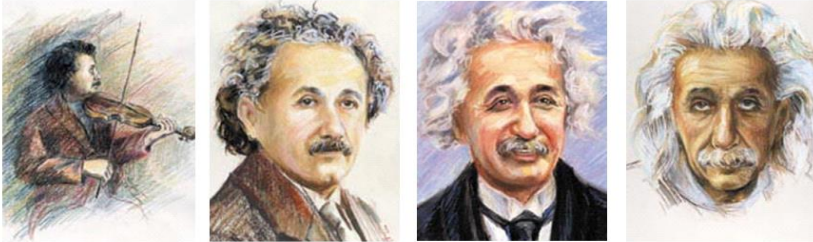




Albert Einstein College of Medicine

Montefiore

EINSTEIN'S INSTITUTE FOR AGING RESEARCH



Staying healthy as we get older!

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The E-Glenn Center for the
Biology of Human Aging

NMRC-2019

Diabetes drives aging and other Sacred Cows

Pope John Paul the 2nd



Things are not what they seem!

Provocations for Diabetes and Aging

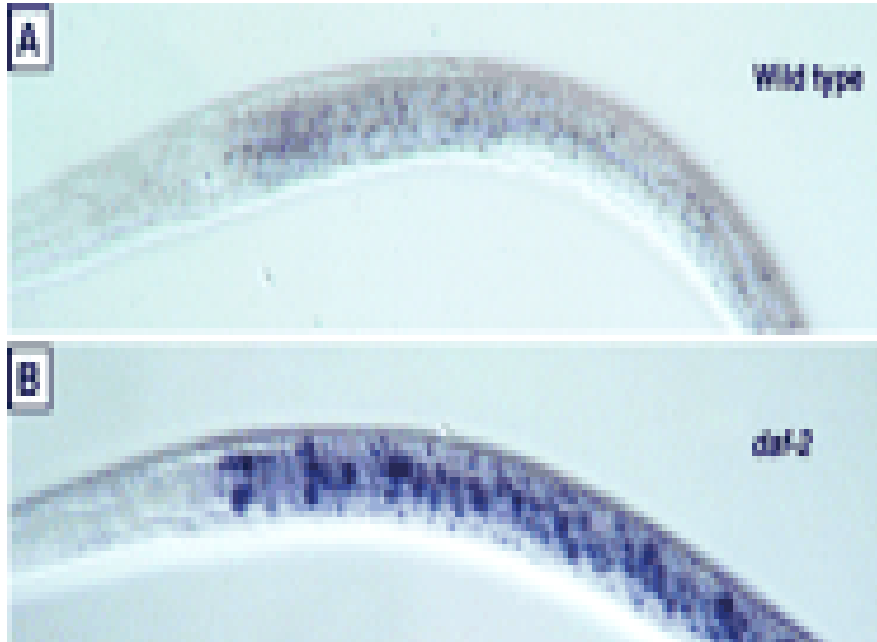
- Insulin resistance not only what you think
- When is T2DM is risk for CVD?
- Are microvascular complications typical to aging?
- Role of the hypothalamus and glucose metabolism in aging

