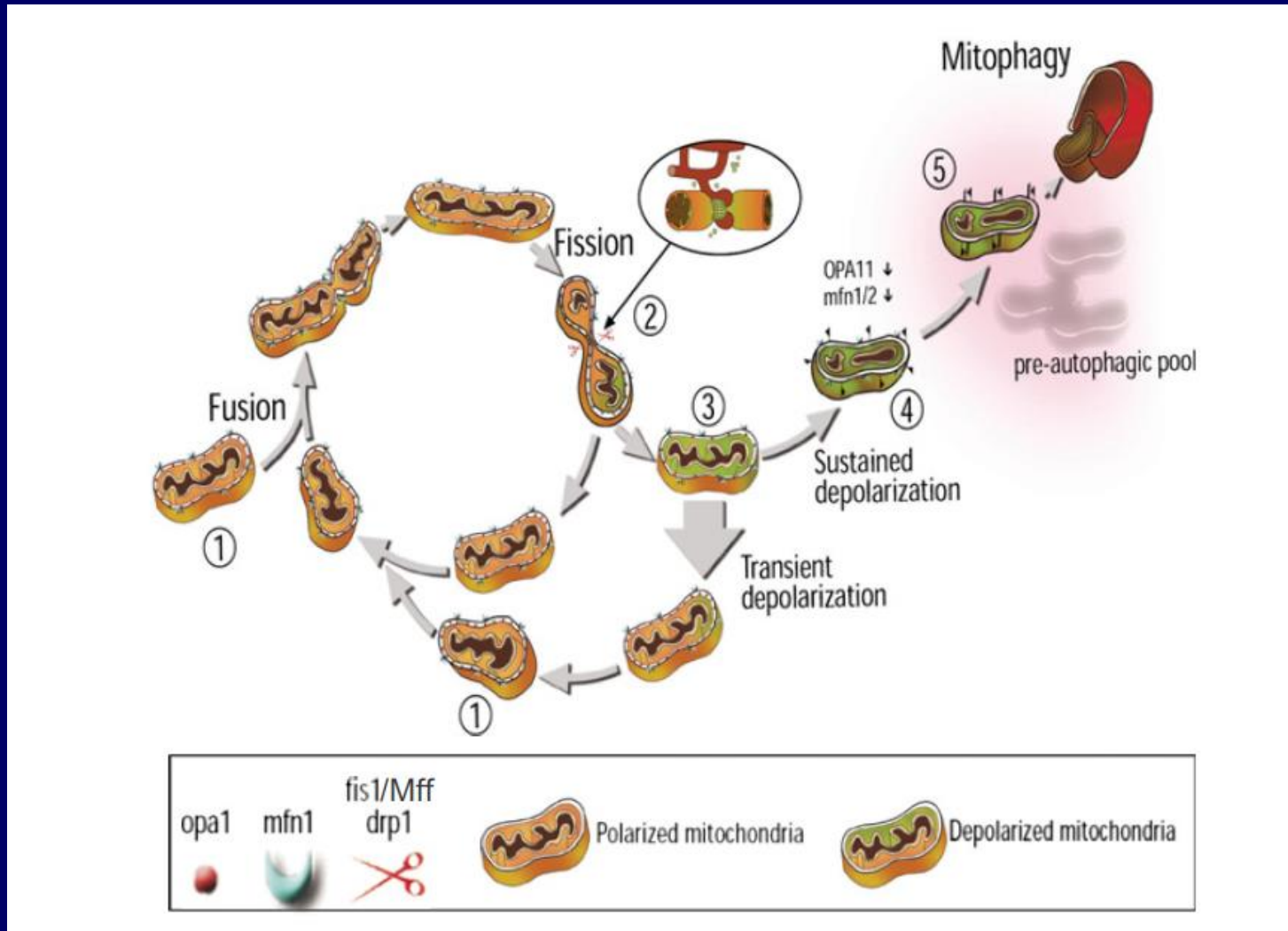
CR Serum Increases Mitochondrial Respiration



