Caloric restriction and lifespan.

Reading: Handbook of Aging, Ch 15

A&S300-002 Jim Lund

Interventions that modify aging and longevity

- Environmental manipulation.
- Caloric restriction.
  - Also called dietary restriction.
- Genetic manipulations.
- Drugs

Discovery of Calorie Restriction

- Environmental manipulations (temperature, feeding) of small, cold-blooded animals (fruit flies, water fleas) were known to alter lifespan.
  - Thought trivial, not relevant to aging in mammals.
- McKay was interested in the effect of the rate of growth on lifespan.
  - Late puberty -> long lifespan and vice versa.
  - Known that reducing food intake slowed growth and development in mice, cows, rats, other mammals.
  - Also observed in humans, on subsistence diet women reach menarche at 18-19, in US at 12-13.

Discovery of Calorie Restriction!

McKay thought that other studies had confounded a reduced calorie diet with malnutrition and starvation, and thus given unreliable results.

McKay's experiment:

Feed rats a reduced diet rich in vitamins and minerals.

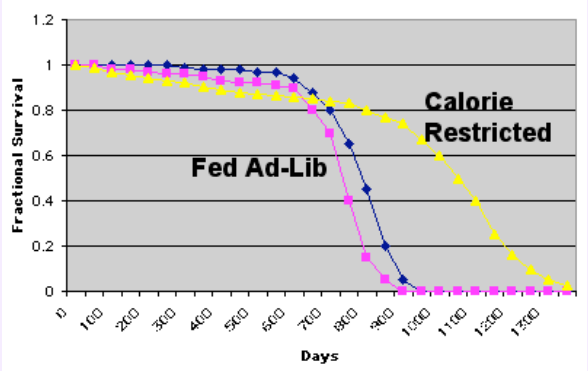
Results:

Caloric restricted male rats lived 75% longer than controls. Maximum lifespan +1 yr., 35% longer.

No difference for female rats.

In later experiments using a reformulated diet, found lifespan extension in both male and female rats.

Survival of Calorie Restricted Rats

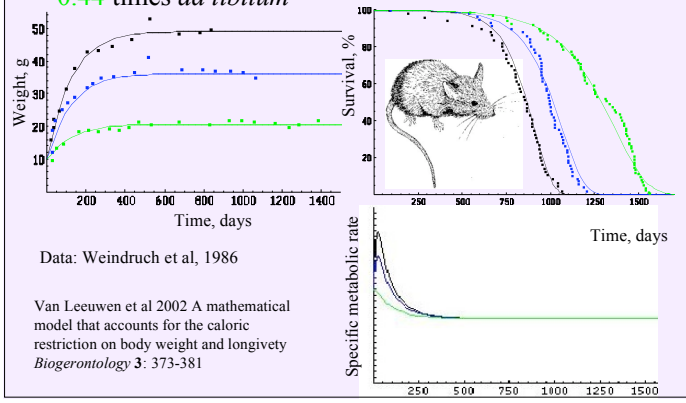


- McCay CM et al. J. Nutrition 1935, 10: 63-79
- McCay, C. M., and M. F. Crowell. 1934. Prolonging the life span. Science Monthly 39:405–414.

CR in mouse

Feeding level: 1, 0.75, 0.44 times *ad libitum*

Caloric restriction extends life span



Data: Weindruch et al, 1986

Van Leeuwen et al 2002 A mathematical model that accounts for the caloric restriction on body weight and longivety *Biogerontology* **3**: 373-381

CR phenotype

- Maintain youthful activity levels longer.
- Maintain immune function longer.
- Better performance in memory tests (water maze), retain memory abilities longer.
- Fewer tumors.
- More resistant to carcinogens.
- Less oxidative damage
  - Collagen crosslinks form slower (less AGEs).
  - Fewer free radicals.
- Lower mean blood glucose.

CR phenotype

- Body temperature lower in mice but not in rats.

- If extreme CR started in juveniles, get reduced rate of reproduction in rats, cessation of reproduction in mice.

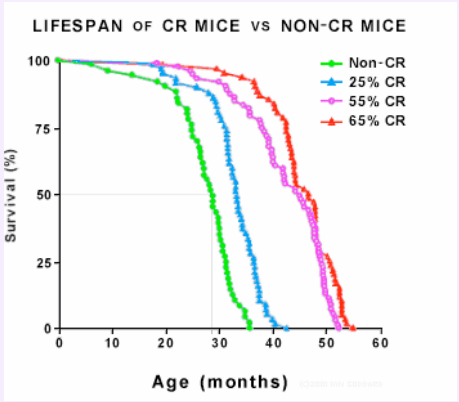
- Metabolic rate per cell falls initially, then recovers (More efficient use of oxygen?).