Great advance

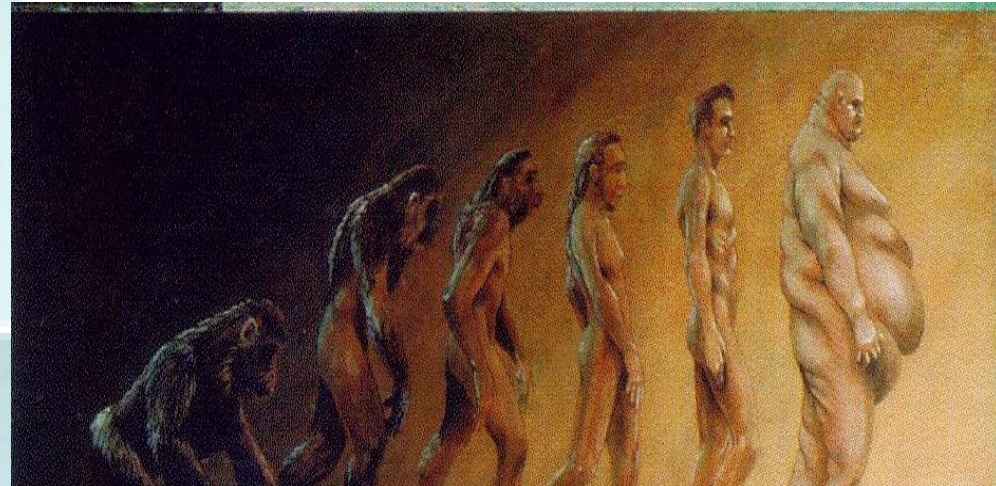
Great paradox

daf-2, an Insulin/IGF Receptor-Like Gene That Regulates Longevity and Diapause in *C. elegans*

Kimura, Ruvkun *Science* 1997; 277: 942-946



Abdominal obesity is a major component of the Insulin resistance syndrome, with risk for many age-associated diseases

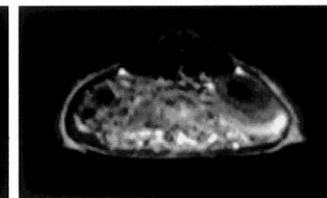
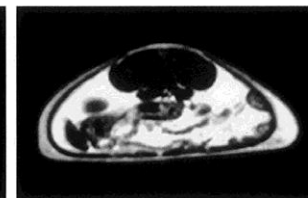
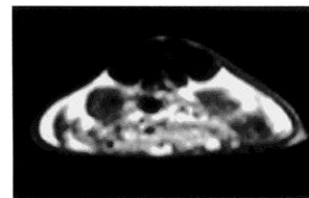


