Hormonal Regulation of Nutrients Food intake & Obesity

PHRM 142

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- √ Endocrine pancreas . . .
- √ Pancreatic Hormones . . .
 - $\sqrt{\text{Properties}}$, Secretion & Actions . . .
- Hormonal Regulation of Nutrients
 - Responses to feeding & post-absorptive state
 - Effects of Exercise
- ❖ Food intake & Obesity

Regulation of Blood Nutrient Levels

Soon after a meal, blood levels of nutrients, such as glucose, amino acids, and fatty acids, increase.

Stomach

Nutrients enter the blood.

Parasympathetic stimulation and increasing blood glucose levels & G cause increased insulin secretion from the pancreas.

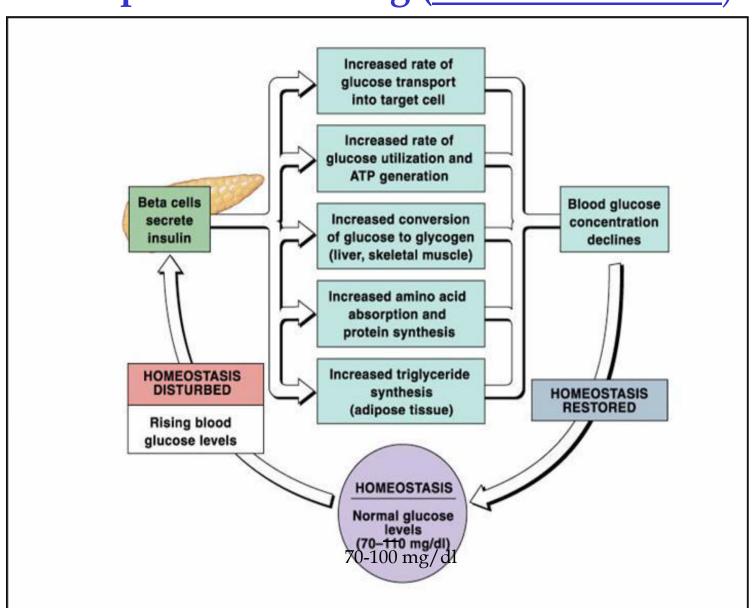
Pancreas

Pancreas

Nutrients move into cells.

Figure. 18.18, Seeley

Regulation of Blood Glucose Concentration Response to Feeding (soon after a meal)



Martini Fig. 18-19

Regulation of Blood Nutrient Levels

nutrient levels decline. nutrient Decreasing blood nutrient levels Decreasing blood glucose levels Decreasing blood glucose levels Decreasing blood levels and increasing sympathetic and increasing sympathetic cause increased GH secretion. cause increased cortisol stimulation cause insulin secretion stimulation cause increased to decrease. glucagon secretion. incr. GH incr. cortisol decr. insulin <u>incr. glucagon</u> Most cells Liver Adipose tissue Releases glucose, Glucose uptake Releases fatty decreases and ketones, and acids into switches to fat triglycerides into circulation and protein circulation

metabolism.

In post-abosorptive state

Within 1-2 hours after a meal.

Figure 18.18, Seeley

Hormonal changes in post-absorptive state

* Decreased insulin secretion

- Decreases muscle uptake of glucose
- Increases hepatic glycogenolysis & gluconeogenesis
- Increases lipolysis

* Increased glucagon secretion

Increases hepatic glycogenolysis & gluconeogenesis

Increased cortisol secretion

- Increases protein catabolism
- Increases gluconeogenesis
- Increases lipolysis

* Increased Growth hormone

- Antagonizes the action of insulin on glucose utilization in muscle
- Activates lipolysis
- Facilitates gluconeogenesis

Table 19-2, G&G

Short-Term Starvation

- ❖ 3 7 day fast → continuation of processes begun in post-absorptive state.
 - Gluconeogenesis, lipolysis, ketogenesis all stimulated.
 - Increased protein catabolism.

Long-Term Starvation

- ❖ At > 7 days fasting:
 - Protein catabolism ↓
 - Blood ketone ↑
 - Brain utilization of ketones ↑ (reduces dependence on glucose).