CR variations in rodents that produce extended lifespans

- Start CR at weaning.
  - Small size, longer development time.
- Start CR in young adults.
- Start CR in adults.
  - Generally, lifespan extension proportional to time on CR.
- Fast and ab libitum diet on alternate days.
- Different diet compositions work:
  - Fats, proteins, or carbohydrates can be cut.

Different levels of CR, 10% - 70%, all work, generally more CR gives longer lifespan extension.

CR in mouse



Weindruch, et al., 1986

CR extends lifespan in every animal tested

Species	Mean lifespan	Max. lifespan	CR mean ls.	CR max. ls
Rat	23 months	33 months	33 months	47 months
Guppy	33 months	54 months	46 months	59 months
Bowl and doily spider	50 days	100 days	90 days	139 days
Protozoan	7 days	14 days	13 days	25 days
Yeast	21 generations	40 generations	26 generations	49 generations
Fly	25 days	47 days	46 days	78 days

Primate CR trials

- **NIA**
  - Juvenile (1 yr) and adult (3–5 yr) male rhesus monkeys (*Macaca mulatta*) and juvenile (1–4 yr) and adult (5–10 yr) male squirrel monkeys (*Saimiri sciureus*).
  - Fed a diet at or near ad libitum levels based on recommended caloric intake for age and body weight or fed 30% less of the same diet with this restriction gradually introduced over a 3-month period.
  - Actual food intake of CR groups 22–24% below control levels.

NIA

Primate NIA experiment

Findings in NIA Primate CR Study	Matches Rodent Data	
(-) Body weight	Yes	
(-) Fat and lean mass	Yes	
(-) Time to sexual maturation	Yes	
(-) Time to skeletal maturation	Yes	
(-) Fasting glucose/insulin	Yes	
(-) Metabolic rate (short-term)	Yes	
(*) Metabolic rate (long-term)	Yes	
(-) Body temperature	Yes	
(*) or (+) Locomotion	Yes	
(-) Triglycerides	Yes	
(+) IGF-1/growth hormone	Yes	
(-) Il-6	Yes	(-) = decrease
(*) Wound closure rate	Yes	(+) = increase
(*) Clonal proliferation	Yes/?	(*) = no change
(*) B-gal senescent cells	?	
(-) Lymphocyte number	Yes	
(*) Lymphocyte calcium response	No	**Lane et al., 1999**

Primate CR trials: UW experiment

- 30 adults (8-14 years old) male rhesus monkeys.
- Adult-onset DR
- Started with a 3-6 month period of baseline data collection.

- 15 animals were assigned to a control group and given free access to a semipurified diet for 6-8 hours per day.
- 15 monkeys were fed the same diet but at 70% of their baseline intake levels predetermined individually.

Primate CR trials: UW experiment

Results after 1 year:

- All monkeys appear to be in excellent health.
- Average body weights for controls increased by 9% while monkeys on DR did not gain weight.
- DR monkeys have less body fat than do control monkeys, whereas the amount of lean body mass has not been significantly influenced by DR.
- Reduction in physical activity for monkeys on DR relative to controls.

- Control monkeys gradually reduced their voluntary levels of food intake during the first year of study, and DR monkeys food reduced to maintain 30% difference.

Why does caloric restriction extend lifespan?

- There is evolutionary competition to successfully reproduce.

- Which drives life history strategies to maximize reproductive success.

Relationship between reproduction and lifespan

Adaptable life history strategies:

- •Semelparity is an extreme case (Salmon, *Antechinus stuartii*, annual plants).
- •Many other organisms alter their breeding time or rate to maximize reproductive success.

The caloric restriction response is an example of this.

•Low food availability -> postpone reproduction, wait for better conditions.

- •Animal puts energy into maintenance rather than reproduction, lives longer.

•High food availability -> reproduce quickly.

How does caloric restriction extend lifespan?

•What cellular processes are altered?

•Is the life span extension an inherent consequence of CR, directly due to low metabolism?

•Or is the organism's response a regulated response to the signal of CR?