J Clin. Invest. 1998; 101:1353-1361

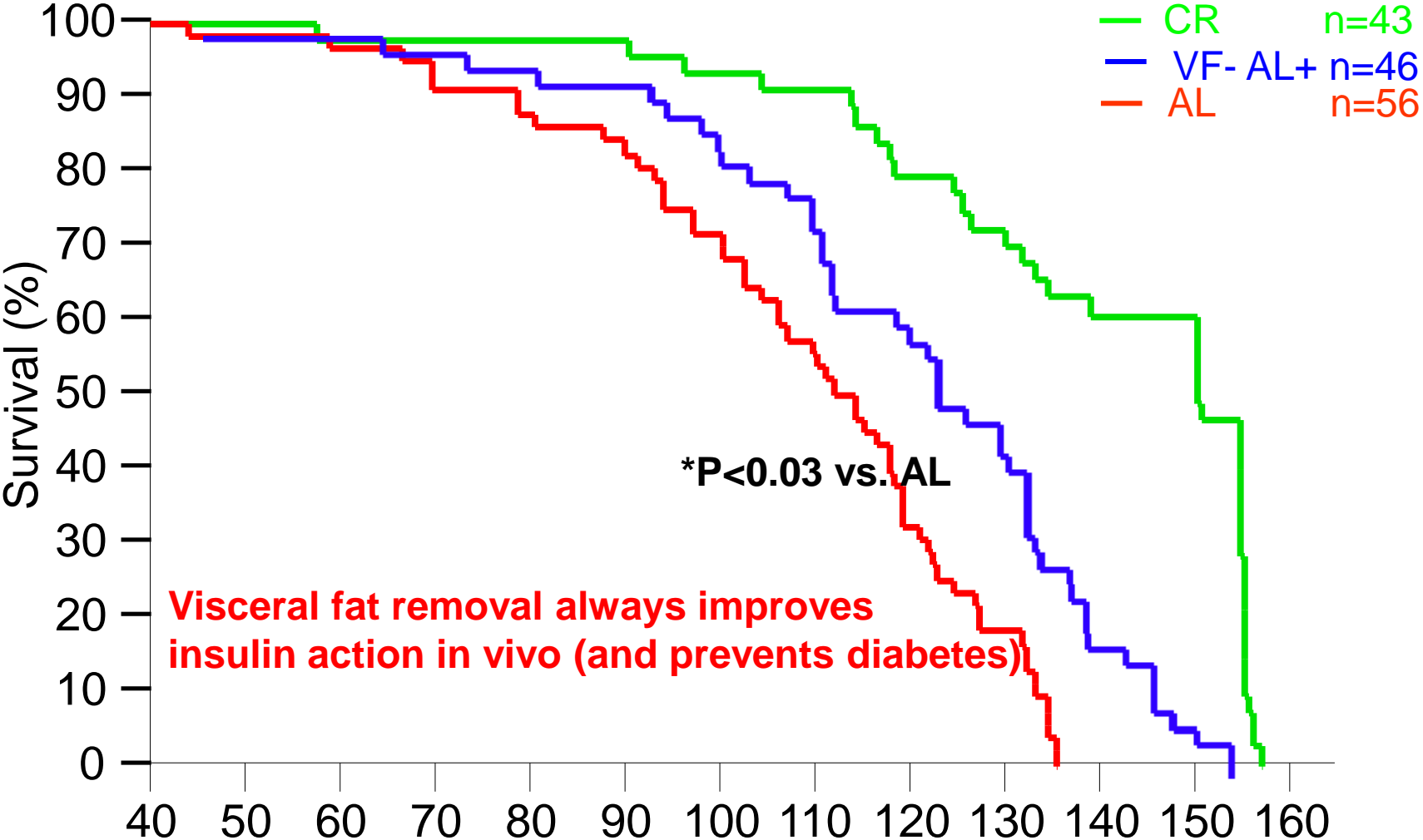
YOUNG

OLD

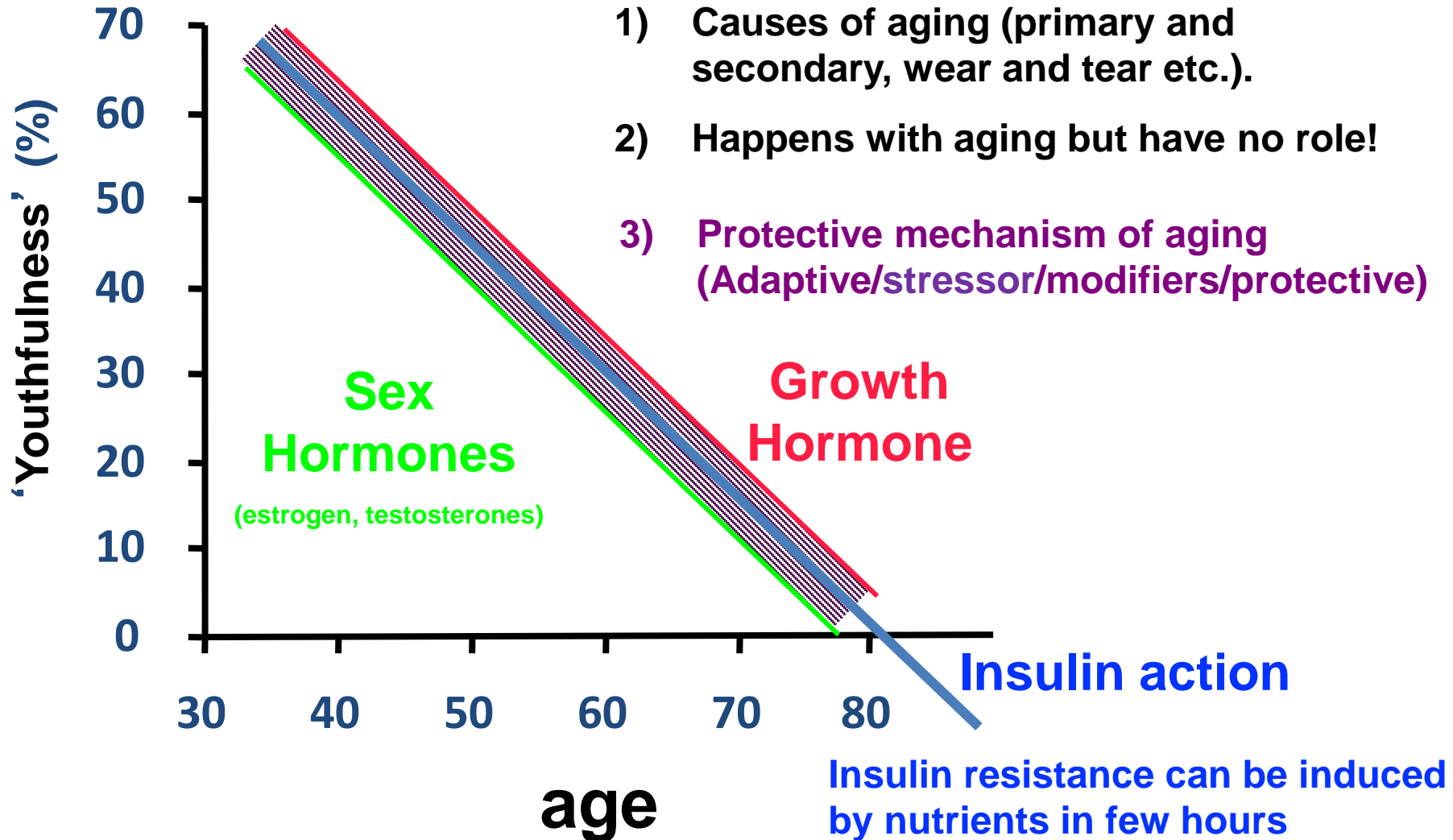
OLD - CR



Does visceral fat removal extend lifespan?



Phenotypes and mechanisms for aging



Insulin Resistance and Longevity: A protective response?

Examples for decreased insulin sensitivity but with increased longevity:

IRKO+/-

IR (*Irf*¹¹⁹⁵ L/wt)

IRS2+/-

IRS2+/- in brain

IRS1-/-

Klotho transgenic mice

Rapamycin-treated mice

If we accept that insulin resistance is also a protective mechanism --we may be closer to the whole truth...

Always better for mammals to be insulin sensitive, but if we need resistance don't just take it away

Examples for increased insulin sensitivity with decreased or unchanged longevity:

