Hormonal Regulation of Nutrients Food intake & Obesity

PHRM 142

Physiology & Pathophys. III

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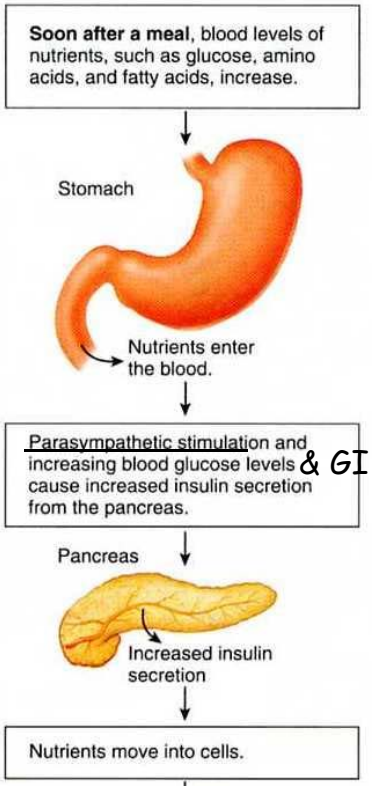
- √ Endocrine pancreas . . .
- √ Pancreatic Hormones . . .
  - √ Properties, Secretion & Actions . . .
- ❖ Hormonal Regulation of Nutrients
  - Responses to feeding & post-absorptive state
  - Effects of Exercise
- ❖ Food intake & Obesity

Regulation of Blood Nutrient Levels

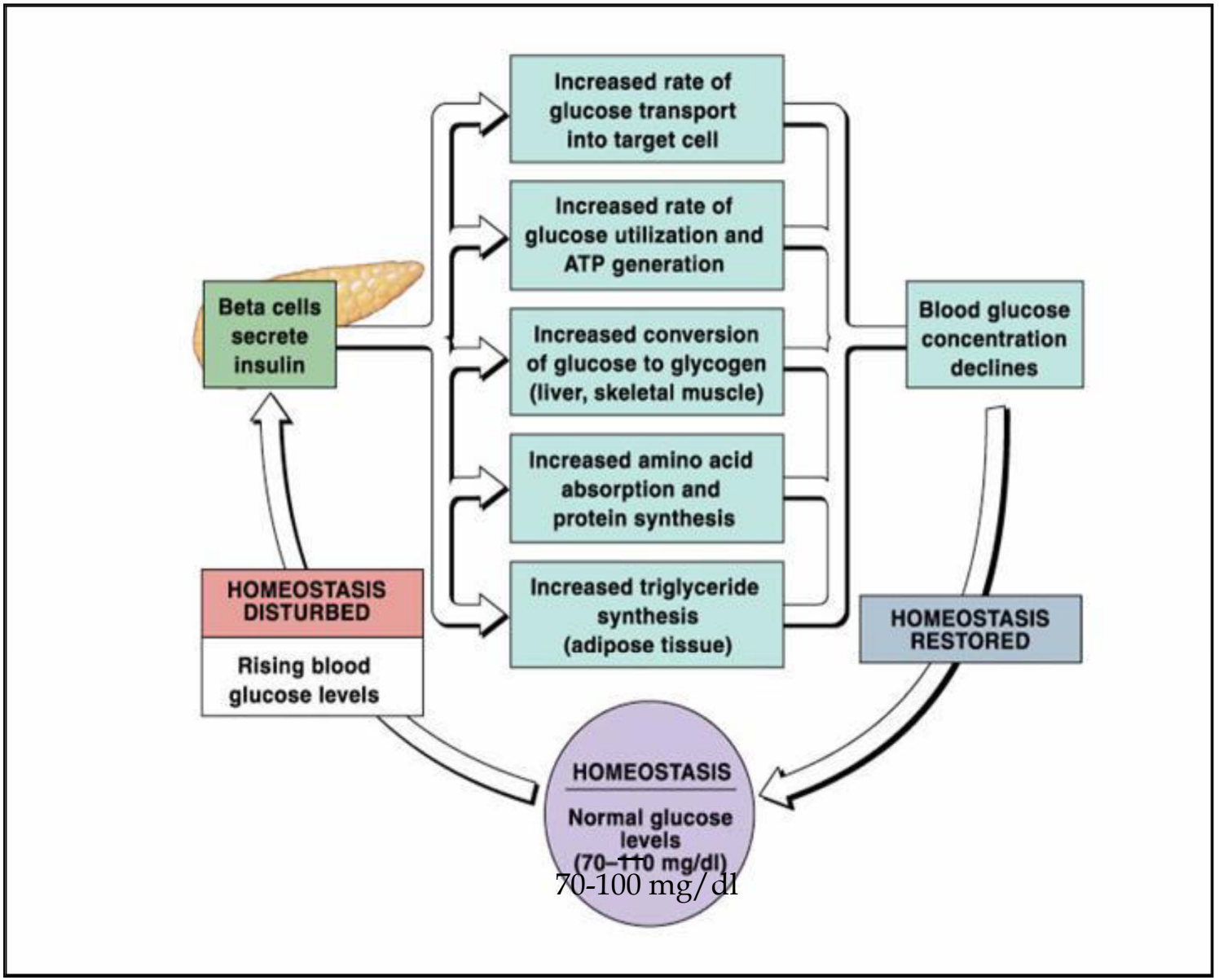


& GI hormones

Figure. 18.18, Seeley

Regulation of Blood Glucose Concentration

Response to Feeding (soon after a meal)