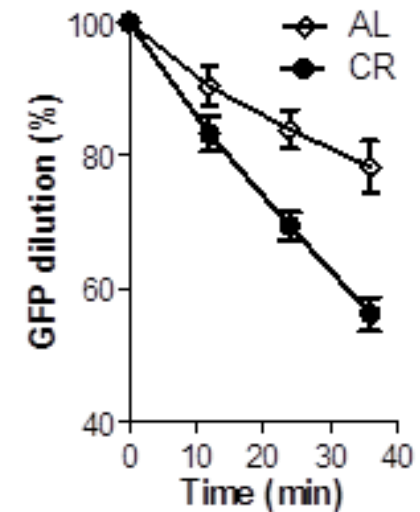
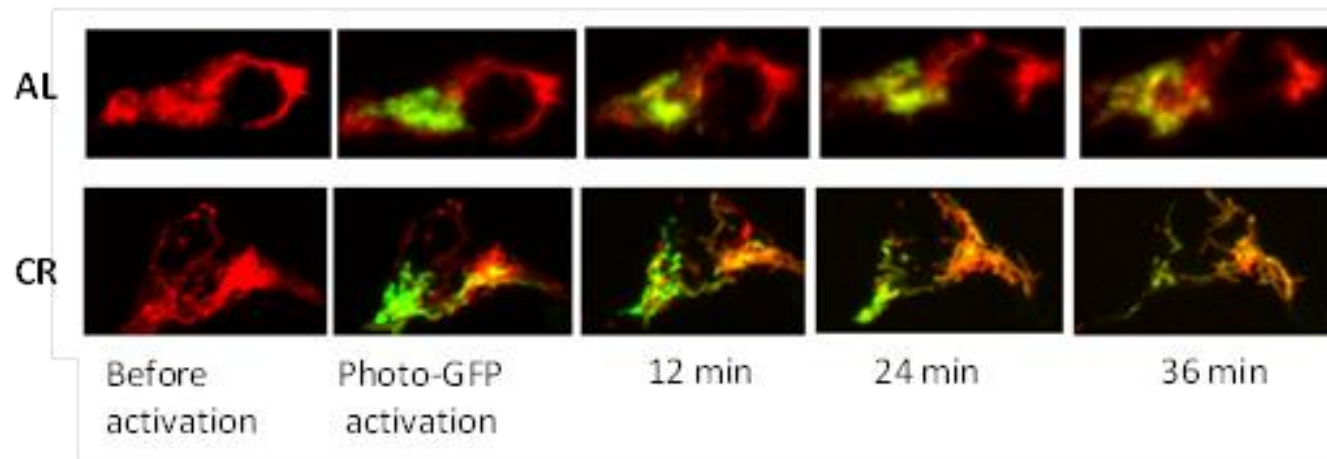
CR Serum Increases Mitochondrial Fusion