PTP1B knockout mice

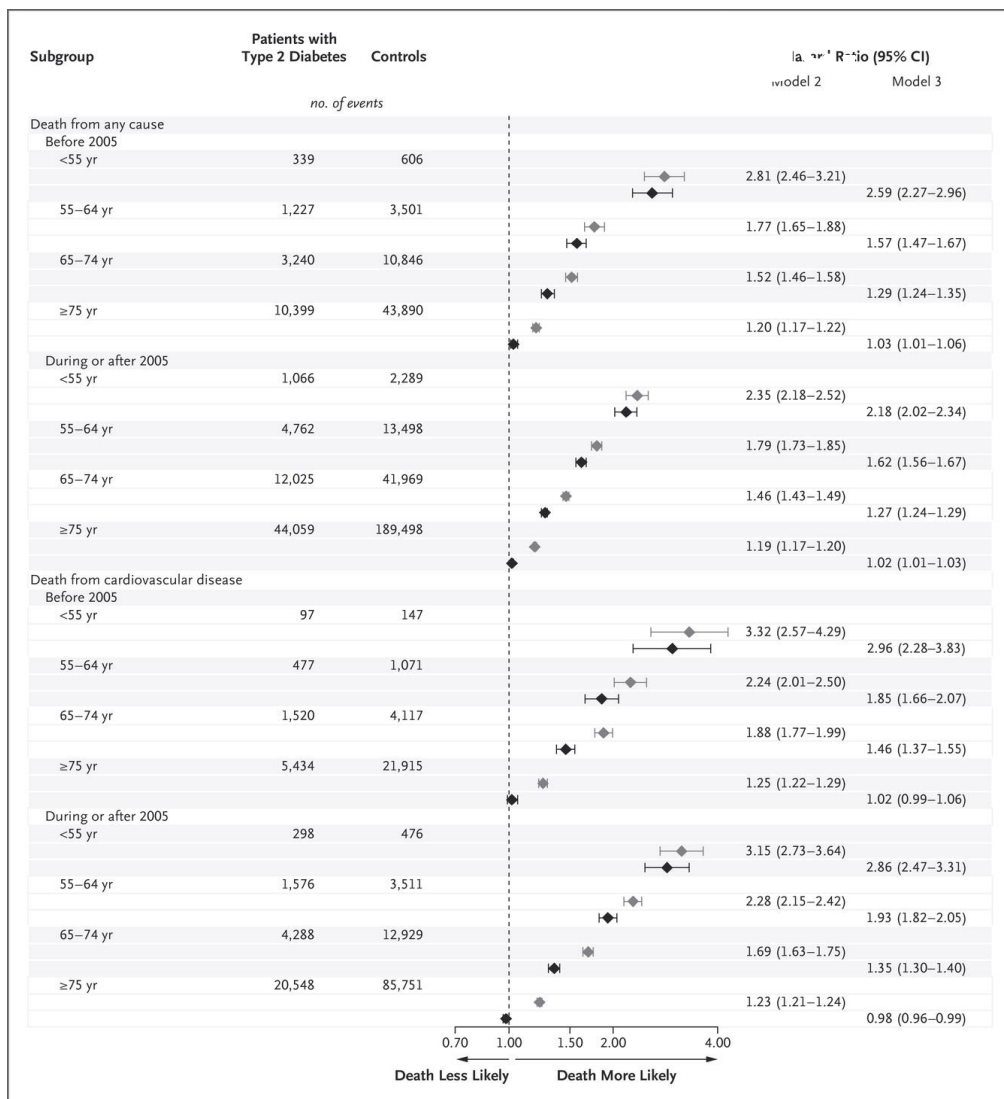
PGC1—a transgenic mice

Resveratrol-treated mice (without high fat diet)

Glut4 transgenic mice

Use of Insulin sensitizers (TZD's) have caused age-related diseases in humans!

Adjusted Hazard Ratios for Death from Any Cause and from Cardiovascular Causes decrease with



Does diabetes add any risk to death and diseases in the elderly?

Can diabetes be protective in elderly?

We need to identify the mechanisms by which hyperglycemia accelerates aging!

Tancredi M et al. N Engl J Med 2015;373:1720-1732.

Potential confounders: Competing risks, survival effects, duration, metformin, statins etc

Diabetes microvascular complications and aging (?)