70-100 mg/dl

Martini
Fig. 18-19

Regulation of Blood Nutrient Levels

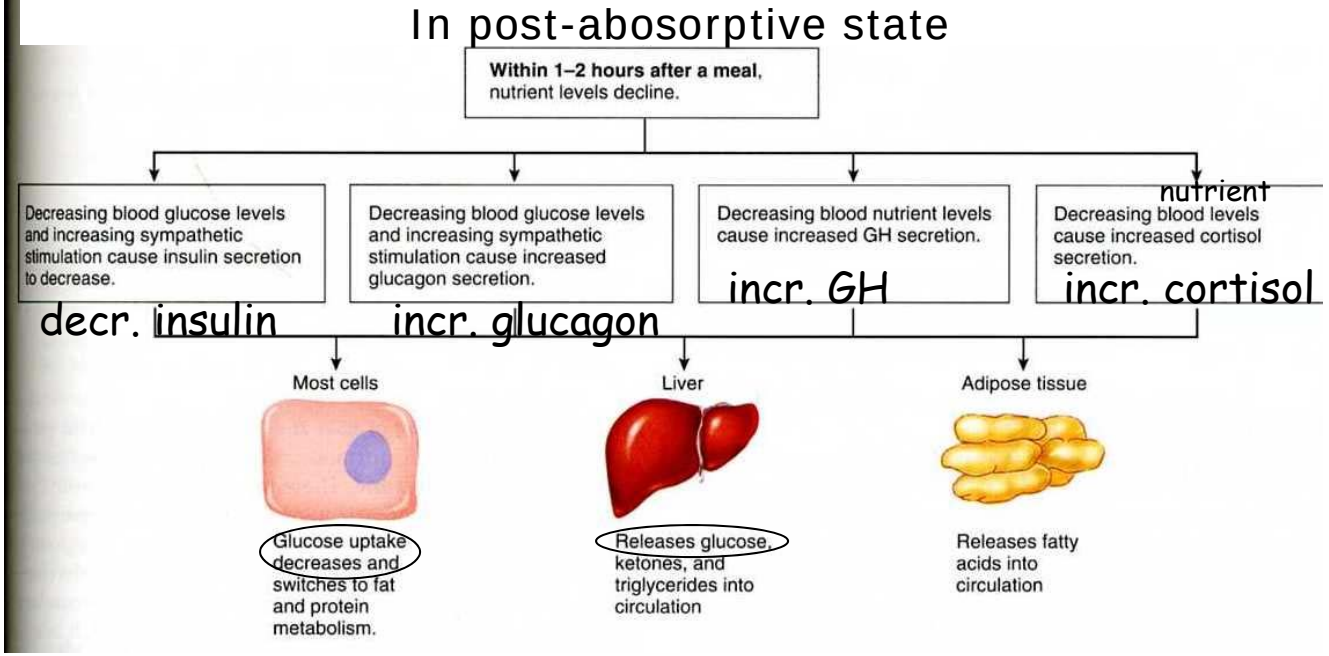


Figure 18.18, Seeley

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

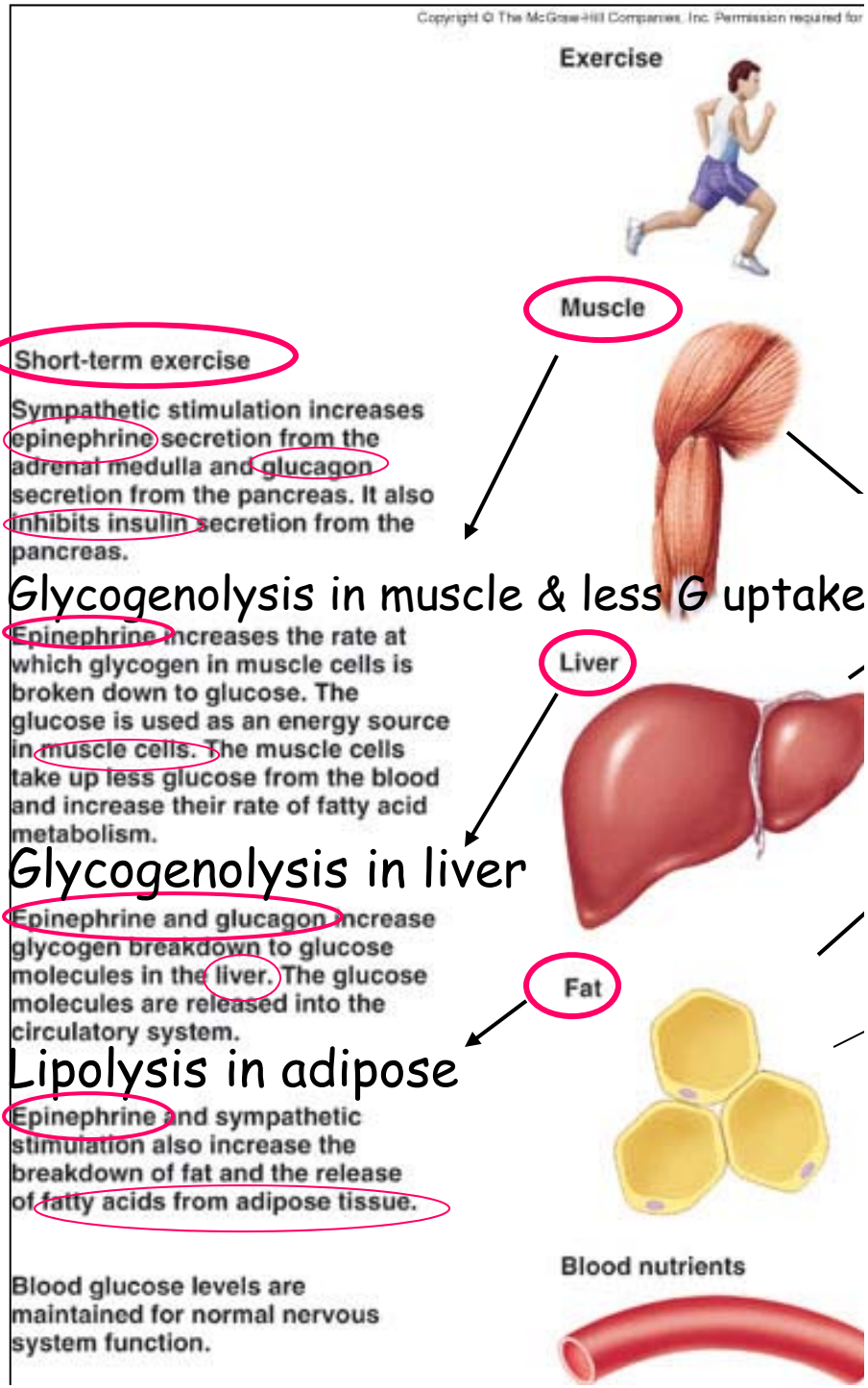
Short-Term Starvation

