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Update on Obesity

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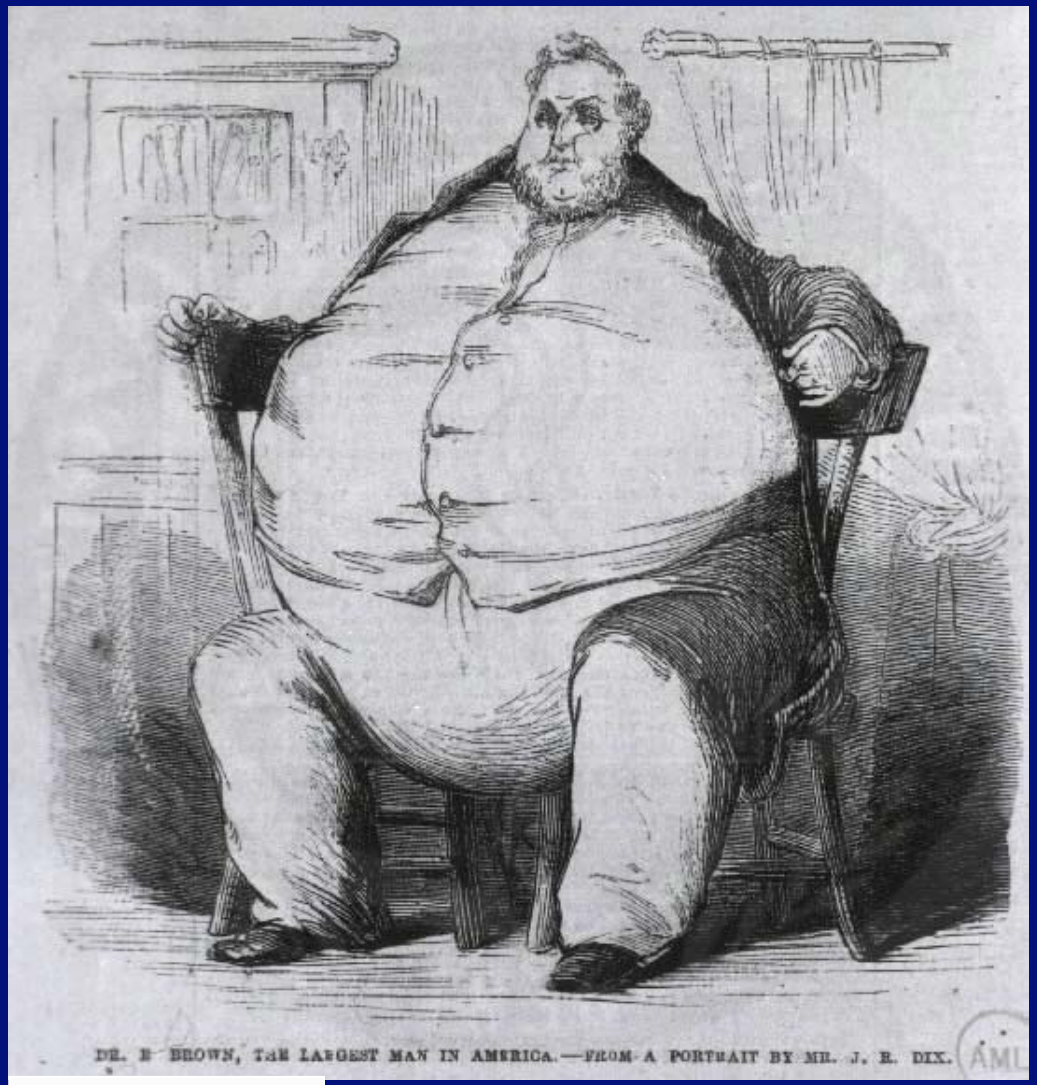
What is obesity?



What is Obesity

Obesity

- Measurement and definition
- Physiology
- Environmental causes
- Genetic causes of obesity
- Endocrine causes of obesity
- Medical risks

Obesity treatment

- Goals of treatment
- Prevention
- Diet
- Exercise
- Behavior modification
- Drug Therapy
  - Specific Drugs
  - Drugs on the horizon
- Gastric surgery

Measurement and Definition

- Increased amount of body fat.
  - Weight (exceptions, such as body builders)
  - BMI
    - BMI=WEIGHT (in kilograms)/HEIGHT in meters)^2
    - BMI=703 x WEIGHT (pounds)/(HEIGHT-in inches)^2.

Classification of Obesity

- BMI 25.0- 29.9 kg/m2 Overweight

- BMI 30.0-34.9 kg/m2 Grade I
- BMI 35.0-39.9 kg.m2 Grade II
- BMI >40 kg/m2 Grade III (morbid) (extreme)

Measurement and Definition

- Distribution of body fat.
  - Upper body (abdomen and flanks, android obesity, "apples")
  - Lower body obesity (legs and buttocks, gynoid obesity, "pears").
  - Visceral adiposity

