Obesity in aging: Hormonal contribution
Hormonal issues in obesity and aging

- Hormonal role in regulation of energy balance
- Genetic component in hormonal regulation
- Life style contribution to hormonal changes
- Age-associated hormonal changes
- Hormonal solutions to obesity
Hormonal role in regulation of energy balance

- Oscillations around energy balance lead to compensatory behaviors and hormone secretion
- Insulin
- Insulin, GH, IGF-I
- Counter-regulatory hormones
  - glucagon, catecholamines, GH, cortisol
- Leptin
Energy regulation = oscillations around energy balance

- Energy expenditure triggers energy release through counter-regulatory hormones
  - GH, cortisol, catecholamines for lipolysis and glycogenolysis

- Energy intake triggers nutrient absorption and glycogen, protein and fat synthesis
  - insulin (with GH, I)
Metabolic effects of GH

- **Carbohydrate metabolism**
  - increased plasma glucose
  - decreased cellular glucose utilization

- **Lipid metabolism**
  - lipolysis after 1 hr delay
  - abdominal (visceral) depot

- **Protein metabolism**
  - IGF-I and growth factors
Metabolic effects of cortisol

- Anabolic and catabolic actions
- Glucoregulatory actions
  - gluconeogenesis
  - glycogen synthesis
- Lipid metabolism
  - lipolytic with GH
  - lipogenic with insulin
Cortisol and obesity

- Cushing’s syndrome
- Oversecretion of cortisol
- Fat deposition
  - visceral
  - facial
  - back of the neck
Metabolic effects of catecholamines

- **Lipid metabolism**
  - lipolysis
    - beta1
    - beta2
    - beta3 adrenergic receptors
  - inhibition of lipolysis
    - alpha adrenergic receptors
    - adenosine receptors
  - increased lipid oxidation

- **Carbohydrate metabolism**
Metabolic effects of insulin

- increased nutrient intake
- increased CHO metabolism
- hexose monophosphate shunt
- reducing equivalents for fat synthesis
  - NADPH
Genetic component in hormonal regulation of energy balance

- Pima Indians
  - obesity in USA
  - lean phenotype in Mexico

- Insulin response and sensitivity

- Leptin genotypes
  - ob/ob obesity due to lack of leptin
  - db/db obesity due to lack of leptin receptor
Insulin response and sensitivity

- Genetic variation in
  - responsiveness to food ("externality")
  - insulin response to food
  - cell sensitivity to insulin
Leptin: adipocyte hormone communicating with the brain

- Leptin
  - secretory product of the adipocyte
  - circulates in the blood at concentrations in proportion to the amount of adipose tissue.

- Modulated by
  - metabolic hormones
  - gender
  - development stage
  - current body energy requirements.
Leptin: postulated signaling role

- The primary role of the hormone leptin is to provide information to the central nervous system, primarily hypothalamic areas, about the amount of energy stored in the adipose tissue.

- In the brain, leptin
  - inhibits neuropeptide Y
  - activates energy expenditure
    - physical activity
    - metabolism
Leptin

Adipose Tissue

WEIGHT LOSS

↓ LEPTIN

Hypothalamus

↓ NPY Y5 Receptor

Response to Starvation

↑ Food Intake

↓ Energy Expenditure

↑ Reproductive Function

↑ Temperature

Parasympathetic Tone

WEIGHT GAIN

↑ LEPTIN

Hypothalamus

↓ MSH

MC-4 Receptor

Response to Obesity

↑ Food Intake

↑ Energy Expenditure

↓ Sympathetic Tone
Upon receipt of the leptin signal, the neural networks responsible for energy homeostasis make appropriate changes in energy intake or energy expenditure to maintain the body in energy balance.
Mutations of leptin and leptin receptor genes lead to obesity.

- Leptin is produced by the *OB* gene
- *ob/ob* mutation lacks leptin and is obese
Leptin receptors

- Leptin receptor is coded by the **DB** gene.
- **db/db** mutation results in abnormal mRNAs made coding for a nonfunctional receptor.
- **db/db** mice become fat because they can’t respond to the weight-regulating product of the **ob** gene, leptin.
Leptin receptors (continued)

- Abnormal RNA splicing of noncoding introns in ob/ob genotype
- mRNA produces the long form of the receptor interrupted by an abnormal insert.
- The extra piece of RNA contains a signal that prematurely stops production of the receptor protein
- Instead of the long form of the receptor, it makes a short form that lacks signaling ability
- Truncated receptors cannot produce STAT signals
Mutation of the db gene

Normal

Ob-R gene

Ob-R mRNA

Ob-R protein

Intracellular signals

Ob

Stop

db/db Mutant

Point mutation

Ob-R gene

Ob-R mRNA

Ob-R protein

No Intracellular signals
Role of leptin in mice

- Mutations in the \textit{ob} gene block the synthesis of leptin in \textit{ob/ob} and wild-type mice.