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

Long-Term Starvation

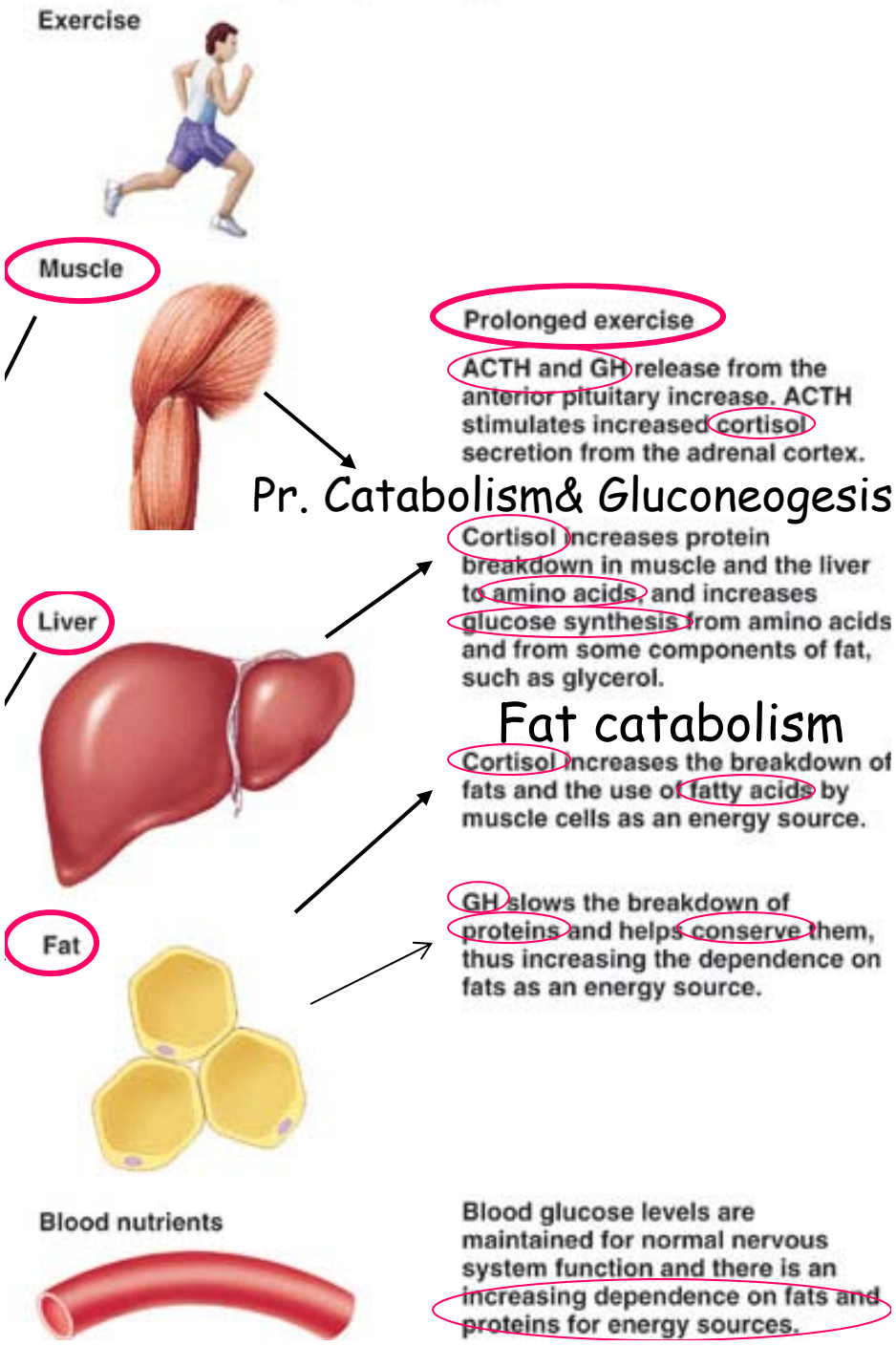
- At > 7 days fasting:
  - Protein catabolism ↓
  - Blood ketone ↑
  - Brain utilization of ketones ↑ (reduces dependence on glucose).