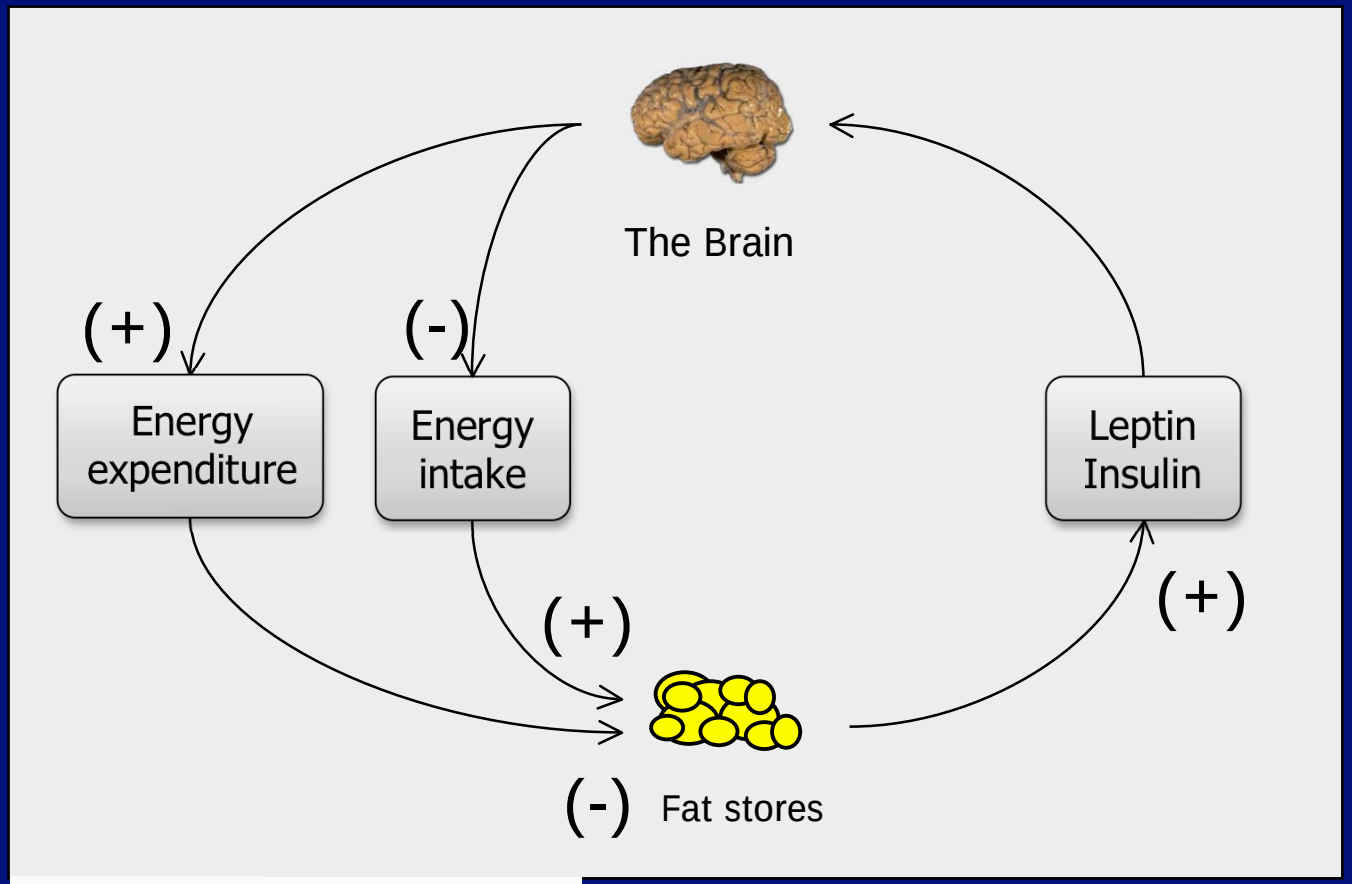
Measurement and Definition

- Research techniques
  - Skin fold thickness
  - Waist : hip ratio
  - Waist circumference
    - >35 inches (88 cm) in women
    - >40 inches (102 cm) in men
  - Bioelectric impedence
  - Infrared interactance
  - Underwater weighing
  - Isotope distribution
  - DEXA
  - CT
  - MRI

Physiology

- Central weight-control center
  - Hypothalamus
- Feed-back control of body weight
  - Leptin and other adipocyte signals
  - Signals from the “gut”
- Balance between energy intake and expenditure

PHYSIOLOGY OF OBESITY



Adapted from Schwartz, M. W. et al. J Clin Endocrinol Metab 2004;89:5889-5897

Physiology: Central Pathways

Anorexigenic

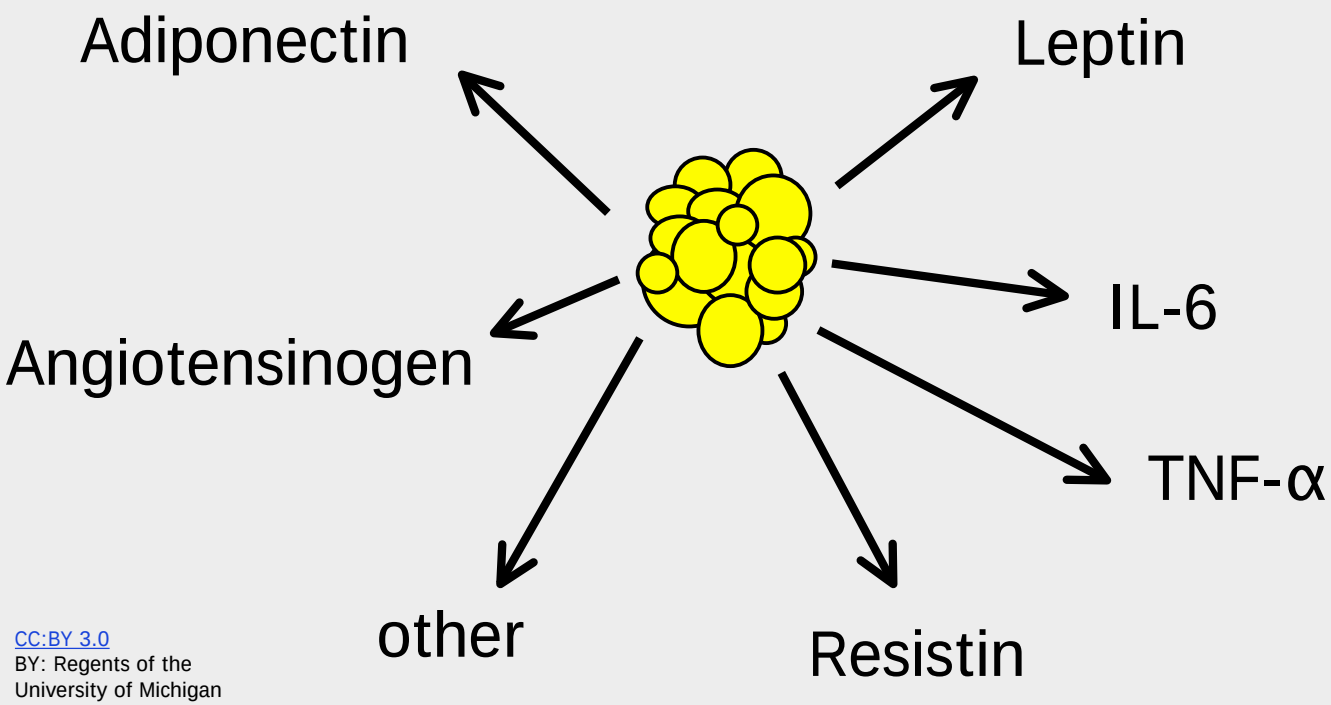
- Leptin
- α-MSH
- CART
- GLP-1
- C-NTF
- CRH/Urocortin
- Neuromedin U
- Serotonin
- CCK
- Insulin
- Bombesin
- Calcitonin
- Enterostatin
- TRH
- IL-1B
- Neurotensin
- Oxytocin
- Vasopressin