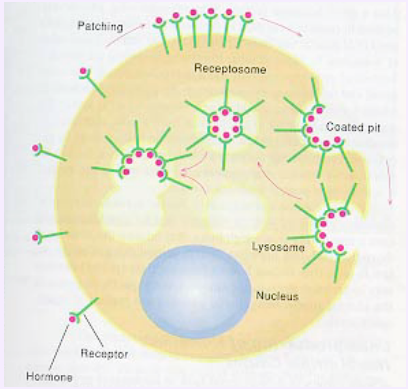
Important characteristics of calorie restricted animals

- Maintenance of mitochondrial energy production
- Maintenance of a better daily balance of insulin and growth hormone that mirrors shifts in glucose vs fatty acid usage.
- Elevated sensitivity to hormonal stimulation, especially to insulin.
- Higher protein synthetic rates especially in old age
  - Ad Lib fed animals have a 40-70% decline over youthful levels

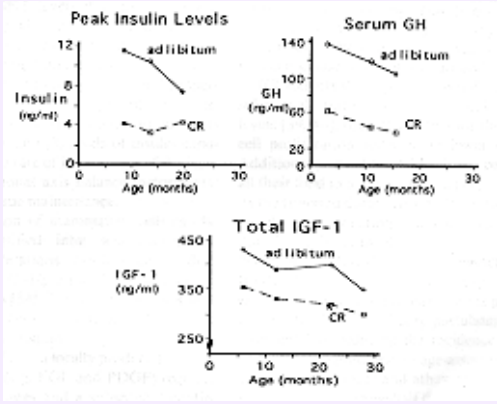
Insulin Receptor Down Regulation

- Constant food
- Constant glucose -> high insulin production
- Less receptors less sensitivity
- More insulin leads to a greater chance of getting adult onset diabetes (Type II).
  - Why? Mechanism not understood in detail.

Receptor Down Regulation
Lower Insulin Sensitivity



Hormone Levels
CR rats Vs *Ad Lib* Fed



Caloric restriction:
Will it work in humans?

Dr. Roy Walford: The 120-Year Diet

Caloric restriction:
Will it work in humans?

Caloric restriction is being tried by a number of individuals.

Calorie Restriction with Optimum Nutrition web site: http://www.cron-web.org

Article describing the experience of a college student on a caloric restricted diet: http://health.ivillage.com/eating/estyles/0,,7559kd1h,00.html?ice=iv%7Cwb%7Ccrfasting1

Caloric restriction in humans

Effects of CR in humans:

Some biological parameters improve:
- Blood pressure reduced
- Blood sugar lowered
- Immune response improved

Some do not:
- Wrinkles
- Hair greying, loss.
- Progression slows

Studies of CR in humans

Big question: Does it extend lifespan?
Can't be answered yet.

Studies look at biological variables in CR humans.

Compare the findings to CR in animals to get a provisional answer. Does CR in humans appear to be having similar effects?

Studies of CR in humans

Comparing people on CR voluntarily to matched controls:

CR group:

21 men and four women

1,400 to 2,000 calories per day for three to 15 years

Mean age 53±12 years, range 35 to 82 years

Controls:

25 age- and gender-matched controls

Typical Western diets

2,000 to 3,000 calories per day

Meyer et al., 2006

Meyer et al., 2006

Examined normal aging-associated impairments in diastolic function.

- Diastolic function indexes of the CR group were similar to those of younger individuals (average 15 yrs "younger")
- Viscoelasticity and stiffness, were significantly lower than in control subjects.

Also inproved in the CR group (measures of inflammation):
- Blood pressure
- Serum CRP levels
- TNF-alpha and TGF-beta(1) levels

Fontana et al., 2004

- 18 individuals who had been on CR
  - average of 6 years and
- 18 age-matched healthy individuals on typical American diets.

- CR group was leaner:
  - Body mass index (BMI)
    - 19.6 +/- 1.9 vs. 25.9 +/- 3.2 kg/m(2);
  - Percent body fat
    - 8.7 +/- 7% vs. 24 +/- 8%

Fontana et al., 2004

Lower in CR group:
- Serum total cholesterol
- Low-density lipoprotein cholesterol
- Ratio of total chol. to high-density lipoprotein cholesterol
- Triglycerides

- Fasting glucose
- Fasting insulin

- Systolic and diastolic BP were all markedly lower

- HDL-C was **higher**

CR in humans and other animals

Only short term changes can be compared at this time.

Human studies	Matches NIA primate study	Matches Rodent Data
(-) Body weight	Yes	Yes
(-) Fat and lean mass	Yes	Yes
(-) Fasting glucose/insulin	Yes	Yes
(-) Triglycerides	Yes	Yes
(-) Body temperature	Yes	Yes(mouse)/No(rat)