Regulation of Blood Nutrients During Exercise



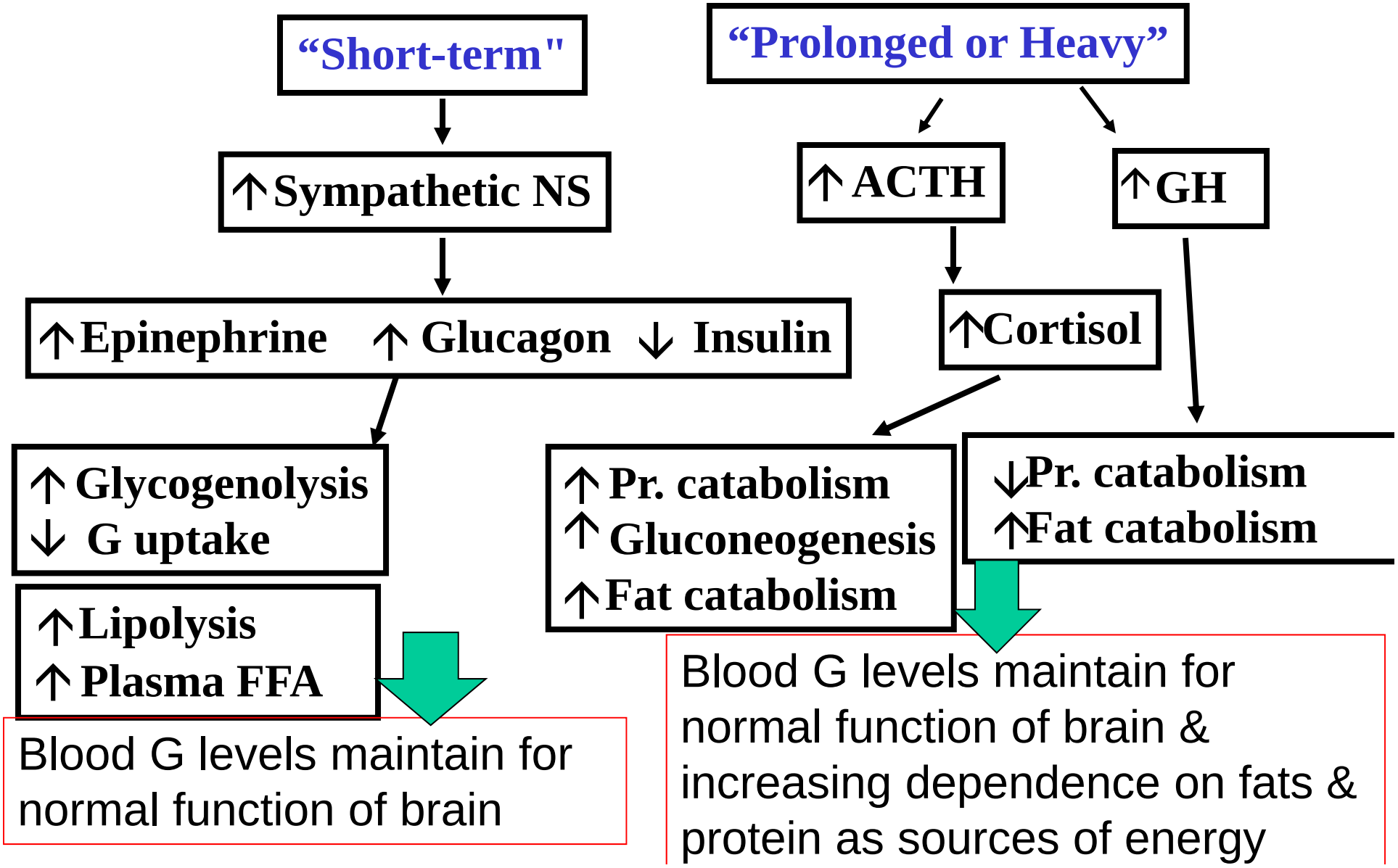
Seeley
Fig. 18.19

Regulation of Blood Nutrients During Exercise



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.

- Body Mass Index (BMI)= $\dfrac{\text{Body weight (Kg)}}{\text{Height (m)}^2}$

  - (e.g., Wt: 120 pounds ≈ 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/m^2)
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)

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)