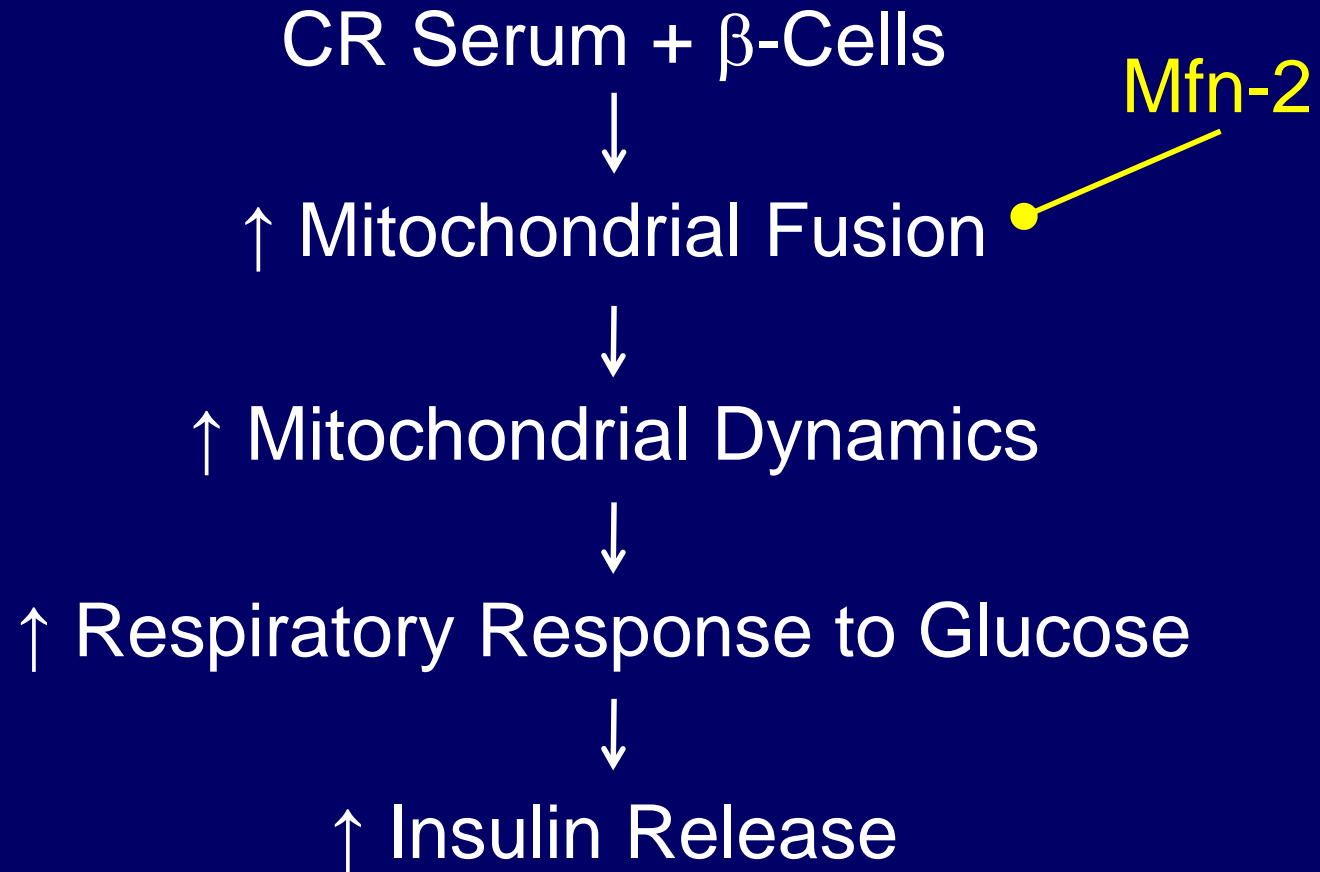


Mitochondria are Dynamic Organelles

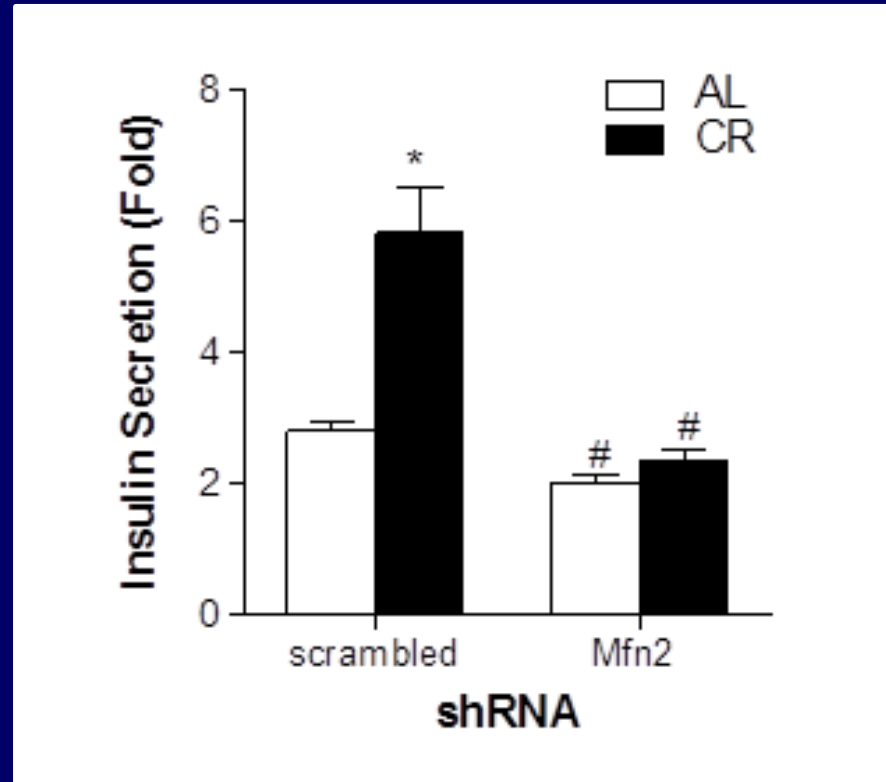


CR Serum Increases Mitochondrial Dynamics