Regulation Short-term exercise of Blood **Nutrients** During Exercise

Sympathetic stimulation increases epinephrine secretion from the adrenal medulla and glucagon secretion from the pancreas. It also inhibits insulin secretion from the pancreas.

Glycogenolysis in muscle & less G uptake

Epinephrine increases the rate at which glycogen in muscle cells is broken down to glucose. The glucose is used as an energy source in muscle cells. The muscle cells take up less glucose from the blood and increase their rate of fatty acid metabolism.

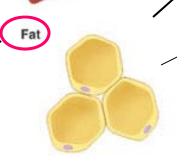
Gly<u>cogeno</u>lysis in liver

Epinephrine and glucagon increase glycogen breakdown to glucose molecules in the liver. The glucose molecules are released into the circulatory system.

ipolysis in adipose

Epinephrine and sympathetic stimulation also increase the breakdown of fat and the release of fatty acids from adipose tissue.

Blood glucose levels are maintained for normal nervous system function.



Blood nutrients

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Muscle

Liver



Seeley Fig. 18.19 Copyright © The McGraw-Hill Companies. Inc. Permission required for reproduction or display.

Regulations of Blood Nutrients During Exercise

Exercise Muscle Prolonged exercise ACTH and GH release from the anterior pituitary increase. ACTH stimulates increased cortisol secretion from the adrenal cortex. Pr. Catabolism& Gluconeogesis Cortisol Increases protein breakdown in muscle and the liver to amino acids, and increases glucose synthesis from amino acids and from some components of fat, such as glycerol. Fat catabolism Cortiso Increases the breakdown of fats and the use of fatty acids by muscle cells as an energy source. GH slows the breakdown of proteins and helps conserve them, thus increasing the dependence on fats as an energy source. Blood glucose levels are **Blood nutrients** maintained for normal nervous system function and there is an

