Obesity

Endocrine Block | Dr. Usman Ghani

Objectives

- Define and characterize obesity in terms of BMI and risk factors
- Compare the anatomic and biochemical differences in fat deposition
- Understand the role of adipocytes in fat storage and release of hormones
- Discuss the hormonal control of obesity by leptin, adiponectin and other hormones
- Understand the mechanism of leptin signaling
- Discuss the management and treatment options for obesity

Overview

- Introduction
- Body Mass Index (BMI)
- Types of fat deposition in the body
- Metabolic changes in obesity
- Adipocytes (fat cells) and weight gain
- Hormones in obesity (Leptin, adiponectin, ghrelin, cholecystokinin
- Mechanism of leptin signaling
- Treatment options

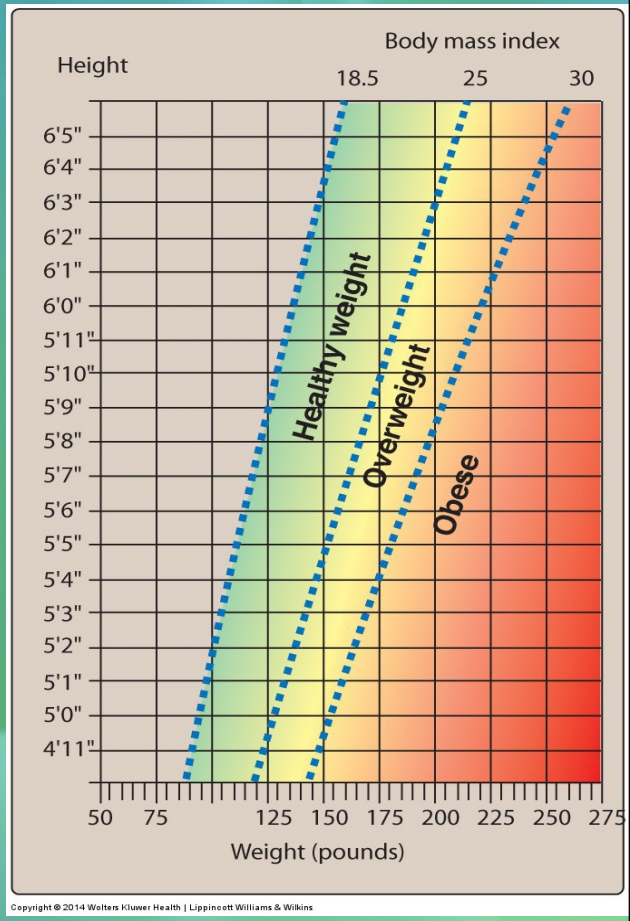
Obesity

- A disorder of body weight regulatory systems
- Causes accumulation of excess body fat
  - >20% of normal body weight
- Obesity is associated with a high risk of:
  - Diabetes mellitus
  - Hypercholesterolemia
  - High plasma triglycerides
  - Hypertension
  - Heart disease
  - Cancer
  - Gallstones, arthritis, gout
  - Mortality

Body Mass Index (BMI)

- BMI is an indirect measure of obesity
- Correlates height, weight and amount of body fat in an individual

	BMI	GRADE
UNDER WEIGHT	≤ 18.5	
NORMAL	18.5 – 24.9	
OVER WEIGHT	25.0 – 29.9	
OBESE	30.0 – 34.9	I
OBESE	35.0 – 39.9	II
HIGHLY OBESE	≥ 40	III



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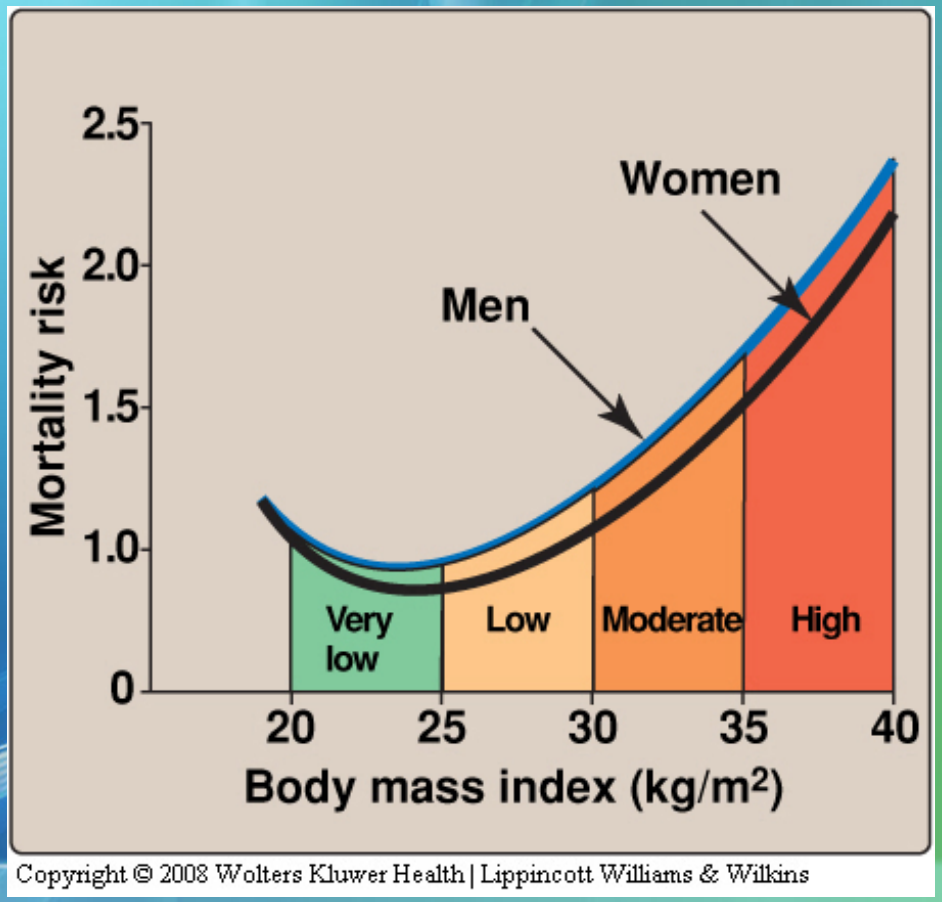
High BMI is associated with increased mortality risk