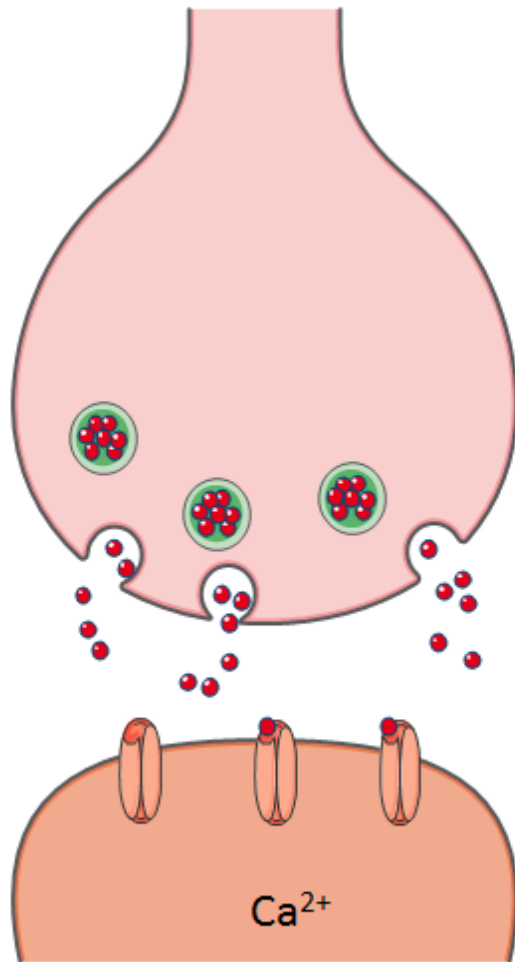


Mfn-2 shRNA Reverses the Effects of CR Serum



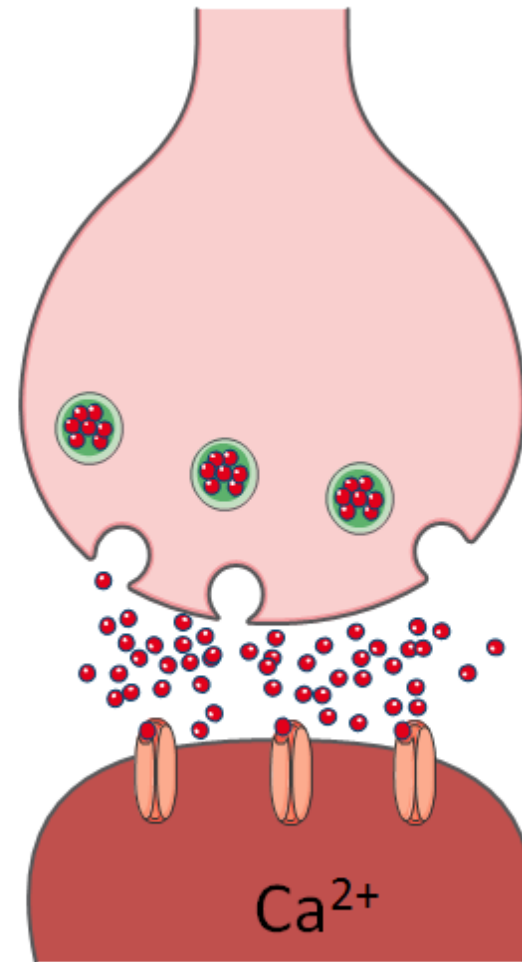
**Does CR protect the brain and
prevent excitotoxicity?**

