



SPRING Seminar Series

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Why is obesity so hard to treat?

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- Takes a more biological approach to the obesity epidemic, rather than political
 - We need to tackle this issue from a variety of perspectives
- Today we will discuss the regulation of body weight both from a genetic and biomedical point of view
 - Energy Expenditure (EE) in weight perturbed rats, R. Keesey looked at body weight maintenance (overfed or underfed)
 - Rats both overfed and underfed will return to a norm depending on modulation of environment
 - Kcal / body weight^{.75}
 - Why .75? This normalizes the value and allows comparison between species
- Why is body weight (fat mass) regulated?
 - UP**
 - Reproduction
 - Environmental vicissitudes (that occurred in our evolutionary history, e.g. famines)
 - DOWN**
 - Predator evasion
 - Wages of Evolution**
 - Defense against loss of fat mass >> gain
- What is the clockwork that allows for this?
 - **Barsh and Schwartz, Nature Rev Genetics, 3:589, 2002**
 - Hypothalamic lesions: set point hypothesis, body weight is regulated at both extremes (anorexia and overfeeding) and body will strive to return to “set point” weight
 - How does the animal do this? How does it know how fat it is?
 - Brain Signalling – where is the input for this set weight coming from?

- **Ob mouse:** homozygous for obesity (ob/ob)
 - These experiments have shown that there are some satiety signals/receptors:
 - LEPTIN - cytokine molecule (146 Amino Acids, produced almost solely in adipose tissue)
 - Lep -/-
 - Lepr -/-
- Leptin hormone secreted from fat in proportion to mass = cell size x number
 - Adiposity signals: leptin and insulin
 - Satiating signals: ghrelin, CCK, GLP-1, PYY, etc.
- Monogenic forms of obesity
 - Leptin pathway, mutations in genes that alter the pathway and lead to obesity
 - There is a human paralogue for every mutation observed in rats
 - Profound effect on body weight
 - MC4R, 4-6% of individuals with BMI over 40/45 have this mutation
- These mutations do not account for all individuals who are obese in our society, obviously. But there is a strong genetic component.
 - In the past, high energy output (hunting) and environment (famine) led to low adiposity and promotion of fat storage
 - Present, low energy output, food availability
 - The gene selection process may have accelerated 15,000 years not 5 million (when animal husbandry and farming was introduced)
 - Gene pool not designed for our present environment
- Changes in MZ twins with overfeeding and negative energy balance
 - Heritability can be calculated
 - *Refer to diagrams on slides*
- Genome wide association studies
 - There are some genes that are picked up by the GWAS, like MC4R, but some genes play a role in the regulation in body weight but cannot be confirmed by GWAS
 - FTO and MC4R alone help explain body weight in major part of BMI
 - Weighted number of risk alleles can be determined
 - If an individual has 13 (for ex) risk alleles what does that mean for their BMI?
 - 1 and ½ units of BMI is all that you can determine from looking at these risk alleles
 - This means we know there is a lot of genetic information not being picked up by the GWAS
- Leptin threshold effects
 - Signal threshold impedance: LEPR, MC4R, POMC, CPE, CB1R, AGRP, etc.
 - Therapeutically when you reduce the body weight of an individual, you are reducing the amount of fat, and thus reducing the leptin signal

- Symmetric and asymmetric endocrine physiology
 - Individuals have thresholds
 - Obese have higher threshold to get over, and once you hit a point where there is a striking increase in anabolic response
 - Threshold differences between lean/obese but response is the exact same
 - weight response to leptin
 - high doses of leptin given to humans
 - no differences in leptin response between lean and obese humans
 - TEE residuals: if a person increased body weight (10%) and then back down, this does nothing for corrective EE
 - If you continue to lower body weight, 10% and 20%, EE decreases
 - When body weight is pushed below the customary body weight, body is fighting to maintain fat stores (for reproduction, etc.)
 - There is no change in resting energy expenditure when individuals (obese and normal) lose 10 – 20% weight. The non-REE declines significantly – they are more efficiently able to exercise. Fuel efficiency!
 - The muscle reduces its use of glucose
 - If you give leptin to these individuals at -10% bw, the effect goes away. Leptin undoes metabolic consequences of reduced body weight - - restores metabolism of individual to pre weight loss

- Bioenergetics of reduced body weight
 - Hypometabolic state goes away when you add leptin
 - Can you ever correct the threshold? Can the NREE ever self-correct?
 - Hypometabolic state does not go away – set point remains the same (for example, among people who have kept weight down by diet and exercise for several years)
 - Administration of leptin will restore brain to pre-weight loss stage

- Can threshold be raised?
 - Modeled in mice: mice overfed high fat diet for 8 months, then following situations:
 - Group 1: continues to eat high fat
 - Group 2: regular mouse diet
 - Group 3: underfed
 - Group 3: underexpending energy by approx. 10%
 - Its defending its hypometabolic state
 - Group 2: they are also underexpending energy by same amount as group 3
 - i.e. if you keep an animal at an elevated body weight for long enough, it will defend this weight
 - Defense against weight gain is low, defense against weight loss high

- Therapeutically, what does this mean?
 - Weight loss induces a non physiologic state
 - Treatment would be better if we tried to figure out how to restore normal physiology once people have reduced their weight
 - It may be easier to remedy the hypo metabolic state, to eumetabolic state
 - Since most people can lose weight, but its hard to keep it off