Orexigenic

- Neuropeptide Y
- MCH
- AGRP
- Orexin A, B (Hypocretin 1,3)
- Galanin
- Dynomorphin
- Norepinephrine
- B-endorphin

Important to know that complex regulation exists, do not need to know individual factors. Identify Leptin as important.

Adipose Tissue: An Endocrine Organ



Leptin: Of Mice and Man

Image of before and after leptin replacement in mouse removed

Image of before and after leptin replacement in boy removed

Physiology: Leptin

- A 16-KD hormone produced predominantly by adipocytes
- Circulating levels are determined chiefly by fat mass
- Increased leptin synthesis/secretion
  - Re-feeding (after fasting)
  - Adiposity
  - Glucocorticoids
  - Insulin
  - Thiazolidinediones while fasting
- Inhibition of leptin synthesis/secretion
  - Sympathetic stimulation
- Circulates partially protein- bound

Physiology: Leptin

- Leptin receptor:
  - is a member of the cytokine receptor family
  - exists as a number of splice variants
    - the long form signaling via JAK2 and STAT3 to regulate transcription.
    - short receptor forms important for leptin transport, clearance, and signaling via non-J AK/STAT pathways.

- Leptin's chief physiologic role:

  A read out of adiposity and nutritional status, allowing the body to respond to starvation

Physiology: Leptin

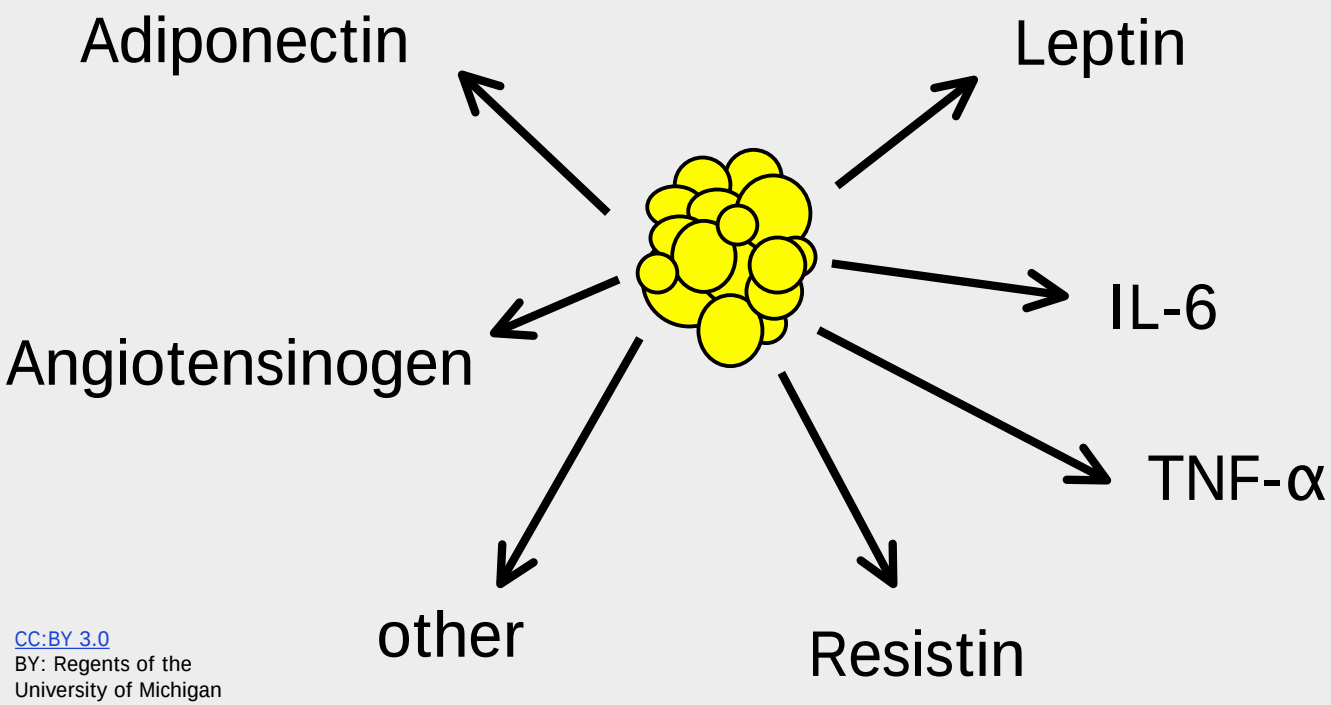
- Leptin's central actions :
  - Increase energy expenditure (via physical activity, sympathetic nervous system activity)
  - Decrease food intake
  - Decrease body weight
  - Increase insulin sensitivity
  - Help signal the onset of puberty
  - Regulate other pituitary hormone axes
- Leptin’s peripheral actions
  - Stimulate angiogenesis
  - Hematopoietic cell proliferation
  - T-cell immnunity

Two key points—the EO rules!

