Revised & Approved

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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Obesity: Role of hormones

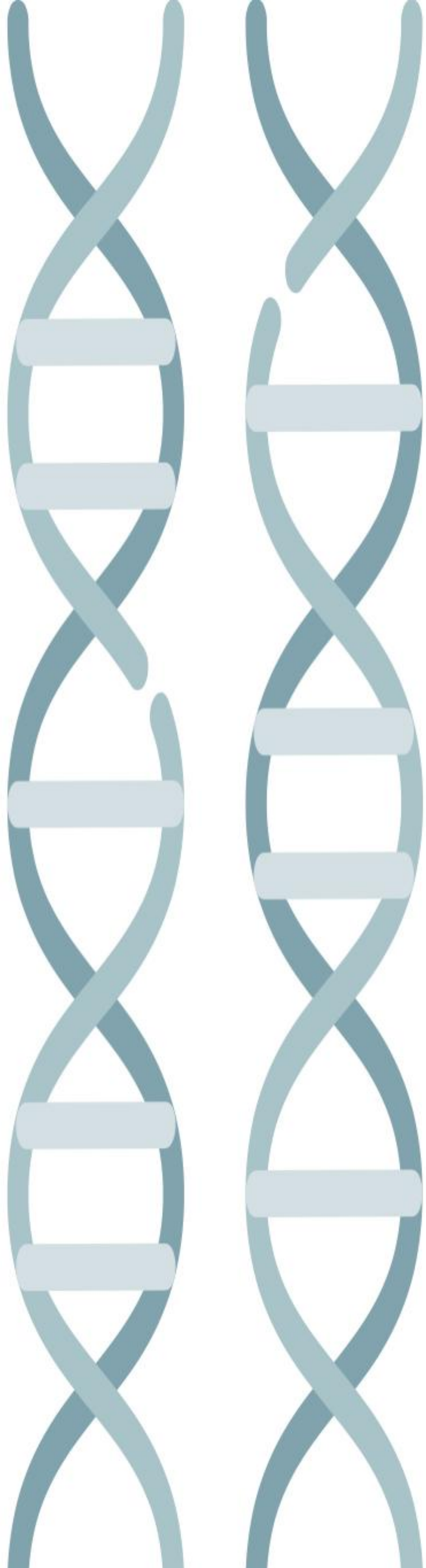
Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

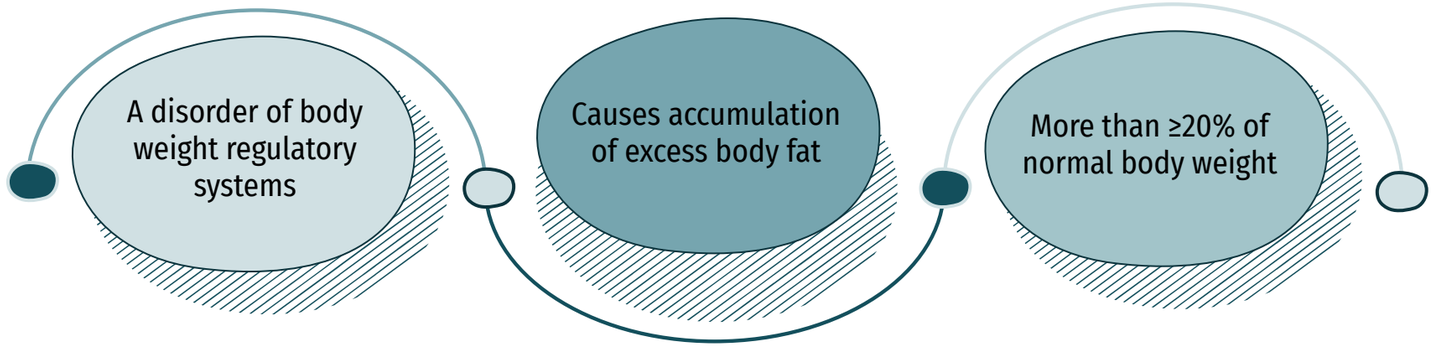
Objectives

- 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.



Obesity

Obesity is an endocrine problem



Body mass index (BMI)

- BMI is an indirect measure of obesity
- BMI = weight (kg) / height²

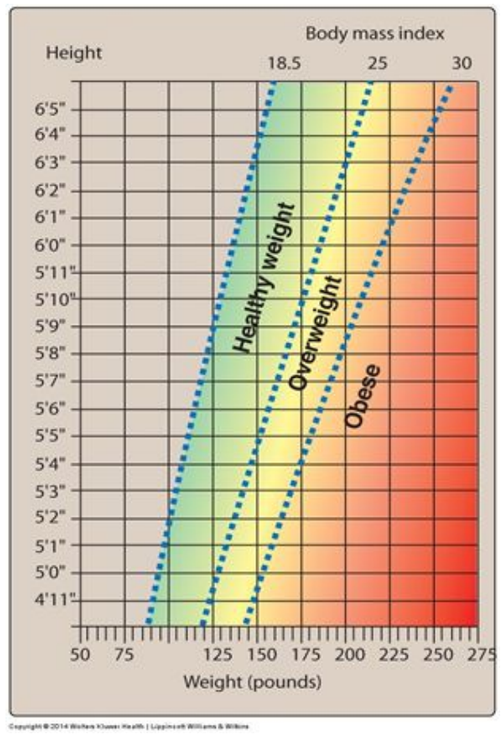
- Correlates height , weight and amount of body fat in an individual
- Doesn't take other things in account e.g. difference between muscle mass or fat mass