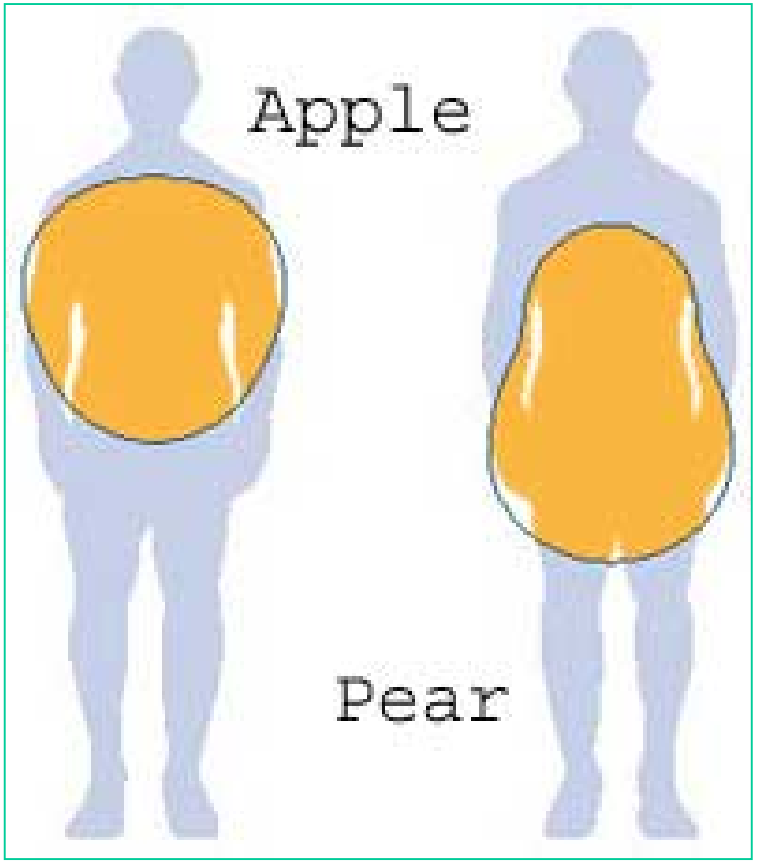
Metabolic syndrome

- A group of risk factors that increases the risk of CVD, stroke and other health problems, such as diabetes.
  - A large waistline: central or abdominal obesity (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 l 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.

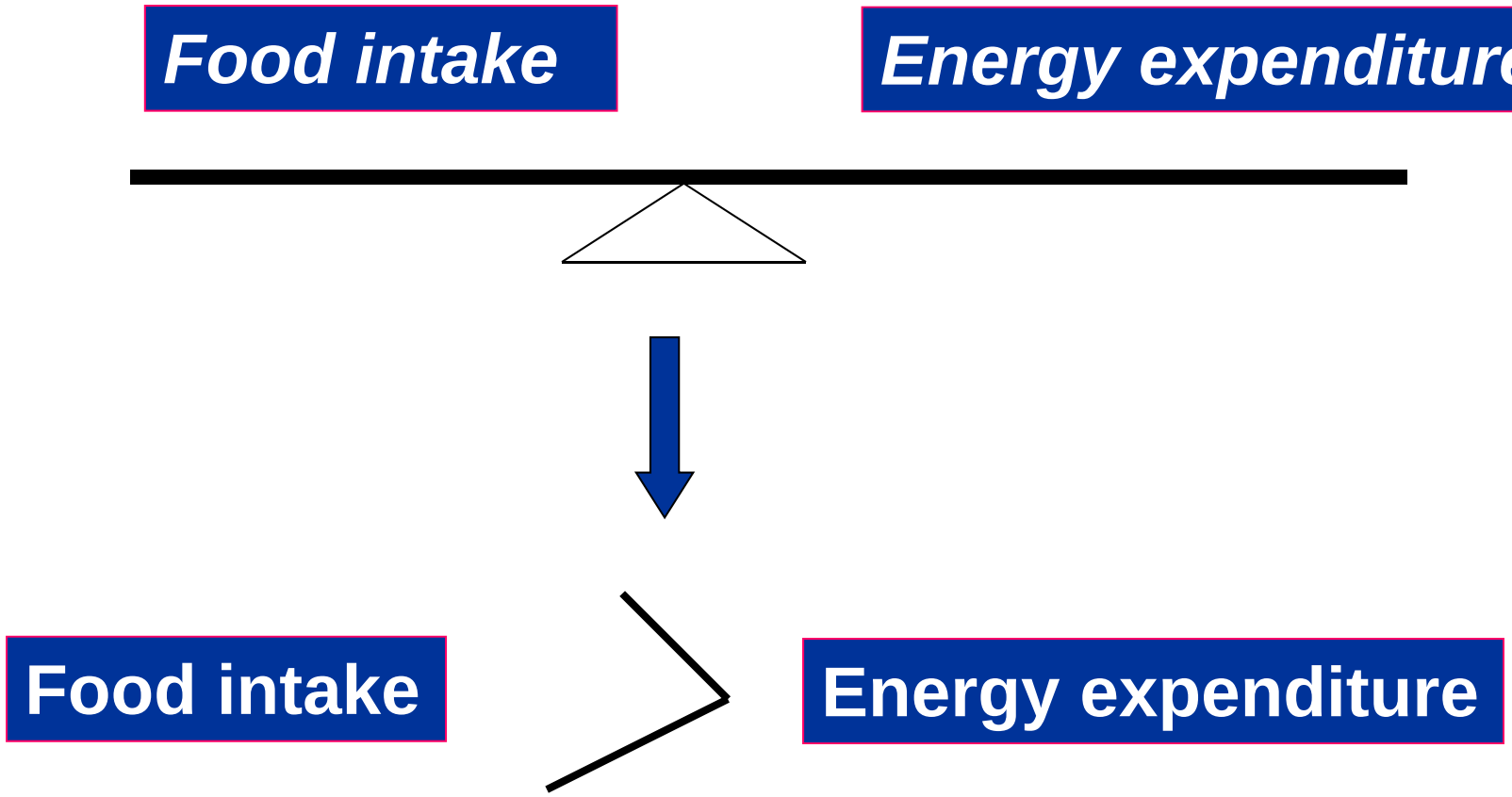
Abdominal obesity!