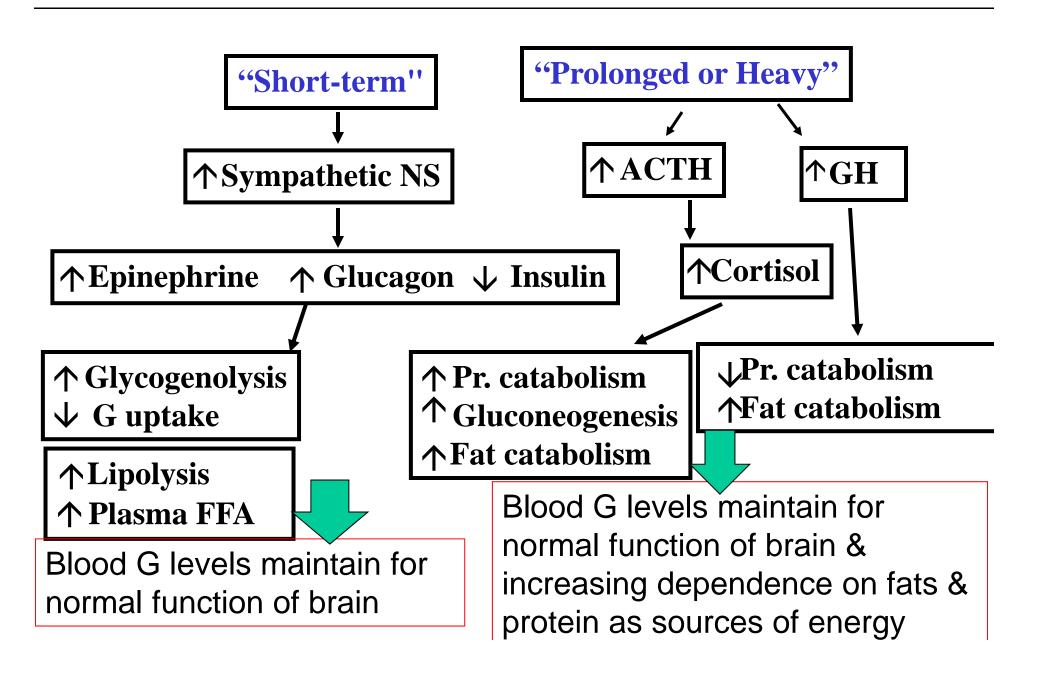
increasing dependence on fats and

proteins for energy sources

Seeley Fig. 18.19

Short-term/Heavy Exercise | REVIEW





- √ Endocrine pancreas . . .
- √ Pancreatic Hormones . . .
 - √ Properties, Secretion & Actions . . .
- √ Hormonal Regulation of Nutrients
- Food intake & Obesity . . .

Obesity

* The presence of "abnormal or excess" amount of body fat leads to higher body weight.

- (e.g., Wt: 120 pounds \approx 54 kg & H: 1.60 m)
- BMI: 54 / 2.56 = 21 1 pound = 0.453 kg

Classification of overweight & obesity based on BMI

	BMI (Kg/m²)	
Underweight	< 18.5	
Normal	18.5-24.9	
Overweight	25.0-29.9	
Obesity		
Grade I	30.0-34.9	
Grade II 35.0-39.9		
Grade III > 40.0		

G&G, Table 21-1.

❖ Waist/Hip Ratio (WHR of Healthy women=<0.8 and men=<0.9)</p>

Diseases Associated with Obesity*

- Hypertension
- Hyperlipidemia & Dyslipidemia
- Atherosclerosis, Coronary Heart Disease, MI & Stroke
- Type 2 Diabetes "Chicken-or-egg" relationships . We view obesity as both cause & consequence of type 2 diabetes!
- Gallbladder Disease
- Osteoarthritis
- Cancer (e.g. endometrial, breast, prostate, and colon cancer)

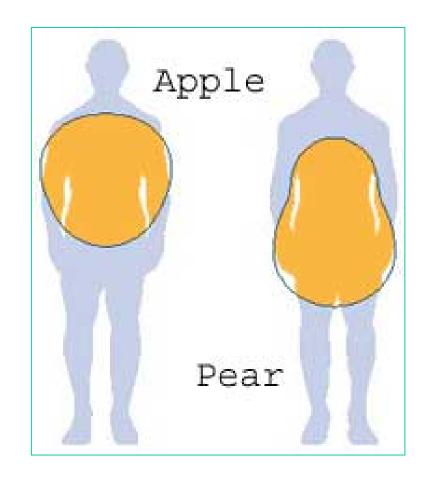
Metabolic syndrome

- A group of risk factors that increases the risk of CVD, stroke and other health problems, such as diabetes.
 - A large waistline: <u>central or abdominal obesity</u> (For men: 40 inches or larger; For women: 35 inches or larger)
 - A high triglyceride level (150 mg/dL or higher) or using a lipid I lowering agent
 - A low HDL level (< 40 mg/dL in males, < 50 mg/dL in females) or using a lipid lowering agent
 - High blood pressure (systolic BP > 130 or diastolic BP > 85 mm Hg) or using a BP lowering agent
 - High fasting plasma glucose level (FPG) (>100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes
- To be diagnosed with metabolic syndrome, you would have at least three of these risk factors.

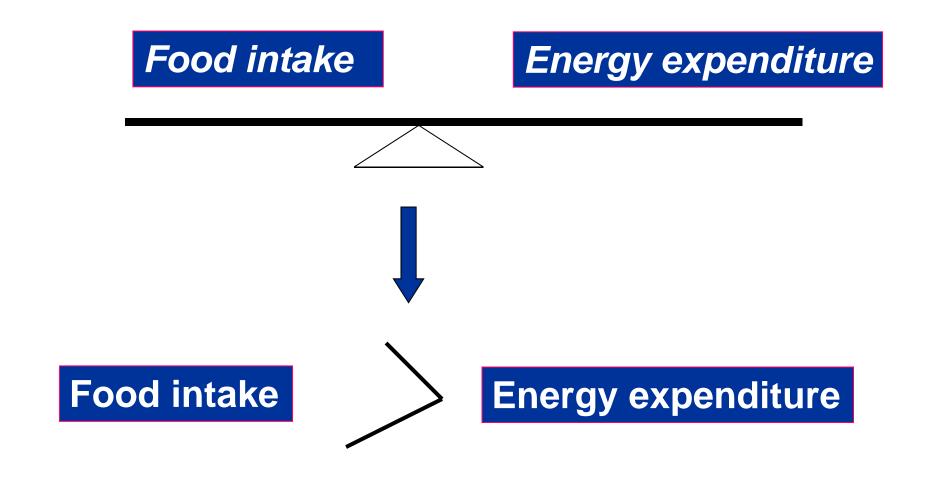
Abdominal obesity!