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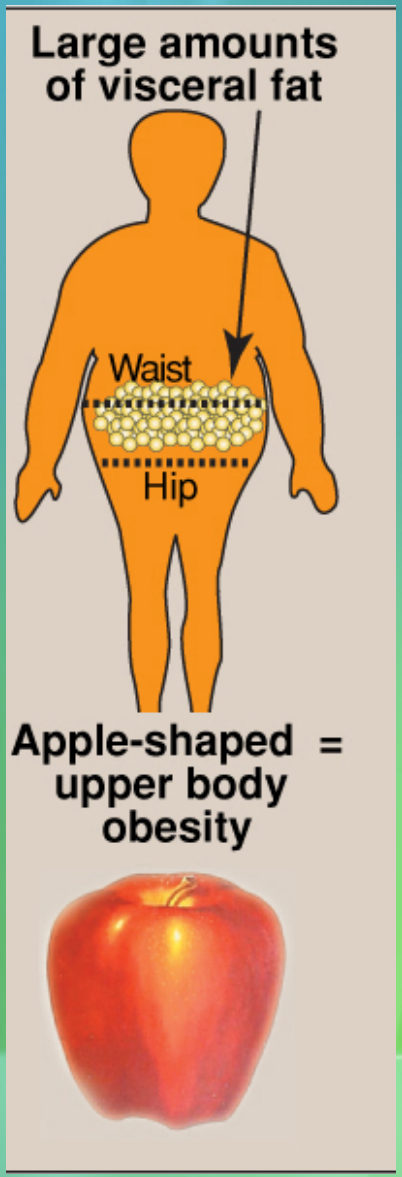
Anatomic differences in fat deposition

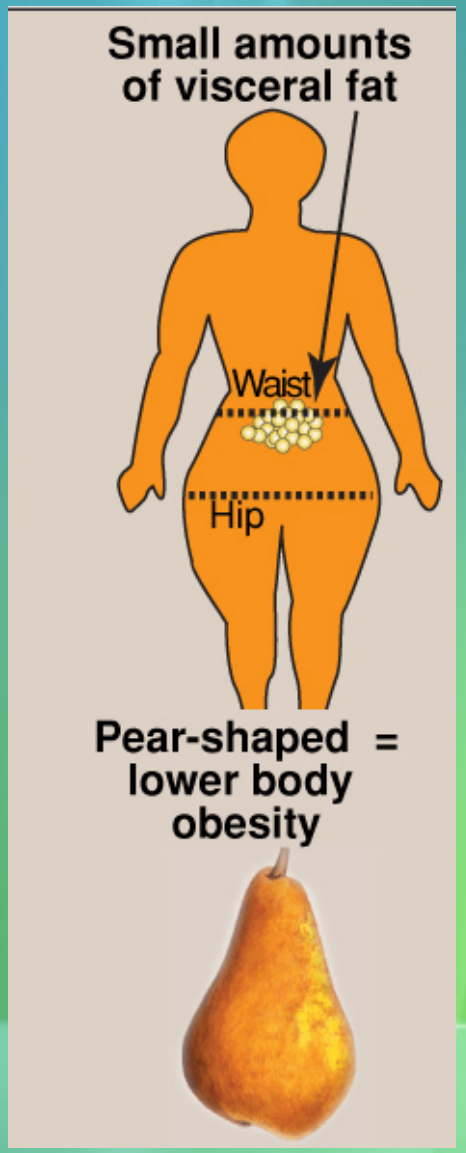
- Health risks depend on the pattern of fat deposition

- Android, "apple-shaped," or upper body obesity
  - Excess body fat deposited in the central abdominal area
  - Associated with risk of hypertension, insulin resistance, diabetes, dyslipidemia, and coronary heart disease



Anatomic differences in fat deposition

- Gynoid, "pear-shaped," or lower body obesity
- Fat deposited around the hips or gluteal region
- Associated risks are low