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

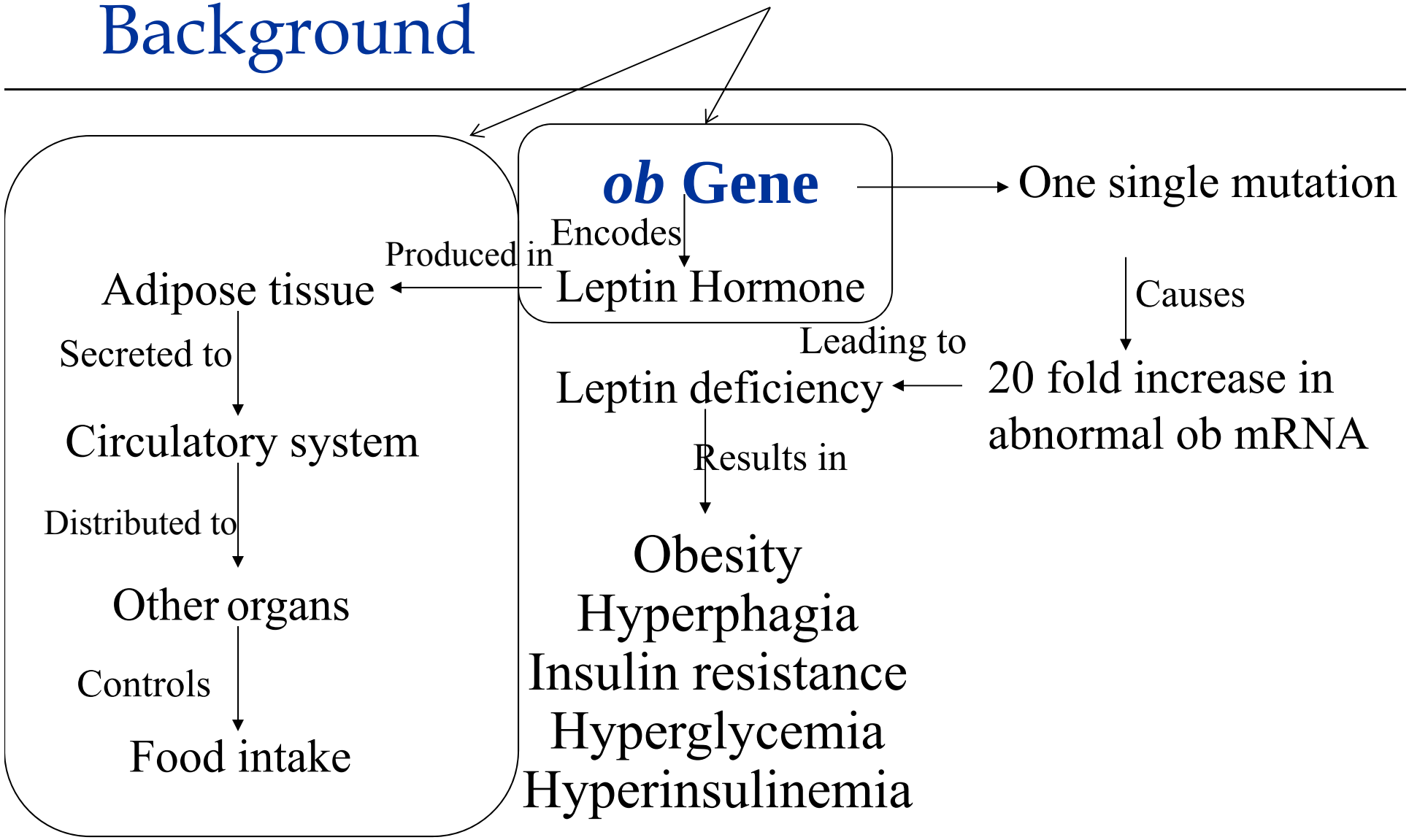


ob/ob Mouse Model of Obesity

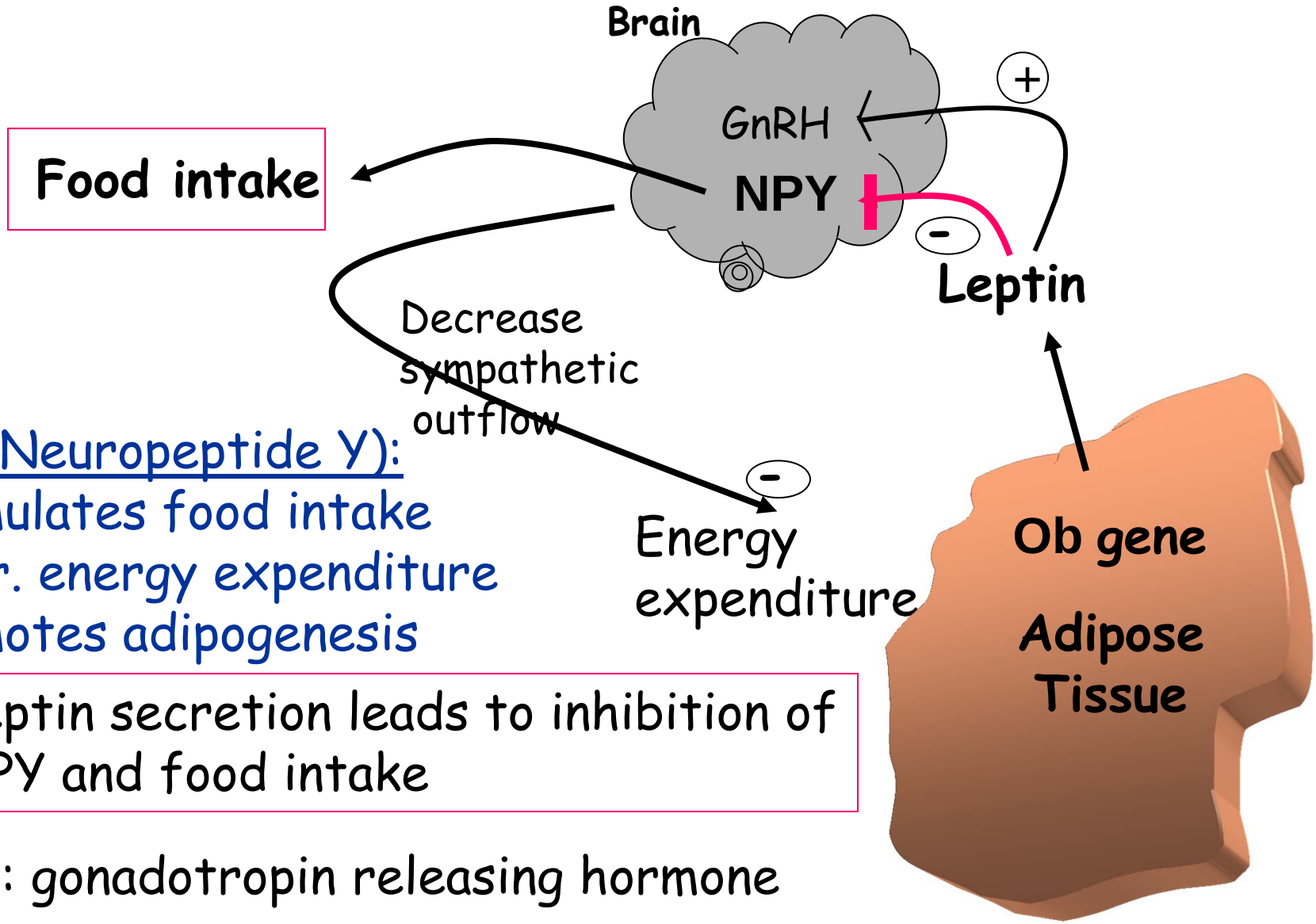
- The mouse *ob* gene encods a 167 aa protein named leptin.
- Human leptin shares 84% sequence identity to mouse leptin.
- A link exist between obesity and leptin resistance.

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

Background


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

How can leptin control food intake?



NPY (Neuropeptide Y):
- stimulates food intake
- decr. energy expenditure
-promotes adipogenesis