- Fat is not our foe, it is a functional endocrine organ.
  - Too much fat is bad. Too little is also bad

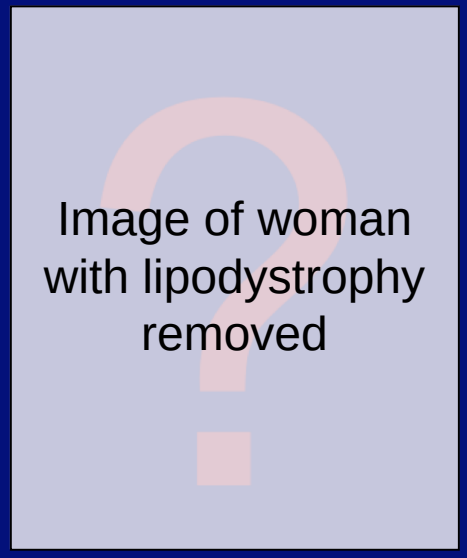
    "Just Right"

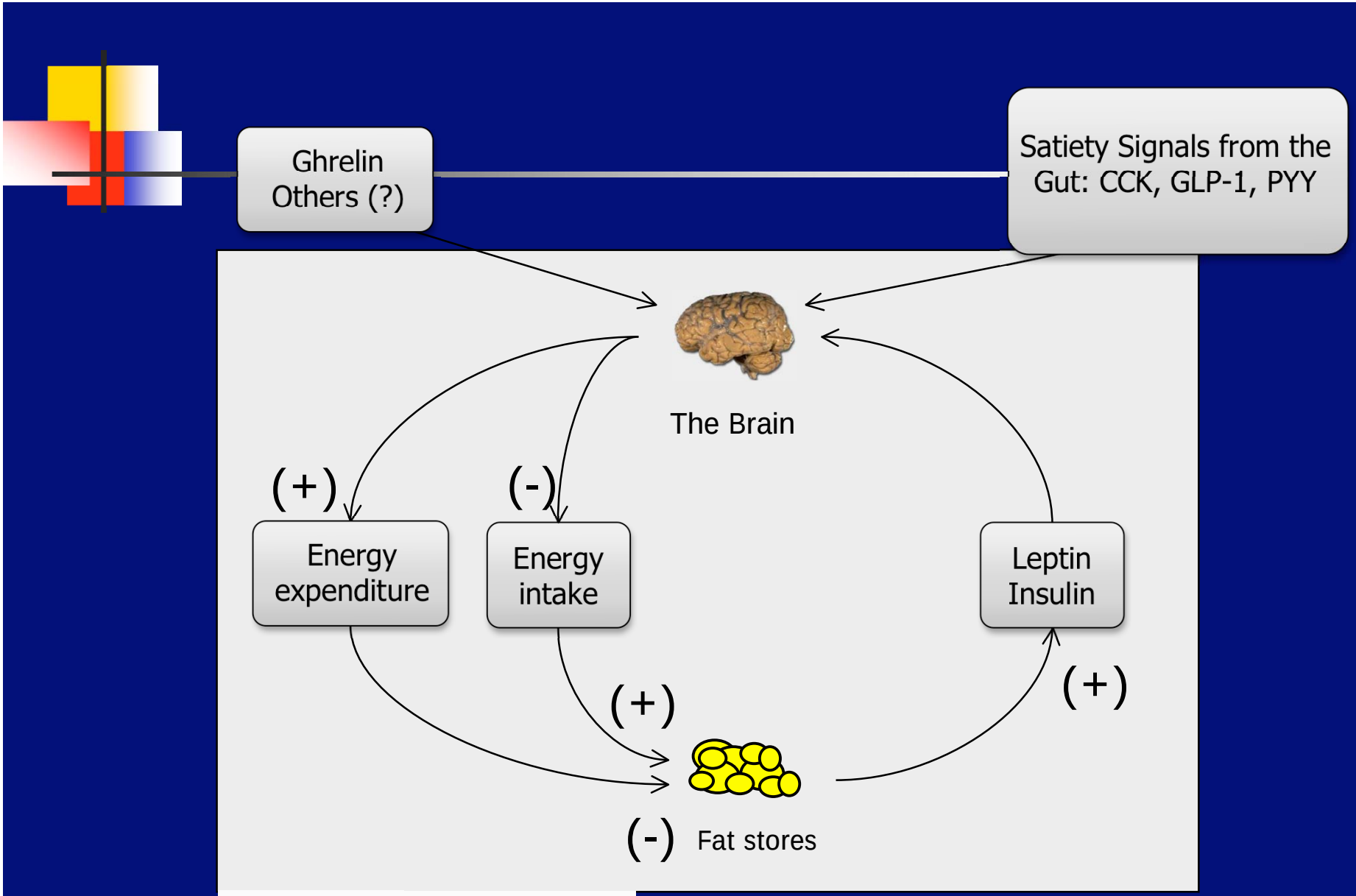
Adipose Tissue: An Endocrine Organ



Lipodystrophy Syndromes

- Paucity of adipose tissue
- Insulin resistance
- Hypertriglyceridemia
- Fatty infiltration of liver and other tissues