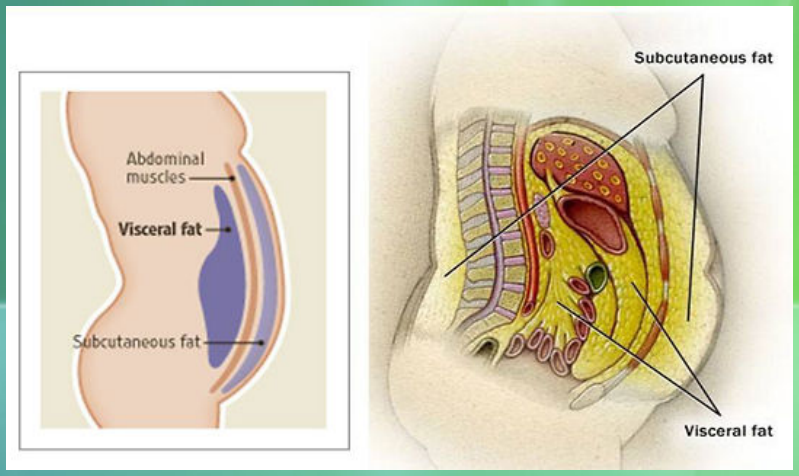
Different fat depots in the body

Subcutaneous Fat

- The fat stored just under the skin in the abdominal and gluteal-femoral region
- Constitutes 80-90% of the total fat in the body

Visceral Fat

- Composed of omental and mesenteric fat present in close association with digestive tract



Biochemical differences in fat deposits

Abdominal fat	Gluteal Fat
Smaller cells	Larger cells
More responsive to hormones (both visceral and subcutaneous)	Less responsive to hormones
Release substances via portal vein to the liver	Release substances to circulation with no effect on the liver

Adipocytes

Triacylglycerols are deposited in adipocytes (fat cells) which can increase in size up to a limit

Prolonged overnutrition stimulates

↓

Pre-adipocytes in adipose tissue

↓

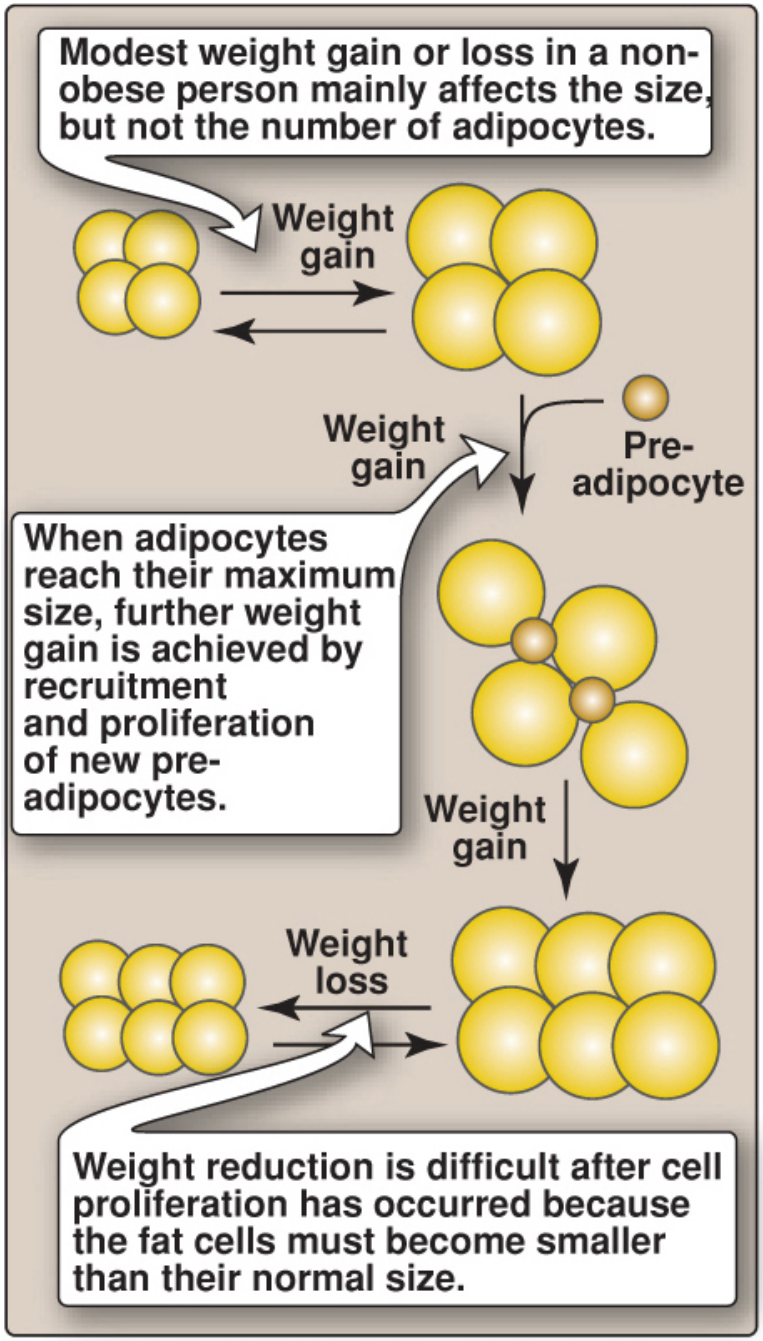
Proliferation / differentiation into mature fat cells

↓

Increases adipocyte number

Adipocytes

- Thus obesity is due to a combination of increased fat cell size (hypertrophy) and number (hyperplasia)
- Fat cells, once gained, are never lost
- Reduction in weight causes adipocytes to reduce in size