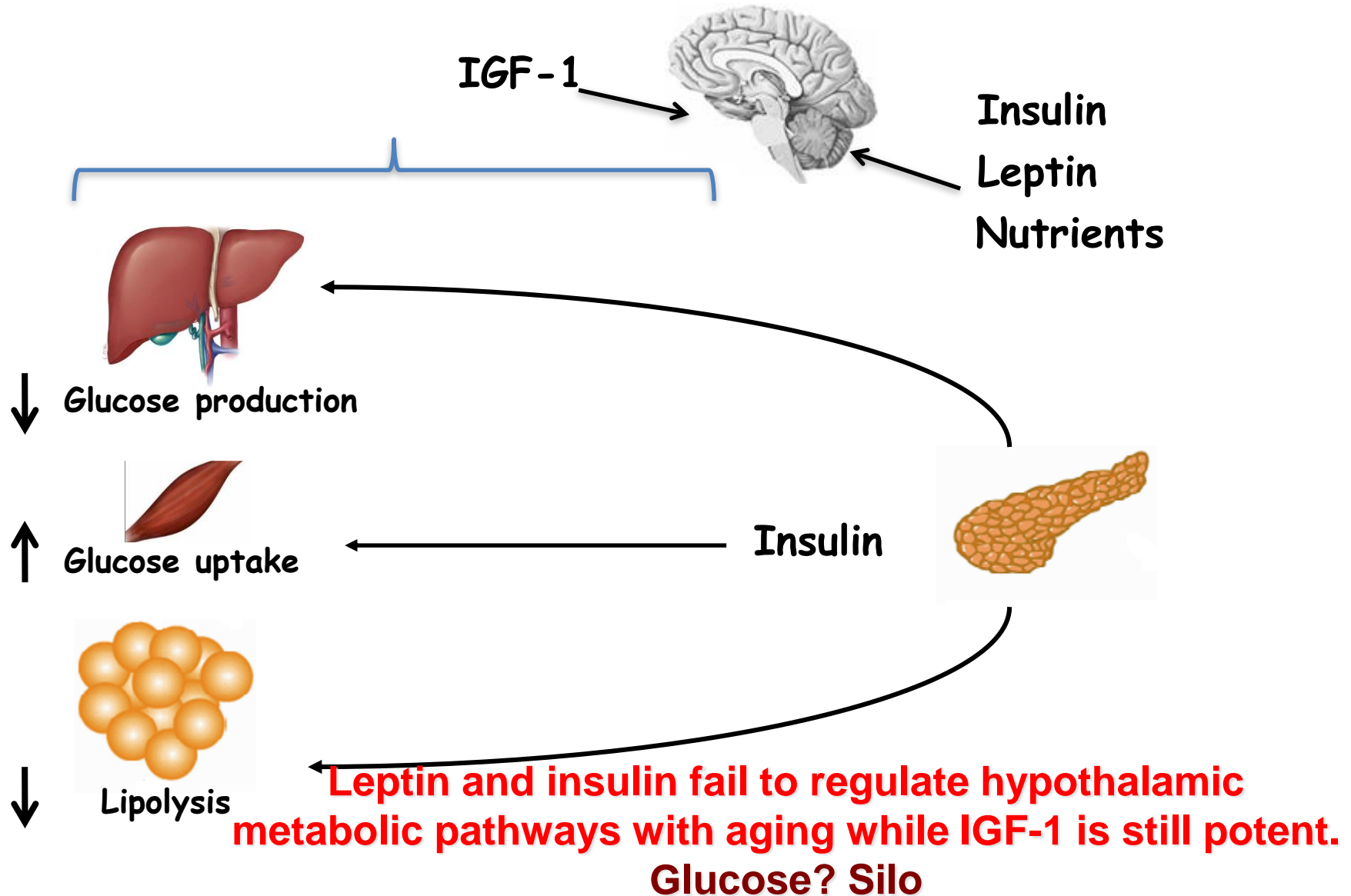
Retinopathy-

Neuropathy-

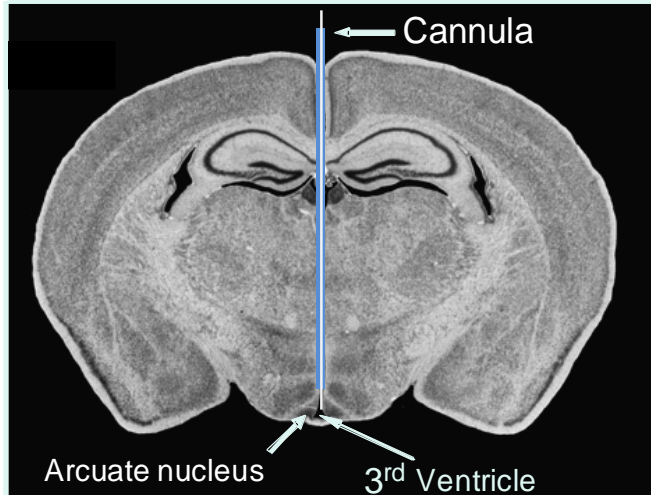
Nephropathy-

- It's the glycemic hypothesis that seems important.
- No data about prevalence of all those in non-diabetic elderly.
- Some overlap of nephropathy and aging, but not typical pathological kidney.

Regulation of glucose homeostasis



Hyperinsulinemic-euglycemic clamp



3MO and 20 MO Male Sprague Dawley Rats

25% dextrose (as needed)

Somatostatin

Insulin 3mu/kg/min



Tritiated glucose infusion

ICV (aCSF/IGF-1/Insulin/Inhibitors)