Is the Apple or Pear-Shaped Body Type More Dangerous?

❖ A new research from Cambridge (The Lancet, August 2012) is challenging the medical notions that "apple-shaped" people with more fat around their waist are at higher risk of MI and strokes than "pear-shaped" people with fatter bottoms and hips.



Obesity: Metabolic Disorder of Energy Balance



ob/ob Mouse Model of Obesity

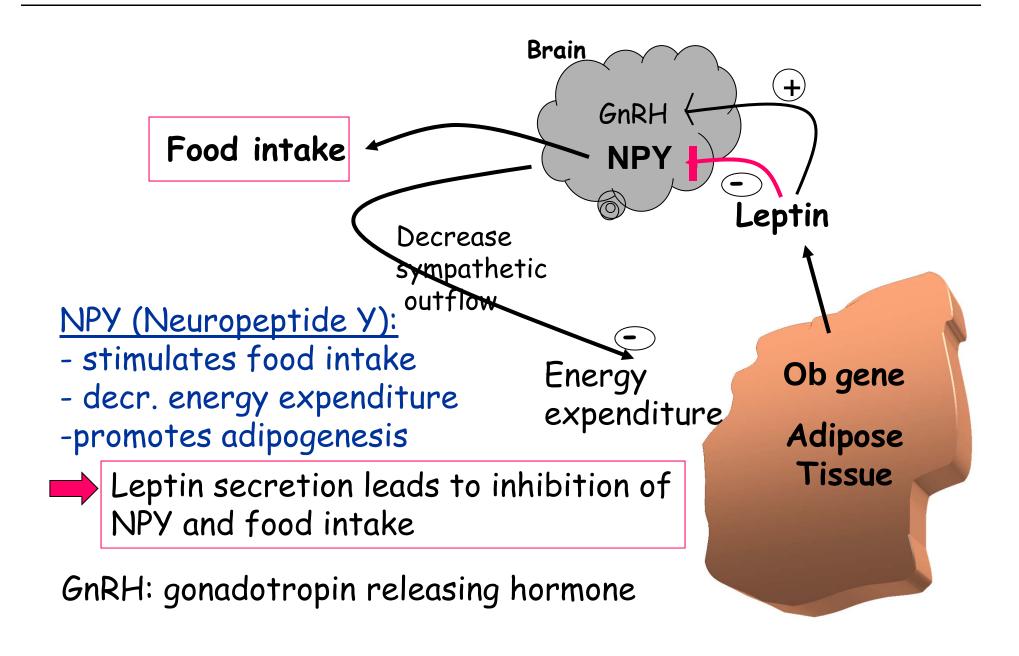
- The mouse ob gene encods a 167 aa protein named leptin.
- Human leptin shares 84% sequence identity to mouse leptin.
- A link exist between obesity and leptin resistance.



A comparison of a ob mouse with leptin deficiency (left) and a normal mouse (right)

Background ob Gene One single mutation Produced in Encodes Leptin Hormone Adipose tissue Causes Leading to Secreted to 20 fold increase in Leptin deficiency + abnormal ob mRNA Circulatory system Results in Distributed to Obesity Other organs Hyperphagia Insulin resistance Controls Hyperglycemia Food intake Hyperinsulinemia

How can leptin control food intake?