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Ectopic fat

- Excessive calories that cannot be stored in adipose tissue “spill over” into other tissues such as muscle and liver

- It is called “ectopic fat” that is strongly associated with insulin resistance

Factors contributing to obesity

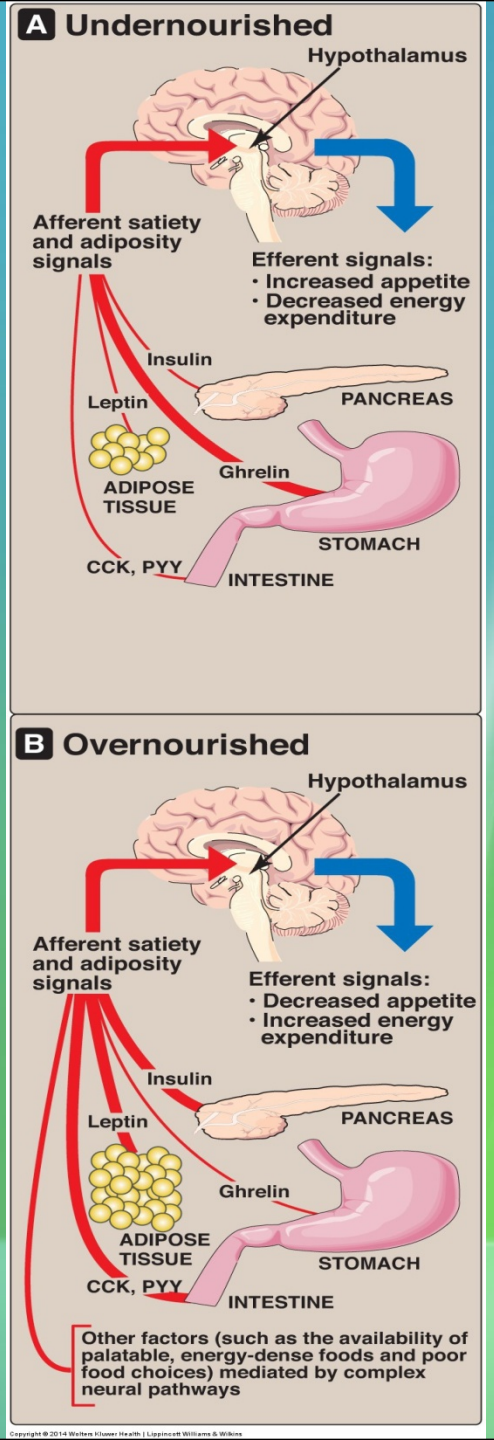
- Genetic: familial tendency
- Environmental and behavioral
  - Sex: women more susceptible
  - Activity: lack of physical activity
  - Psychogenic: emotional deprivation/depression
  - Alcohol: problem drinking
  - Smoking
- Drugs: e.g. tricyclic derivatives

Causes of weight Gain

- Energy imbalance
  - calories consumed not equal to calories used
- Over a long period of time
- Due to a combination of several factors
  - Individual behavior
  - Social interaction
  - Environmental factors
  - Genetics

Hypthalamic hormonal control

- Appetite is influenced by
  - Afferent neural signals, circulating hormones, and metabolites
- These signals cause the release of hypothalamic peptides and activate efferent neural signals
- Adipocytes also function as endocrine cells
- They release many regulatory molecules:
  - Leptin, adiponectin, resistin



Leptin

- A protein hormone produced by adipocytes
- Required to keep the body weight under control
- Signals the brain about fat store levels
- Regulates the amount of body fat by:
  - Controlling appetite and energy expenditure
- Leptin secretion:
  - Suppressed in starvation (depletion of fat stores)
  - Enhanced in well-fed state (expansion of fat stores)
- Leptin causes overweight mice to lose weight and maintain weight loss

Leptin and obesity

- Leptin increases metabolic rate and decreases appetite in humans
- Plasma leptin levels are in proportion to adipose tissue mass
- Two mechanisms by which this leptin-adiposity balance is lost:
  1. Leptin resistance
  2. Defect in leptin signaling

Leptin Resistance

- The receptor for leptin in the hypothalamus is produced by ***db*** gene
- Mutation in the ***db*** gene causes leptin resistance in mice
- Leptin resistance may have some role in human obesity
  - Dieting decreases leptin levels
  - Reducing metabolism, stimulating appetite

Leptin signaling (hypothalamic leptin action)