ICV Surgery

IV catheters



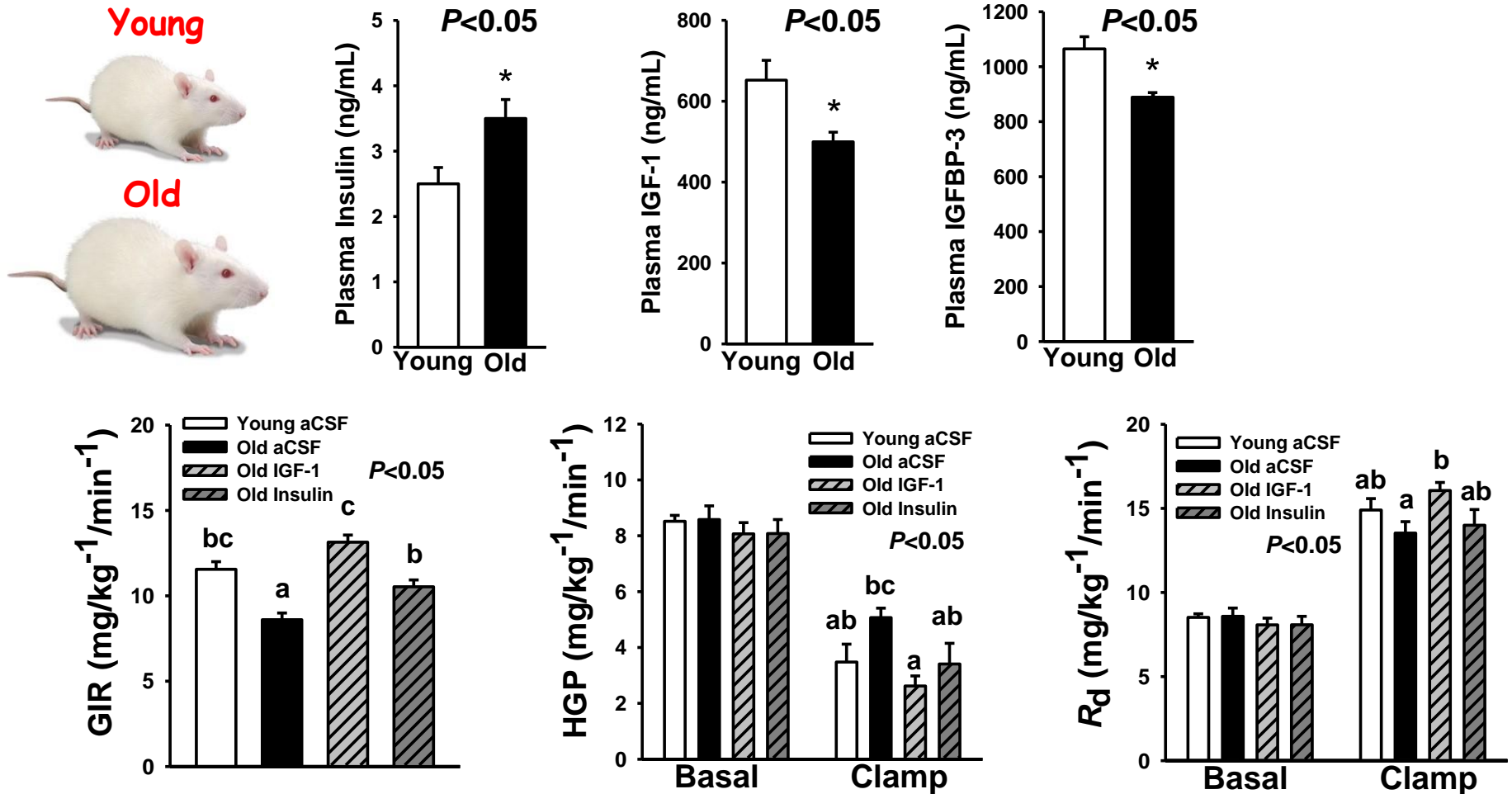
Day -21

Day -7

Day 0

6-hour Clamp Study

Central IGF-1 Restores Insulin Sensitivity in an aging model



Summary:

- **The glucose hypothesis of some diabetes complications is not generally consistent with driving aging.**
- **Insulin resistance in aging may represent defense/adaptation and may not necessarily accelerate aging (but it does accelerate diabetes).**
- **Mechanisms that may fail in diabetes and aging include:**
 - Hypothalamic regulation of peripheral metabolism
 - Insulin regulation in cognitive areas of the brain
 - Proteostasis/Autophagy in a variety of tissues (beta-cells, neurons etc...), although hyperglycemia induces autophagy.
- **The mechanisms by which drugs (metformin and acarbose) that target diabetes also increase longevity should be defined.**
- **It is a challenge is to identify the mechanisms of aging that are being accelerated with hyperglycemia!**