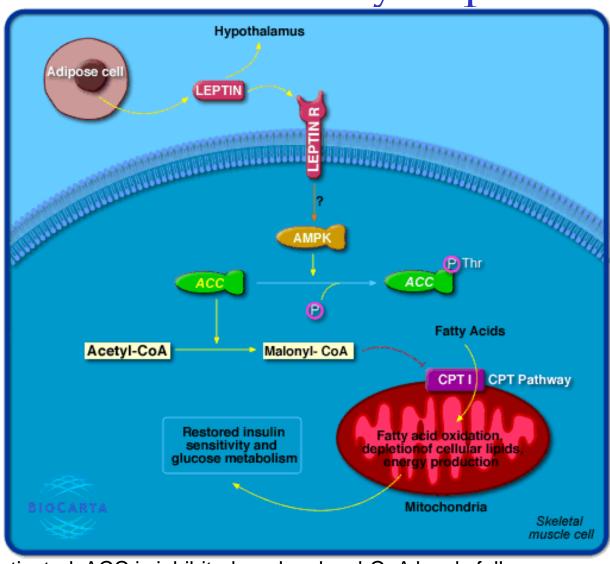


Is there a specific receptor for leptin?

- Located in brain as well as in peripheral tissues:
 - SKM, liver, kidney, pancreas, GI, heart

Reversal of Insulin Resistance by Leptin

- Insulin resistance of type II diabetes partly due to high levels of lipids in SKM.
- SKM is one of the primary glucose-consuming tissues, giving it a central role in insulin resistance.
- Leptin activates AMPK.
 AMPK phosphorylates and inactivates ACC, acetyl-CoA carboxylase.
- ACC catalyzes the production of malonyl-CoA from acetyl-CoA.
- Malonyl-CoA in turn is an inhibitor of the import of fatty acids into MQ by carnitine palmitoyl-transferase I for oxidation and energy production .



In presence of leptin, <u>AMPK is activated</u>, <u>ACC is inhibited</u>, and <u>malonyl-CoA levels fall</u>, <u>increasing the oxidation of FA</u> and <u>reducing the lipid content of cell</u>s. The reduced lipid content in SKM <u>allows</u> insulin signaling & glucose consumption to return to their normal levels, reducing insulin resistance.
Adapted from BioCarta

Summary: Reversal of Insulin Resistance by Leptin

- Insulin resistance of type II diabetes partly due to high levels of lipids in liver and SKM.
- ❖ Leptin acts directly on liver and SKM cells where it <u>activates</u> <u>AMPK and stimulates FA oxidation in mitochondria</u>. This reduces the storage of fat in those tissues.
- The <u>reduced fat content</u> in SKM and liver <u>allows</u> insulin signaling & glucose utilization to return to their normal levels, reducing insulin resistance or increasing insulin sensitivity.
- In liver, reduces gluconeogenesis

In Obesity:

- Defect may be present in:
 - Leptin
 - Leptin transport across bbb
 - Leptin receptors (db/db mouse model of diabetes)
 - Leptin signal transduction
 - Human obesity involves <u>leptin resistance</u> in the face of <u>high endogenous leptin rather than leptin deficiency</u>.