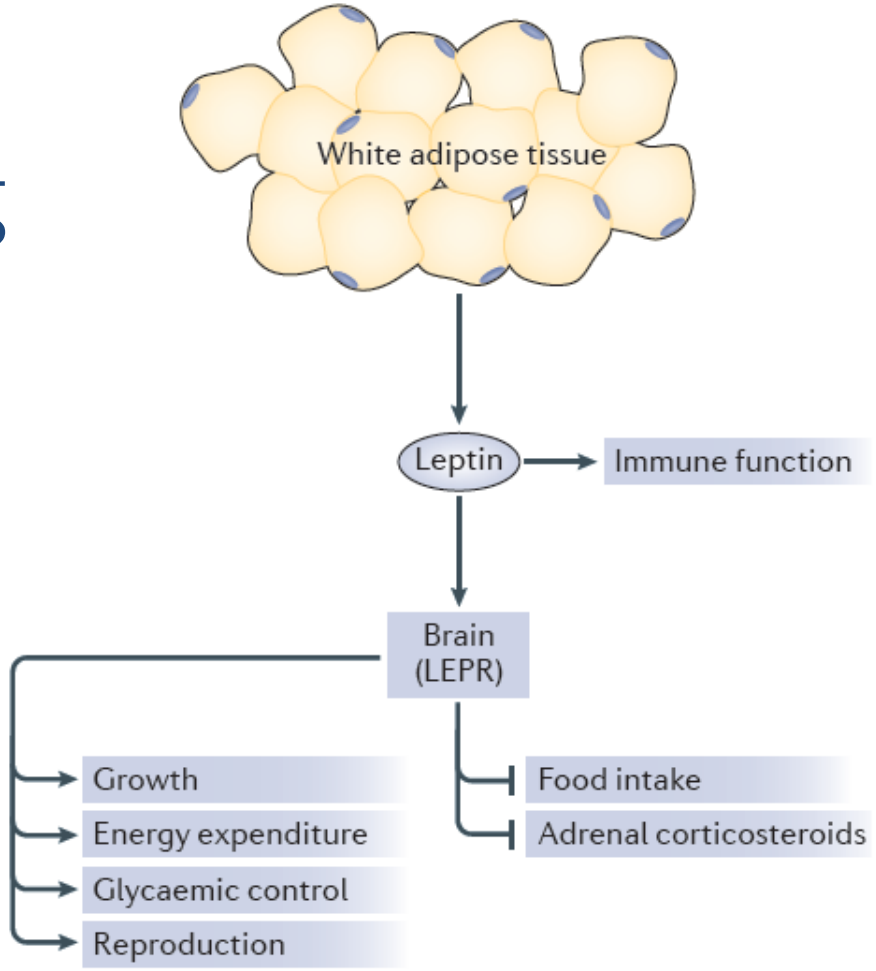
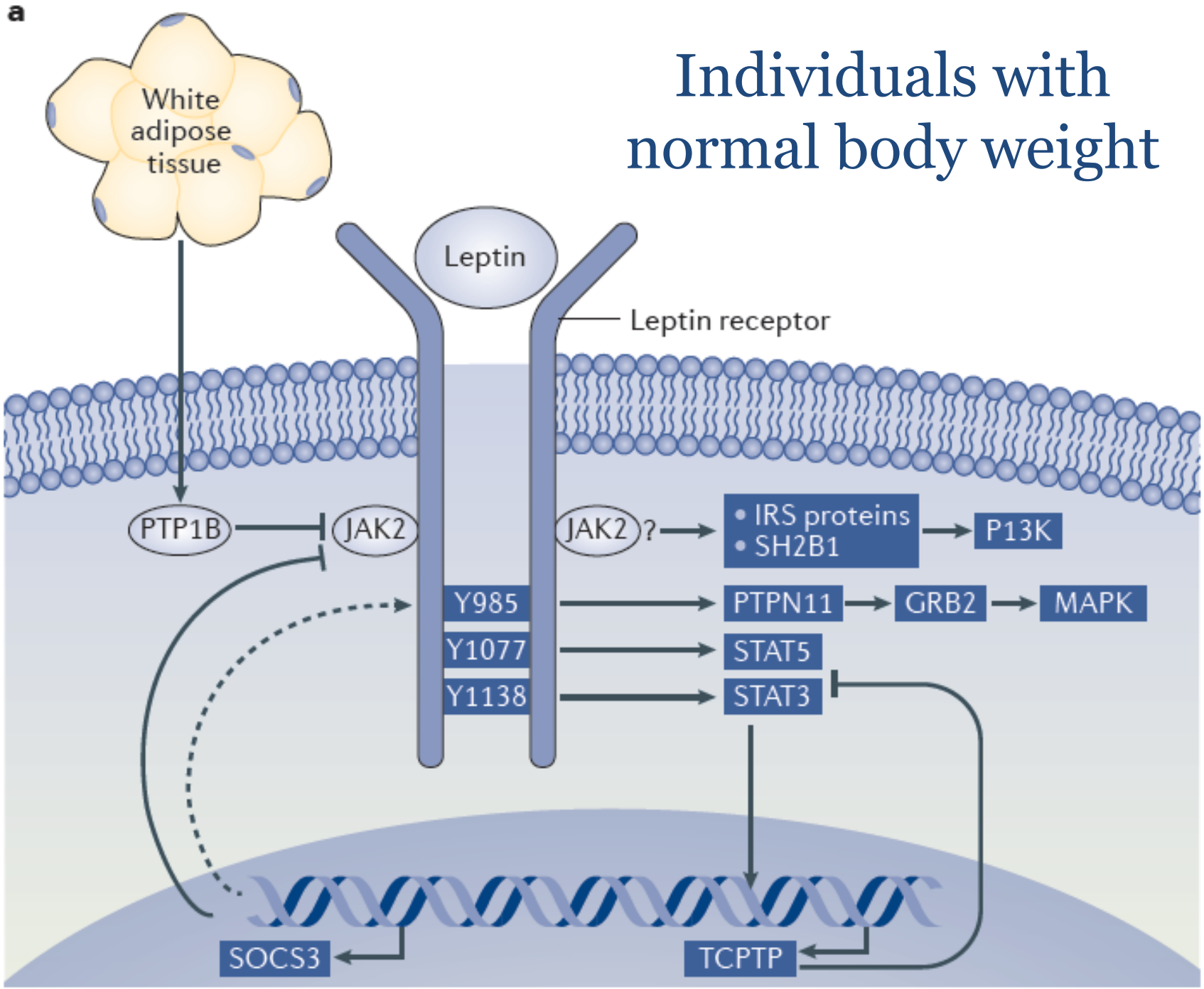