Physiological synapse



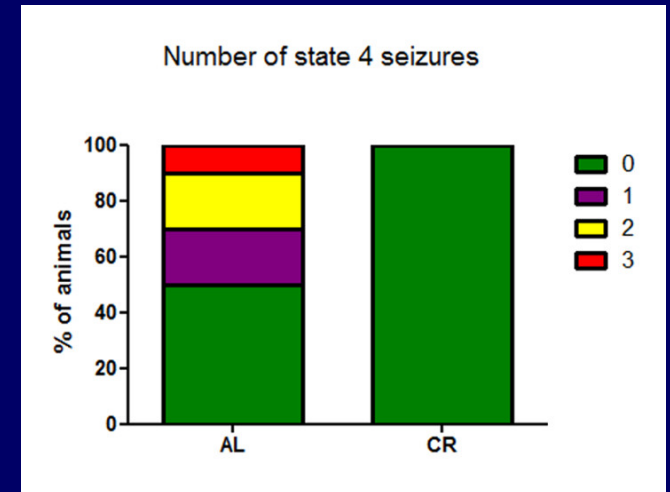
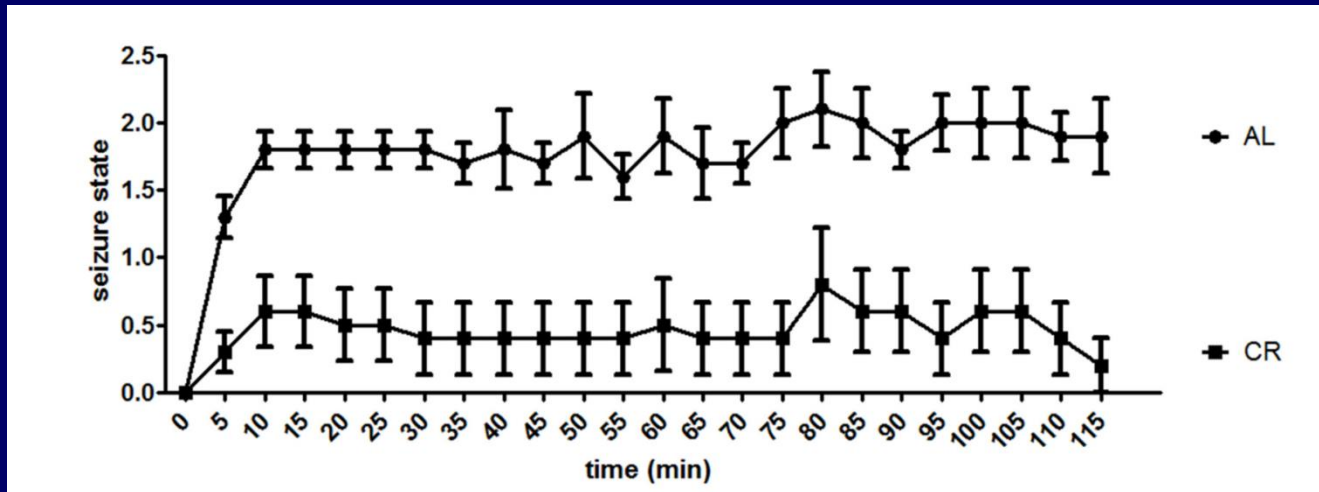
Signal is rapidly terminated