Additional Factors Causing Obesity

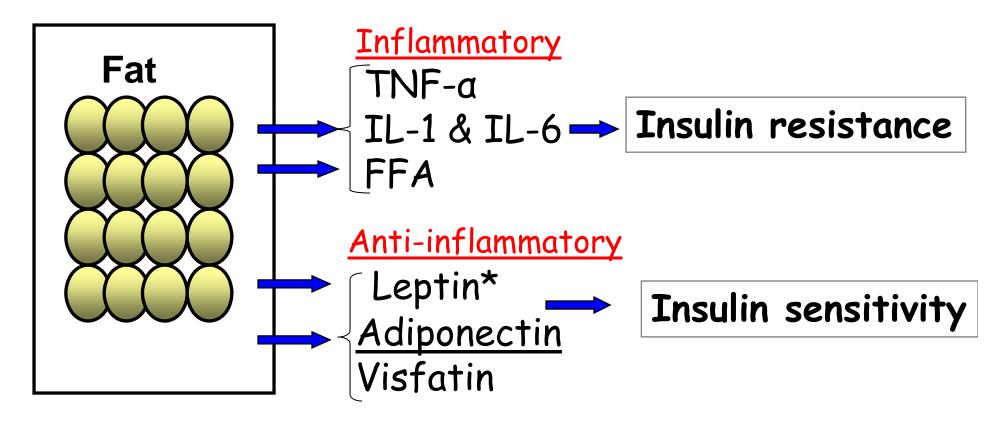
- Underlying disease (eg., hypothyroidism)
- Eating disorders
- Certain medications (eg., anti-psychotics)
- Inactive lifestyle
- Insufficient sleep!
 - Increased Ghrelin (a hunger hormone), decreased
 leptin (a hormone that tells your stomach that it's full)
- Chronic stress!
 - increased Ghrelin may predispose people to posttraumatic stress disorder (PTSD)
- Sudden smoking cessation

Some Facts Regarding Obesity

Number of fat cells is likely established during infancy, and obesity during adulthood may result from <u>hypertrophy</u> rather hyperplasia.

Where fat is deposited is more important than how much is deposited. Visceral or central obesity is far more important than subcutaneous or peripheral fat. (Atten: New research from Cambridge published in the Lancet, 2012)

Specific Role of Adipocyte-released Secretagogues



- □ Adipocytes, consisting of over one billion cells not only store TG in fat depots to provide energy reserves, but constantly communicates with other tissues by adipocyte-released secretagogues.
- \square <u>Visceral fat depots release inflammatory adipokines</u>, along with FFA, provide the pathophysiologic basis for insulin resistance & type 2 diabetes.

Anti-inflammatory Secretagogues

- To counter the inflammatory secretagogues (eg., FFA, TNF-α), adipose cells also secrete anti-inflammatory hormones, such as adiponectin and visfatin.
- Adiponectin, visfatin and leptin enhance insulin sensitivity.
- Adiponectin deficiency, inflammatory adipokines and excessive FFA, all contribute to insulin resistance, obesity, hypertension, dyslipidemia, and atherosclerosis.
- Interestingly, <u>leptin</u> may act as both an anti-inflammatory and pro-inflammatory secretagogue, in that it enhances insulin sensitivity for glucose uptake in muscle but may promote some inflammation and angiogenesis at other sites.

Treatment of obesity

- Diet & Physical activity
- Medications
 - Appetite suppressant drugs such as amphetamines and *leptin**
 - Drugs such as NPY inhibitor promotes weight loss (e.g. fluoxetine)
- Thermogenic agents
 - such as leptin* and exercise (exercise is most effective prescription for weight loss)
- Surgical treatment of obesity

Treatment of obesity

- Although administration of leptin may be effective in a few who are leptin deficient, most obese individuals are leptin resistant & have high levels of leptin.
- ❖ This explains in part why administration of leptin has not been shown to be effective in suppressing appetite in most obese.
- But why amphetamines and SSRI?

TABLE 140-2. Effects of Various Neurotransmitters, Receptors, and Peptides on Food Intake

Neurotransmitter/ Receptor/Peptide	Action	Food Intake
Norepinephrine	Increase concentration	Decrease
α1	Stimulate receptor	Decrease
α_2	Stimulate receptor	Increase
β_2	Stimulate receptor	Decrease
Serotonin	Increase concentration	Decrease
5-HT _{1A}	Stimulate receptor	Increase
5-HT _{1B}	Stimulate receptor	Decrease
5-HT _{2C}	Stimulate receptor	Decrease
Histamine		
H ₁	Stimulate receptor	Decrease
H ₃	Stimulate receptor	Decrease
Dopamine	·	
D_1	Stimulate receptor	Decrease
D ₂	Stimulate receptor	Decrease
Leptin	Increase concentration	Decrease
Neuropeptide Y	Increase concentration	Increase
Galanin .	Increase concentration	Increase