Figure 1 | **Leptin action.** Cells of white adipose tissue secrete leptin in approximate proportion to their triglyceride content. Circulating leptin binds to the long form of the leptin receptor (LEPR) in the brain and, in doing so, promotes growth, energy expenditure, glycaemic control and reproduction. Leptin also suppresses food intake and the production of adrenal corticosteroids. Leptin also influences the production and function of immune cells.

Individuals with normal body weight



The LEPR-STAT3 pathway

Leptin + Receptor (LEPR) → Activates JAK2 → Phosphorylaion of LEPR tysorine residues (Y985, Y1077, Y1138)

Y1138 → Activates STAT3 transcription factor → Gene expression → Control of energy balance

STAT3 → activates suppressor of cytokine signaling 3 (SOCS3) → Binds to Y985 → Inhibits leptin signaling

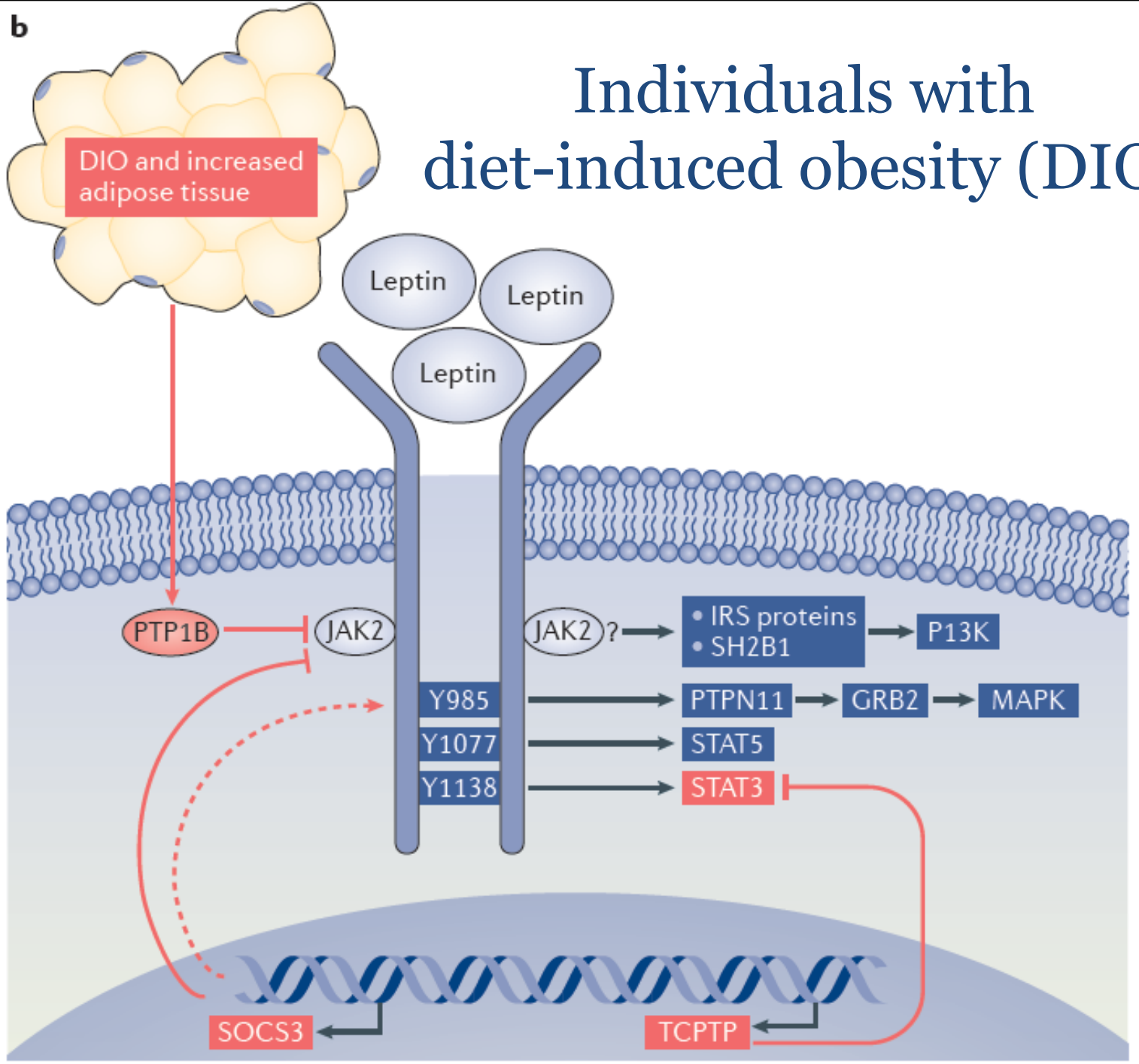
PTP1B from WAT and TCPTP → dephosphorylate JAK2 and $STAT_3$