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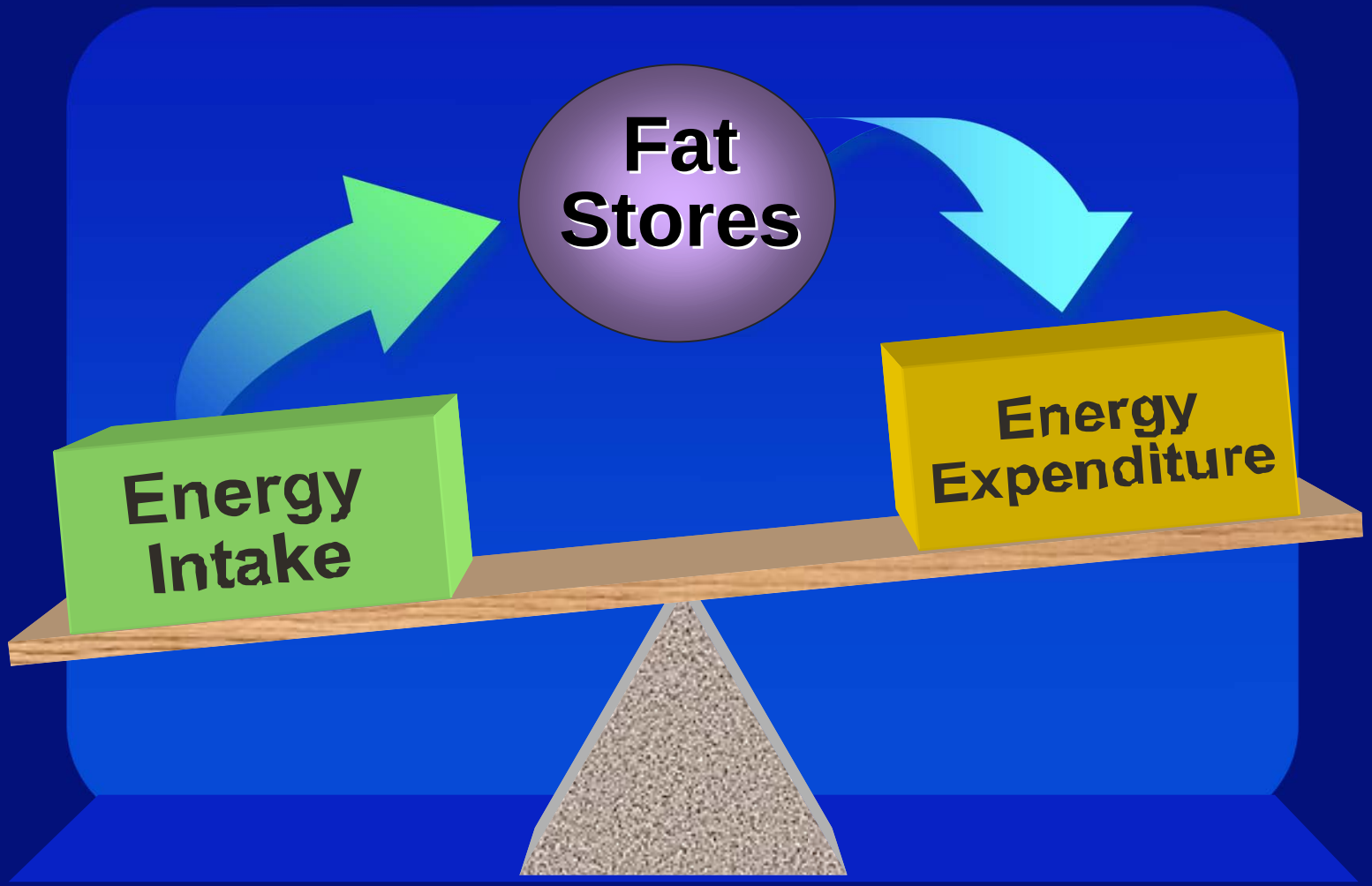
Obesity Is Caused by Long-Term Positive Energy Balance



Balancing Intake vs Expenditure

Changes in the environment

Energy dense food overabundant

Opportunity for expenditure reduced

The Origins of Obesity:
Environment and temptations

Eating habits are learned early

Role of Environment: Increased Food Intake

Wendy's Sandwich	**Big Bacon Classic = 570 kcal**
Wendy's Potatoes, Chili, & Nuggets	**Great Biggie Fries = 530 kcal**
Wendy's Beverages & Desserts	**Large "Frosty" = 440 kcal** **Cola = 140 kcal**