Excitotoxicity

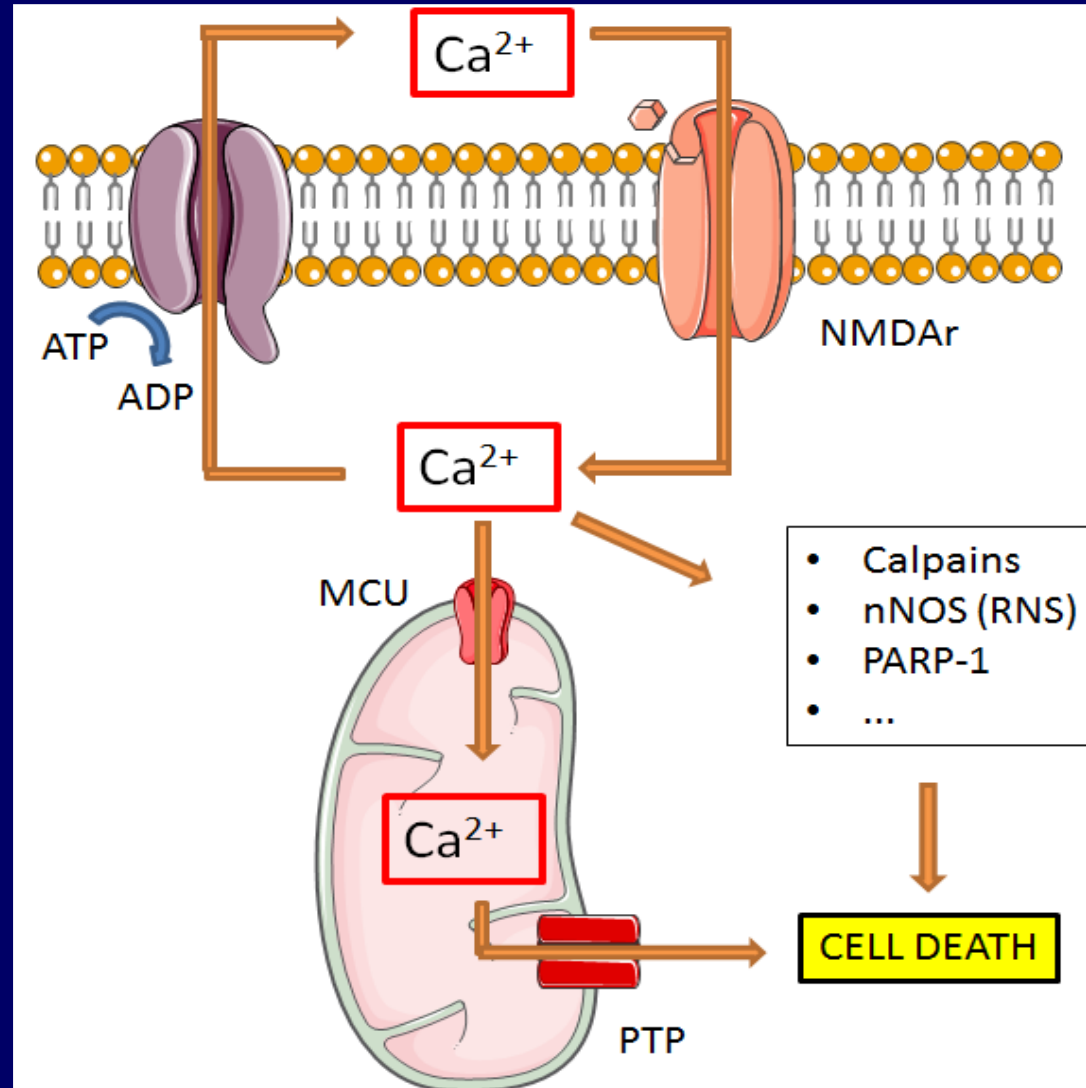


Signal is persistent