In obese individuals (DIO)

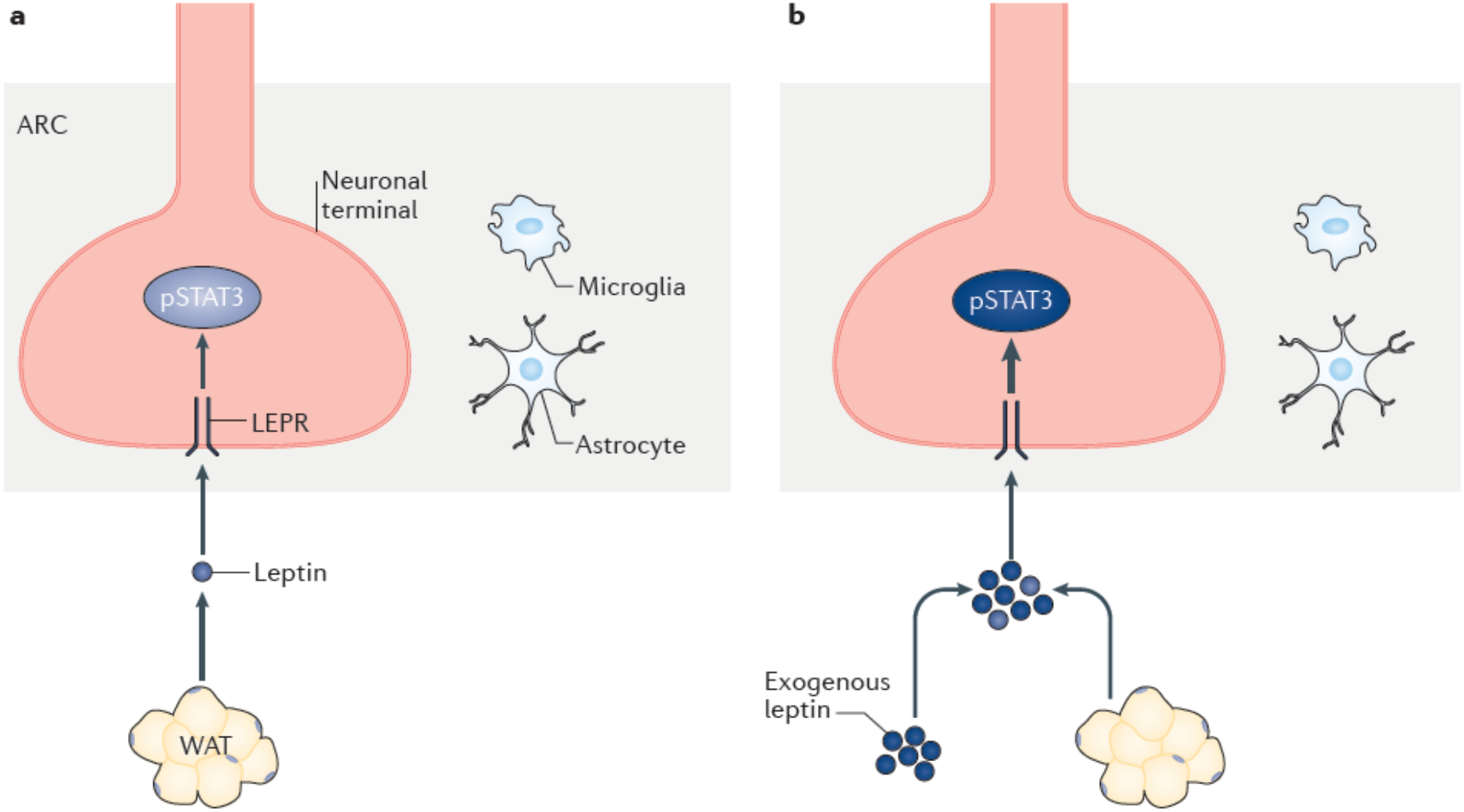
Increased adipose mass → increases leptin levels → high LEPR signaling → increased expression of $SOCS_3$, TCPTP and PTP1B → Decrease the amplitude of leptin response

PTP1B (Protein tyrosine phosphatase 1B)
TCPTP (T cell protein-tyrosine phosphatase)