Total 1680 kcal

Decreased Physical Activity

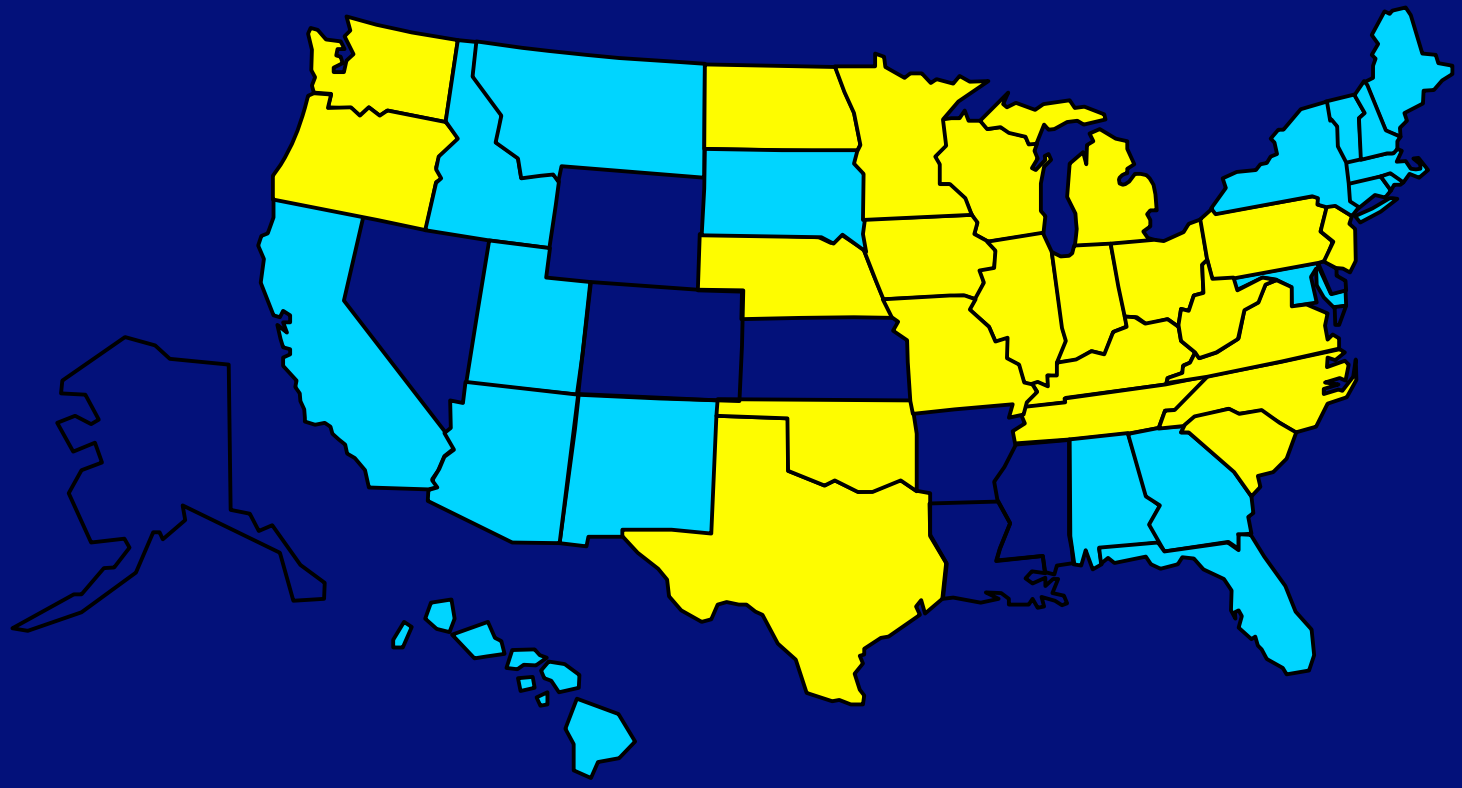
TV

Cars

Computers

One big couch potato

Prevalence of Obesity Among Adults:1989

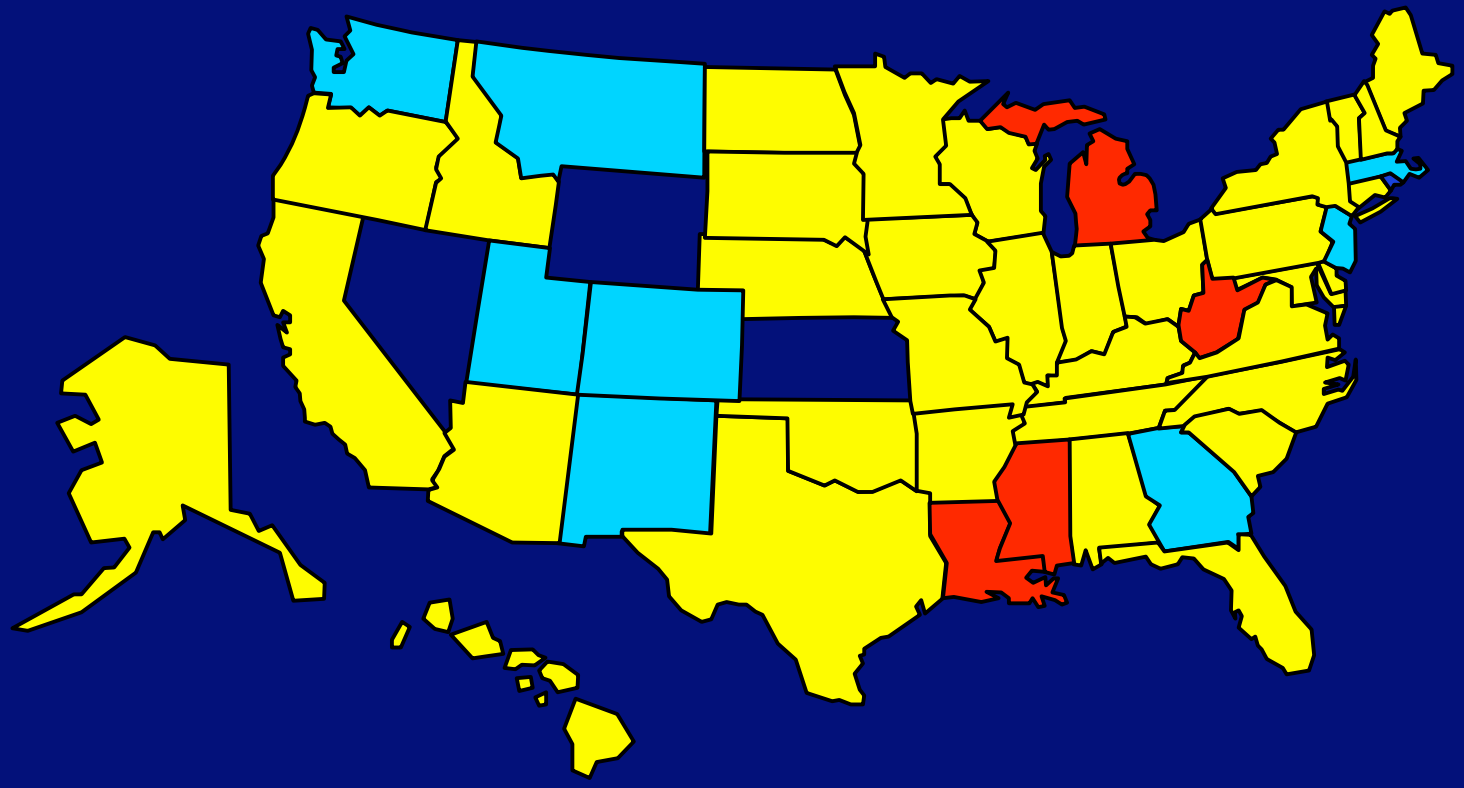


< 10% 10-15% > 15%

Source: Mokdad, et al.