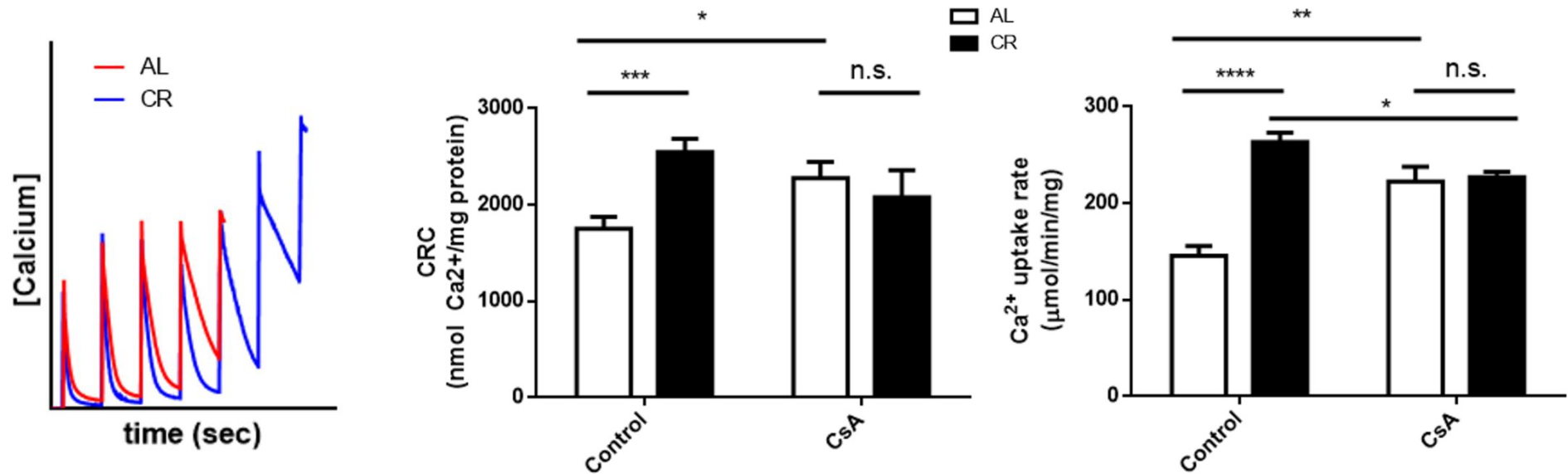
CR Prevents Kainic Acid-Induced Seizures