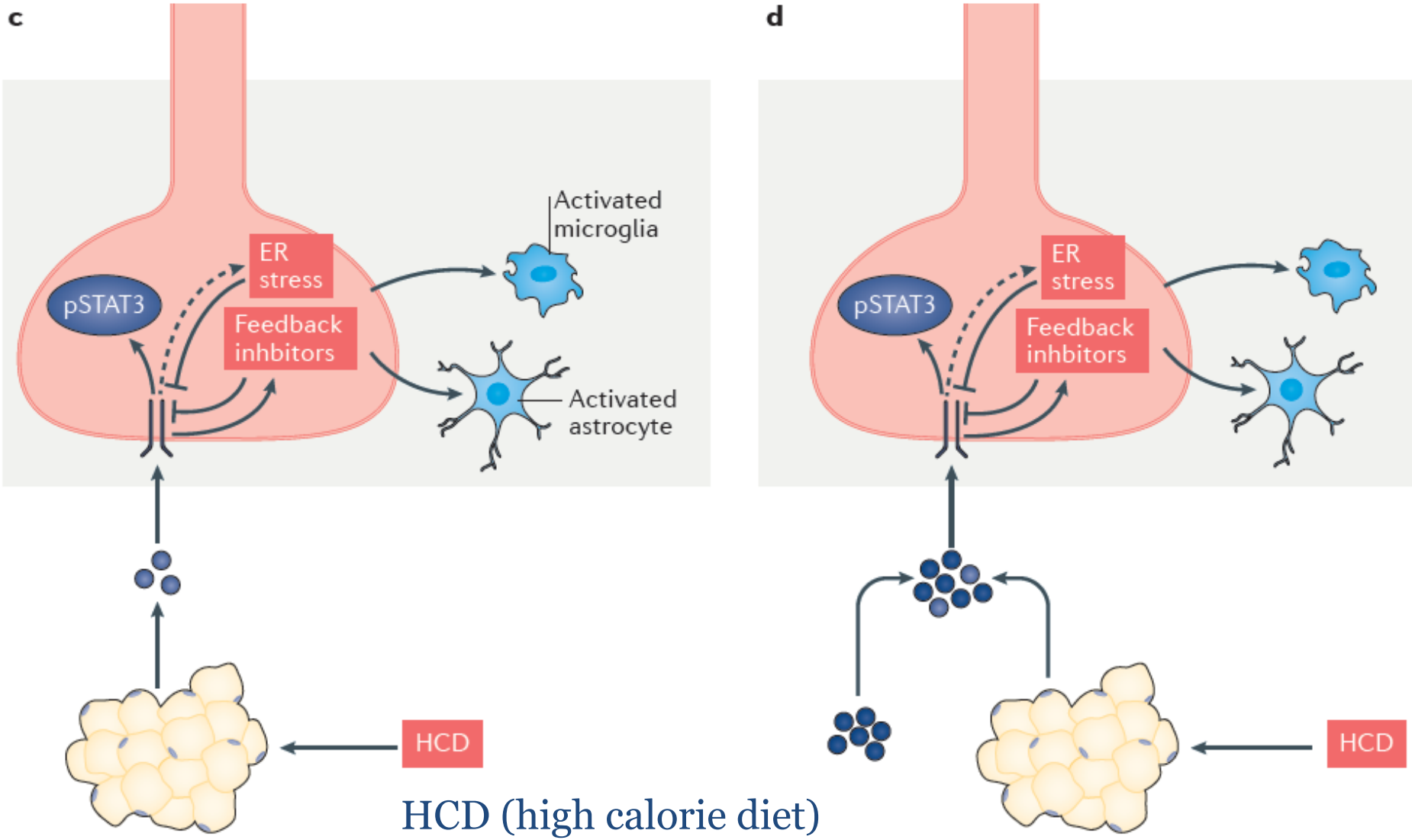
Individuals with diet-induced obesity (DIO)



In lean individuals



In obese individuals



HCD (high calorie diet)

Adiponectin

- A protein hormone exclusively and abundantly secreted by adipocytes
- Promotes uptake and oxidation of fatty acids and glucose by muscle and liver
- Blocks the synthesis of fatty acids and gluconeogenesis by hepatocytes
- Net effect is to increases insulin sensitivity / improve glucose tolerance
- Adiponectin levels are inversely correlated with body fat percentage and parallels with HDL levels
- Low levels are seen in metabolic syndrome and diabetes mellitus

Other Hormones

Ghrelin: A peptide hormone secreted by stomach

- Stimulates appetite
  - Secretion increases just before meals and drops after meals
  - Increases food intake
  - Decreases energy expenditure and fat catabolism

  Levels in dieters are *higher* after weight loss

Other Hormones

- The body steps up ghrelin production in response to weight loss
- The higher the weight loss, the higher the ghrelin levels

- **Cholecystokinin**: Peptides released from the gut after a meal
- Sends satiety signals to the brain

- **Insulin**: Promotes metabolism

Metabolic Changes in Obesity

- Adipocytes send cytokine signals to liver and other organs causing:
- Dyslipidemia
- Glucose intolerance
- Insulin resistance

Benefits of weight loss in obesity

Weight loss decreases risk factors for obesity leading to:

- Lower blood pressure
- Decreased serum triacylglycerols
- Lower blood glucose levels
- Increase in HDL levels
- Decreased mortality
- Beneficial changes in BMR
- Decreased energy requirement
- Slow weight loss is more stable

Treatment options

- Physical Activity combined with healthy diet decreases level of obesity
  - Reduces risk of heart disease and diabetes
- Dieting
  - Use of low-calorie diet
  - Restriction of excessive energy intake

Drugs

- Orlistat
  - A pancreatic and gastric lipase inhibitor
  - Decreases the breakdown of dietary fat

Surgery

- Surgical procedures are designed to reduce food consumption in patients with BMI >40
- Used when other treatment options fail

Take home message

- Obesity is correlated to an increased risk for a number of chronic conditions and mortality
- Energy balance in the body is hormonally controlled
- Defect in leptin signaling is prevalent in obesity

Reference

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- Pan, W.W. and Myers, M.G. Leptin and the maintenance of elevated body weight. *Nature Reviews Neuroscience* Vol. 19, 2018, 95-105.