Mokdad A H, et al. *J Am Med Assoc* 2001;286:10

Prevalence of Obesity Among Adults: 1994



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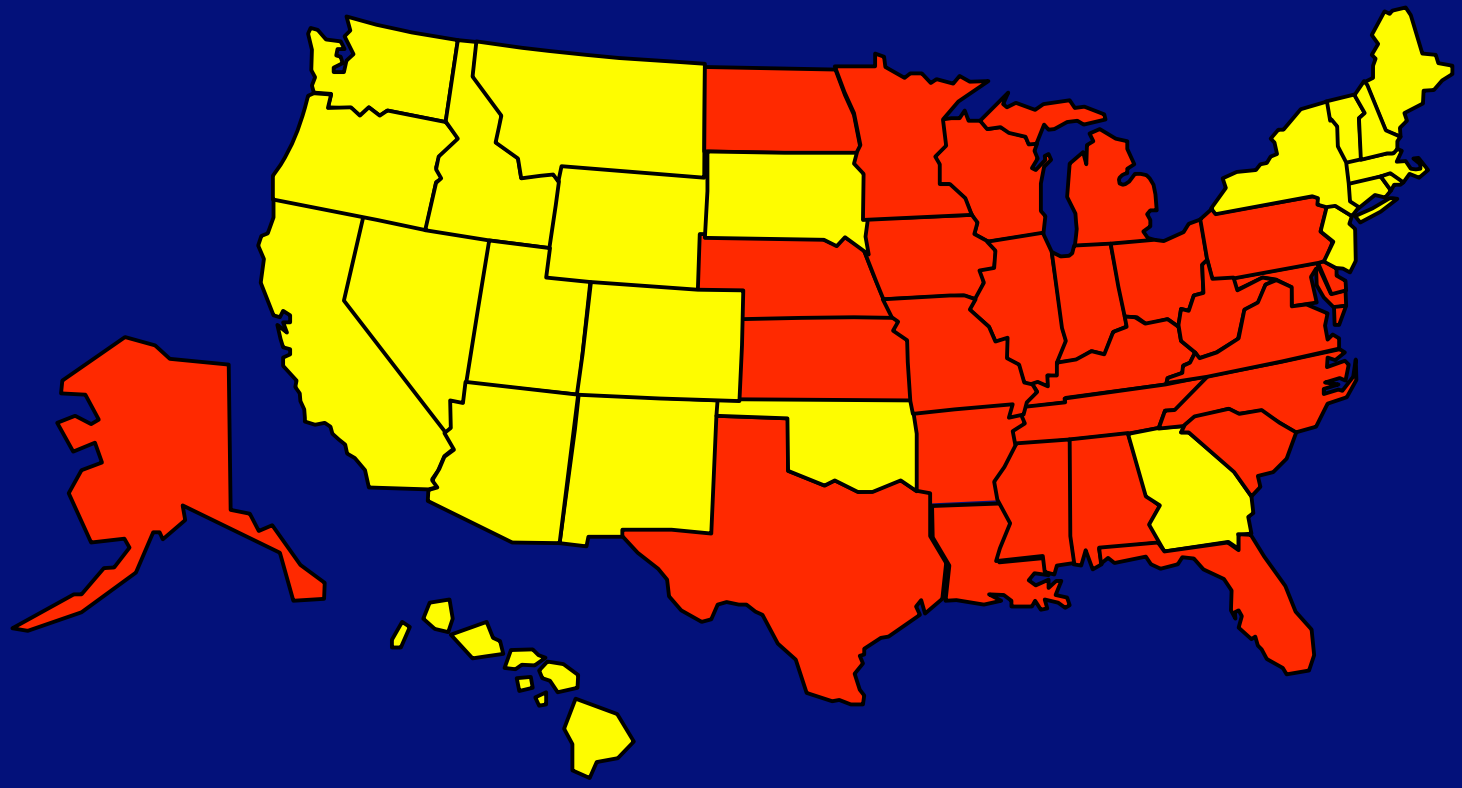

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Genetic bases of obesity

- Big genetic component
  - Estimated at 40-70%
- Most of obesity polygeneic or oligogeneic
  - Thrifty gene hypothesis
- Monogeneic forms of obesity
  - Isolated genes
  - Syndromic obesity

Monogeneic obesity

- Leptin
  - A few families
- Leptin receptor
  - A single family
- MC4-Receptor
  - Most common defect

Endocrine Causes of Obesity

- Hypothalamic injury or tumor
- Cushing's syndrome
  - Hypothyroidism
  - Hypogonadism
  - Growth hormone deficiency
- Polycystic ovarian syndrome
  - Manifestation of obesity versus cause

Heterogeneity

- Important concept
- Not all obese are equal

Medical Risks of Obesity

- Mortality (less in African Americans)
- Insulin resistance/Type 2 diabetes
- Hypertension
- Hyperlipidemia
- Arthritis
- Obesity/hypoventilation syndrome=sleep apnea
- Gallbladder disease
- Cancer (breast, colon, prostate, ovarian, endometrial)

Not increased: osteoporosis or psychiatric disease

Obesity treatment

- Goals of treatment
- Prevention
- Diet
- Exercise
- Behavior modification
- Drug Therapy
  - Specific Drugs
  - Drugs on the horizon
- Surgical therapy

Goals of treatment

- Reduce co-morbidities
- Maintain minimum of 5% weight loss

5-year success only 5%

Key Features of Long-Term Losers

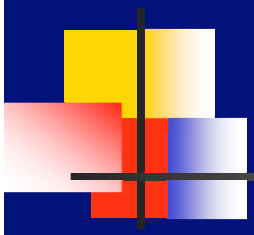
- Adopted a routine exercise regimen
- Weighed routinely (and taking action)
- Eating breakfast, not skipping meals

Diet

- Caloric restriction (fat <30%, unsaturated fat <10%)
- High fat, low carbohydrate diets
  - Regaining popularity
  - CHO<20%, fat >50%
  - Many variations

Two views:

1) Simple law of thermodynamics
2) Human metabolism is complex and futile cycles between CHO and fat metabolism exist. Thus, composition of diet matters.