Mitochondria and Excitotoxicity



CR Increases Mitochondrial Ca²⁺ Uptake



CR



↑ Sirt3 levels



↓ Acetylation



↓ Cyclophilin D Activity



↓ Mitochondrial Permeability Transition



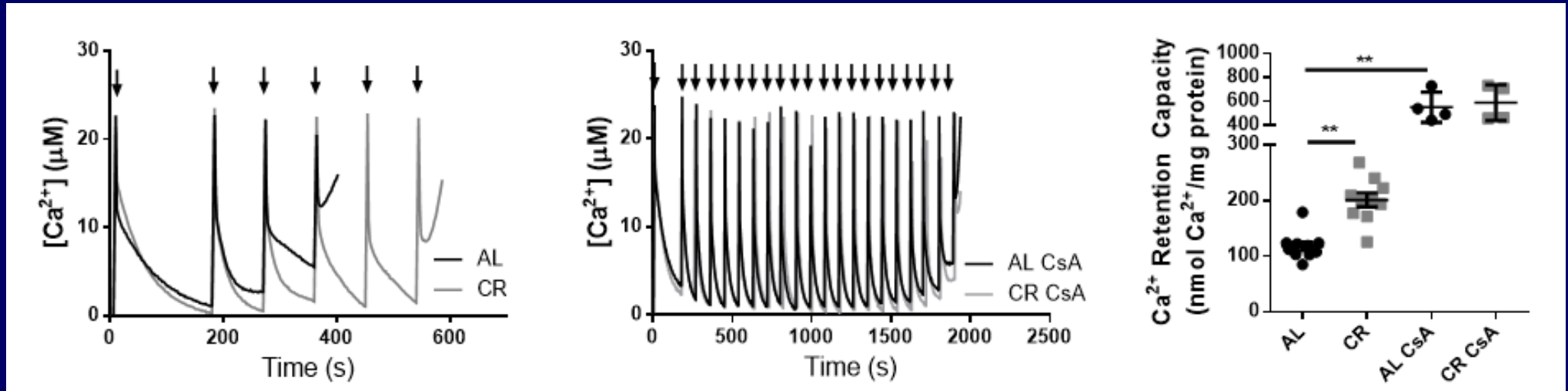
↑ Mitochondrial Ca²⁺ Uptake



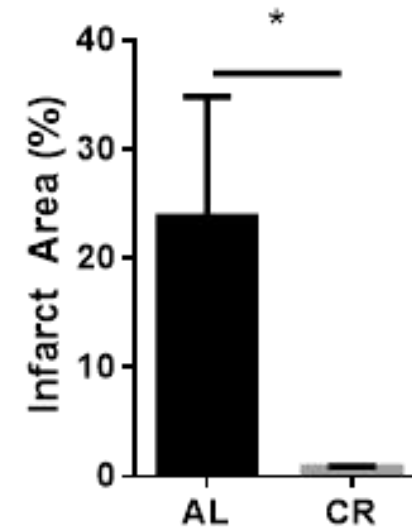
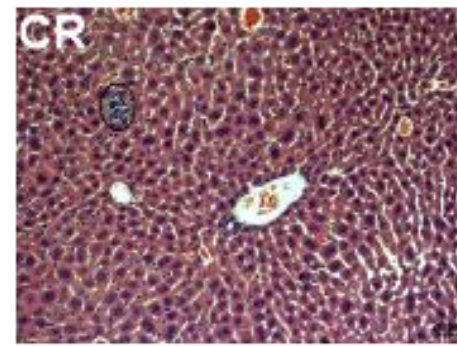
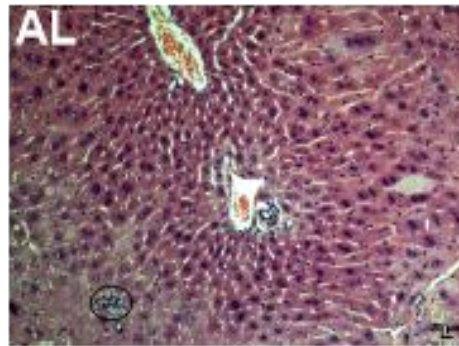
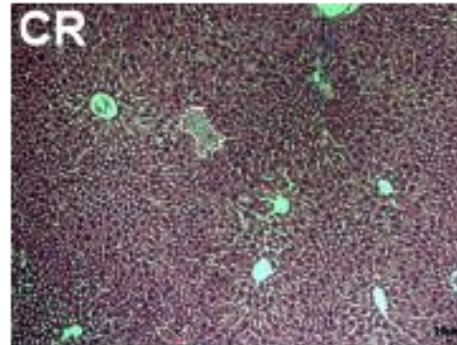
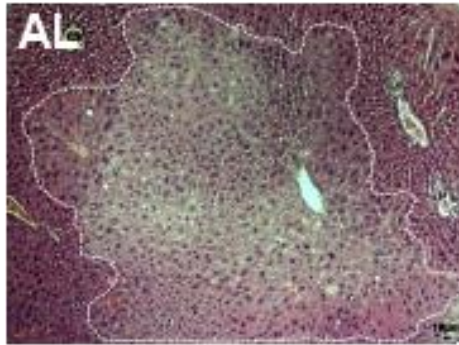
↓ **Excitotoxicity**

What about the liver?

CR Increases Liver Mitochondrial Ca^{2+} Uptake



CR Strongly Protects Against Liver Ischemia



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

Acknowledgements



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