- Injecting \textit{ob/ob} and wild-type mice with leptin resulted in a dose and time-dependent decrease in body weight.

- Leptin-induced weight loss in \textit{ob/ob} mice was due to:
  - increased oxygen consumption
  - higher body temperature
  - increased locomotor activity
  - decreased food intake.
Role of leptin in humans

- In most cases the *ob* gene is functionally normal in human obesity.
- Obese humans have high leptin levels and are insensitive to leptin.
- A mutation in the *db* gene, which causes a defect in the receptor may interfere with peripheral signals of the level of obesity.
- Leptin probably plays a minor role in human obesity.
Life style contribution to obesity in aging

- Meal eating
- Secular changes in nutrient intake
- Inactivity
- Stress
Meal eating

- Inverse relationship between meal size and body fatness
- Societal pressure to eat spaced large meals
- Meal sizes in USA vs Europe
- Large meals lead to oversecretion of insulin
Huge and calorically dense servings offered commercially

- Au Bon Pain Blueberry muffin
- 430 Kcal and 18 grams fat
Huge and calorically dense servings offered commercially

- Cinnabon cinnamon roll
- 670 Kcal and 34 g of fat
Huge and calorically dense servings offered commercially

- Pizza Hut
  - Pepperoni
  - Lover’s Pan
  - Pizza, 2 slices
- 700 Kcal and 34 grams of fat
Huge and calorically dense servings offered commercially

- Deli tuna salad sandwich with mayo
- 833 Kcal and 56 grams of fat
Fat synthesis due to large meals

- RQ > 1 indicates fat synthesis
- Only when carbohydrate load/meal is excessive
Secular trend in food and nutrient intake

- Calories level
- Fat intake on the rise
- Carbohydrate intake in decline

Fat intake: added fats

- Fat intake continues to rise
- Fat accumulation is largely due to increased fat intake
Age-associated hormonal changes

- Insulin oversecretion and resistance
- GH undersecretion
- Thyroid hormone undersecretion
- Menopause and andropause
- Adrenopause
- Changes in the pattern of hormone secretion
- New hormone synergisms
Insulin oversecretion and resistance

- Aging is often associated with obesity
- Reduced insulin-induced glucose uptake is seen both in aged and obese
- This is due to reduced peripheral sensitivity to insulin, principally in the muscle
Insulin oversecretion and resistance

- Aging is often associated with obesity
- Oversecretion of insulin is seen in both aged and obese
- High fasting plasma insulin
Age-associated hormonal changes

- GH undersecretion is a manifestation of somatopause
  - reduced lipolysis
  - reduced IGF-I and lean tissue growth

- Thyroid hormone undersecretion
  - About 10% of older women are hypothyroid
  - reduced T3/T4 is associated with reduced mitochondrial oxidative metabolism
Age-associated hormonal changes

- Menopause and andropause
  - Sex hormones suppress LPL (dietary lipid uptake)
  - Visceral fat has more androgen receptors than E2 receptors
  - Sex hormones stimulate IGF-I secretion
  - Sex hormones influence levels of physical activity

- Reduced sex hormone binding globulin
Age-associated hormonal changes

- Adrenopause
  - secretion of glucocorticoids remains normal
  - secretion of DHEA or DHEAs declines

- Changes in the pattern of hormone secretion
  - less distinct hormone pulses produce less distinct biological effects
Age-associated hormonal changes

- New hormone synergisms:
  - Reduced joint lipolytic effect with cortisol

- Reduced GH secretion

- Life stresses
  - Increased trough cortisol values are associated with increased abdominal fat

- Increased insulin secretion
  - Increased lipogenic effect with cortisol
Hormonal solutions to obesity: the magic bullet

- **Cholecystokinin injections**
  - increased satiety signal

- **Insulin receptor drugs**
  - increased tissue sensitivity in spite of obesity

- **GH, GHRH/GHRP injections**

- **Arginine intake**
  - increased IGF-I and lipolysis