➡ Leptin secretion leads to inhibition of NPY and food intake

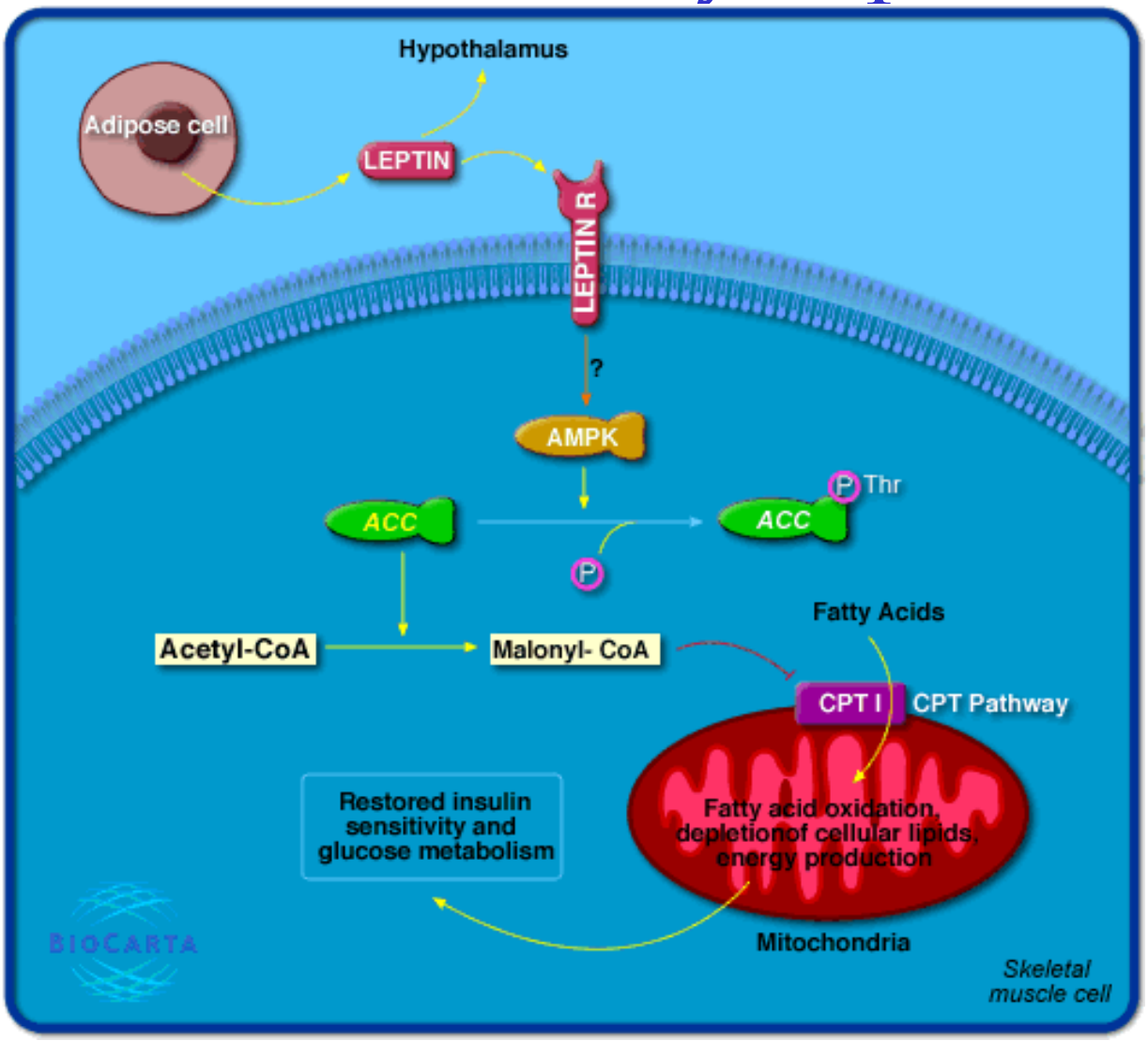
GnRH: gonadotropin releasing hormone

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, AMPK is activated, ACC is inhibited, and malonyl-CoA levels fall, increasing the oxidation of FA and reducing the lipid content of cells. The reduced lipid content in SKM allows 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 activates AMPK and stimulates FA oxidation in mitochondria. This reduces the storage of fat in those tissues.
- The reduced fat content in SKM and liver allows 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 leptin resistance in the face of high endogenous leptin rather than leptin deficiency.