Exercise

- More benefit than just the calories burned
- Goal: make long-lasting
- Minimum regimen: 30 minutes of brisk walking 5 times a week
  - (Diabetes Prevention Program)
- More active lifestyle: fidget, walk more for chores, use stairs, etc.

Behavior Modification

- Self-monitoring
- Goal setting
- Slow eating rate
- Food log
- Adequate sleep –especially age <40 years

individualized

Obesity treatment

Drug Therapy

- Approved Drugs
- Drugs on the horizon

Approved Drugs

- Sibutramine (Meridia)
- Orlistat (Xenical)
- Other FDA Approved drugs

Two important questions

- *Whom to treat?*
- *For how long?*

Focus on co-morbidities
"Metabolic fitness "

For FDA and insurance carriers:
BMI>30 or >27 kg/m^2 with comorbidities

Sibutramine (Meridia)

- *Approved* : 1998
- *Mechanism:* Serotonin, norepinephrine and dopamine reuptake inhibitor, does not promote serotonin release
- *Responders* lose >4 pounds in the first 4 weeks of treatment
- *Side-effects*: hypertension, increased heart rate, dry mouth, constipation, insomnia, and headache
- *Contraindicated* with PPH, valvular heart disease, MAOI or serotoninergics

Orlistat (Xenical)

- *Approved*: 1999
- *Mechanism:* non-absorbed inhibitor of pancreatic lipase.
- Administered with meals
- *Side-effects:* GI bloating, flatus, oily stools, urgency, fat leakage, deficiency of B-carotene and A,D,E,K vitamins
- *Contraindicated* in chronic malabsorbtion, cholestasis, known hypersensitivity
- Improves lipid status and slows progression to diabetes

Phentermine (Adipex, Ionomin, Fastin)

- Approved for short-term use only
- Mechanism: Adrenergic
- Side-effects: over-stimulation and nervousness, insomnia, and headache
- Contraindicated with PPH, valvular heart disease, symptomatic cardiovascular disease, glaucoma, moderate hypertension

Drugs not indicated

- Fluoxetine (Prozac)
- Thyroid hormone
- Androgens
- Growth hormones
- Amphetamines
- Diueritcs
- Digitalis

Other approved drugs with weight loss potential

- Exanatide - -(Byetta)
- Metformin- - (Glucophage)
- Pramlinitide- - (Symlin)
- Topiramate – (Topamax)
- Zonisamide
- Other mood-stabilizers (Buprapion, etc).

Drugs on the horizon: in later stages of development

- Leptin
- Cannabinoid Receptor 1 Antagonist: Rimonabant (ACCOMPLIA)

  Newer generation under development
- New intestinal lipase inhibitor-ATL692
- PYY 3-36
- Growth hormone fragment AOD9604 (aa 177 to 191)

Bray G: Medical Clinics of North America 91 (2007):1225-1253

LEPTIN (recombinant human methionyl leptin METRELEPTIN ; AMYLIN CORP.)

- Administered subcutaneously
- Very effective in leptin-deficiency related obesity (mutations in *ob* gene)
- Phase II in general obesity with a wide range of effect in individuals
- Factors that determine responders not clear (relative deficiency at baseline?)
- Role in long-term weight maintenance?
- Role in combination therapies?
- Surprising metabolic benefits in lipodystrophy, role in HIV lipodystrophy?

Cannabinoid Receptor 1 Antagonist: Rimonabant (ACCOMPLIA, Sanofi)

- Works by selectively blocking the CB1 receptors, helping normalize the over-activation of the Endocannabinoid System
- Weight loss
- Less food-craving
- Less tobacco-craving
- Improved lipid profiles with raised HDL levels
- Improved insulin sensitivity
- Side-effect tolerability (?): profound nausea / dysphoria or depression, increased suicide (?)
- US market projected date: FDA rejected in 2007, but approved in Europe and Canada

Emerging Concepts in Medical Therapy

- Chronic therapy (continuous or intermittent)
- Individualized therapy (one-drug-for-all not realistic)
- Combination therapy (very successful preclinical results with Symlin and Leptin combination)

Surgical Treatment of Obesity

- Highly effective and reduces mortality
- 1% mortality
- Life-long commitment with behavior modification
- Life-long need for medical follow-up
- Indications:
  - BMI>40 (or >35 with co-morbidities)
  - Failure of previous weight loss attempts
  - Well-informed and highly motivated patient

Some considerations

- Patients need to understand
  - What is going to happen
  - Requirement of a support system
  - Eating disorders and emotional eating need to be addressed
  - Lifelong need for supplementation
  - Unknown medical risks
    - Exaggerated reactive hypoglycemia?

PEDIATRIC OBESITY

- Extreme cases deserve work-up for specific monogeneic or syndromic causes
- Major goal: prevent adult obesity and co-morbidities
- Focus on diet/exercise and behavior modification (stress adequate sleep)
- Only approved drug: Orlistat

CONCLUSIONS

- Treatment of obesity should be directed at achieving metabolic fitness.
- Diet, exercise, behavior modification are rarely effective for long-term.
- No magic bullet exists so far.

Sample Question 1

- If a patient has height of 150 cm and a weight of 150 kg, how would you classify this patient's habitus?
  - A) Normal weight
  - B) Overweight
  - C) Mildly obese
  - D) Morbidly obese

Sample Question 2

- What would you like to know before you assume that patient needs therapy for his condition?

Sample Question 3

- What would you recommend as the first step of his management?
- For how long?
- What would be the goal for his therapy?
  - If he returns to his 6 month f/u visit with a weight of 140 kg, what would you recommend next?
  - What if he had returned at 160 kg?

Sample Question 4

- What gene defect is responsible from the most common monogeneic form of obesity?

Sample Question 5

- What are the predictors of successful weight maintenance for long-term?

Disclaimer—remember when evaluating the lecture quality...

- Dr. Kumagai is responsible for the contents of this lecture, though he will adamantly refuse responsibility and blame Dr. Lash for how boring it is.
- Dr. Oral is a very pleasant person and cannot take criticism very well.