Additional Factors Causing Obesity

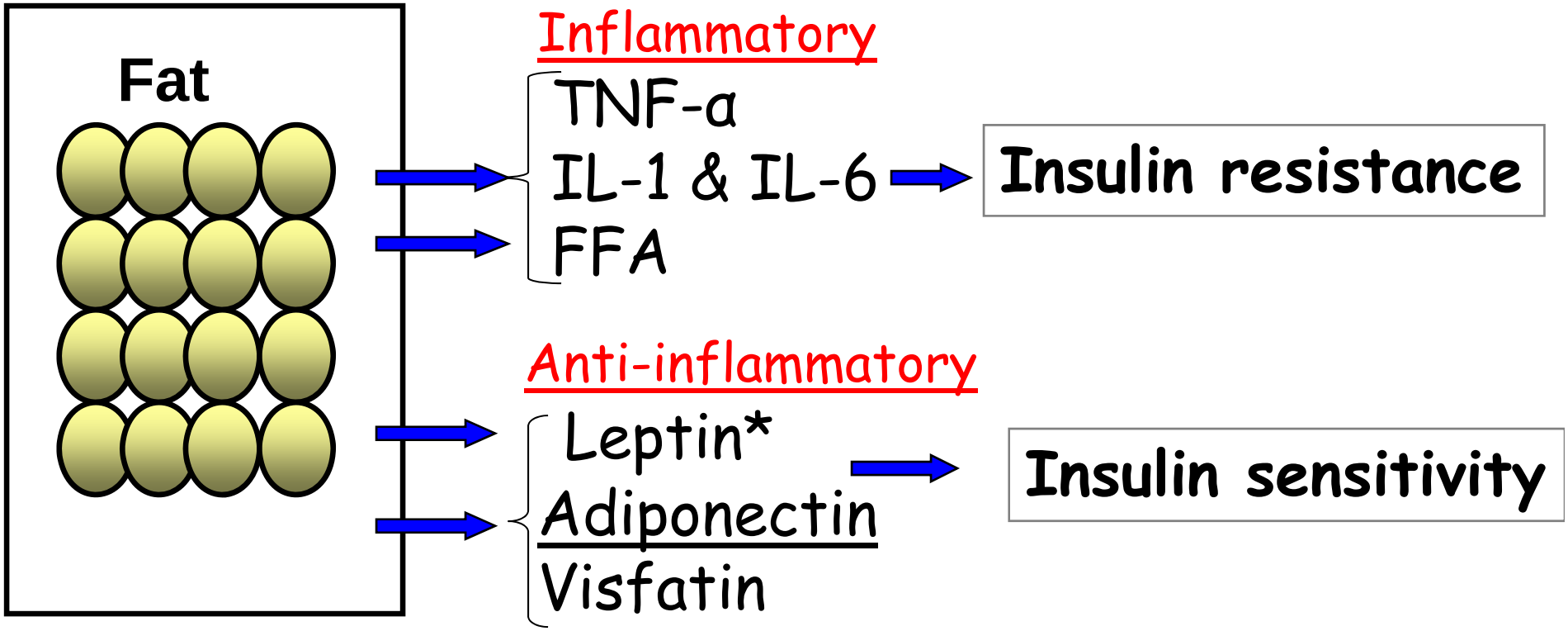
- Underlying disease (eg., hypothyroidism)
- Eating disorders
- Certain medications (eg., anti-psychotics)
- Inactive lifestyle
- Insufficient sleep!
  - Increased Ghrelin (a hunger hormone), decreased leptin (a hormone that tells your stomach that it's full)
- Chronic stress!
  - increased Ghrelin may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

- Visceral fat depots release inflammatory adipokines, 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, leptin 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
α_1	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