High BMI is associated with increased mortality risk

Other ways:
- Measuring the waist circumference
- Measuring the Ratio (waist circumference:hip circumference)

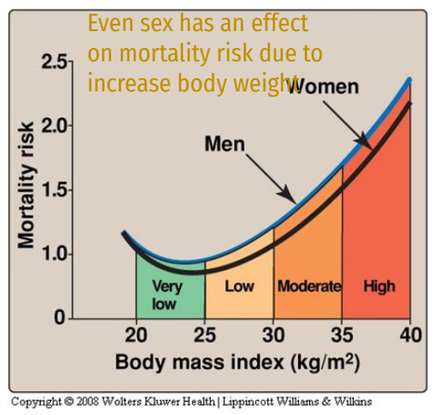
overweight is a Warning sign: Person should start do the lifestyle modification and calories restriction

	BMI	Grade
Underweight	≤ 18.5	-
Normal	18.5-24.9	-
Overweight	25-29.9	-
Obese	30-34.9	I
Obese	35-39.9	II
Highly obese	≥40	III



Risk factors associated with obesity

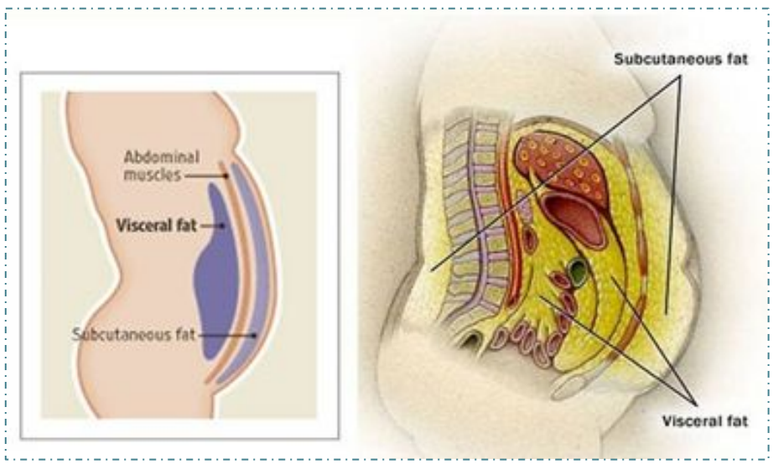
1. Mortality — Depending on how much obese the person is
2. Diabetes mellitus
3. Hypercholesterolemia
4. High plasma TAGs
5. Cancer — Most of the types
6. Heart disease
7. Hypertension
8. Gallstones, arthritis, gout



Different fat depots in the body

Subcutaneous fat	Visceral fat
The fat is stored just under the skin in the abdominal and gluteal-femoral region	Composed of omental and mesenteric fat
Constitutes 80% - 90% of the total fat in the body . Mainly Gynoid because there is no organs in these areas	Present in close association with digestive tract around and in between the organs

Both types present in Android pattern

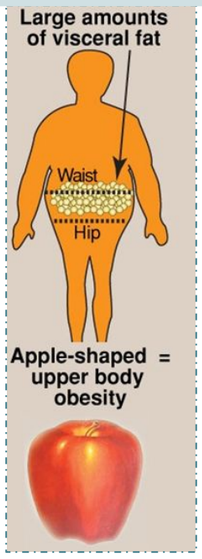


Anatomic difference in fat deposition

(Health risks depend on type of deposition)

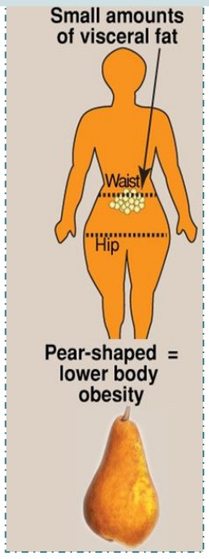
1 Android

- (**Apple shaped**) or upper body obesity
- Excess body fat deposited in the central abdominal area
- **Associated risk factors are :** hypertension , coronary heart disease, dyslipidemia, diabetes and insulin resistance. Because these adipocytes releases substances (cytokines and fatty acids) and start inflammatory signaling to other organs



2 Gynoid

- (**Pear shaped**) or lower body obesity.
- Fat deposited around the hips or gluteal region and the femoral region
- Associated risks are lower



Biochemical differences in fat deposits

1 Abdominal Fat

- **Smaller cells.**
- More responsive to hormones (Both visceral and subcutaneous) metabolically active! And easily lost. that's why it's more dangerous
- Release substance (pro-inflammatory molecules) via portal vein to the liver and contributes in Insulin resistance

2 Gluteal Fat

- **Larger cells.** Can take up larger amount of fat
- Less responsive (subcutaneous) less metabolically active! (stubborn fat)
- Release substance to circulation with no effect on the liver

Adipocytes

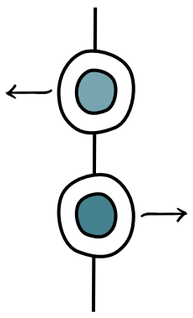
- Excess Triacylglycerols (Fats) are deposited in adipocytes (fat cells) Which can increase in size up to a limit

Prolonged overnutrition stimulates → **Pre-adipocytes in adipose tissue** (A kind of stem cells) → **Proliferation/ differentiation into mature fat cells** (Recruitment of more fat cells) → **Increases adipocyte number**

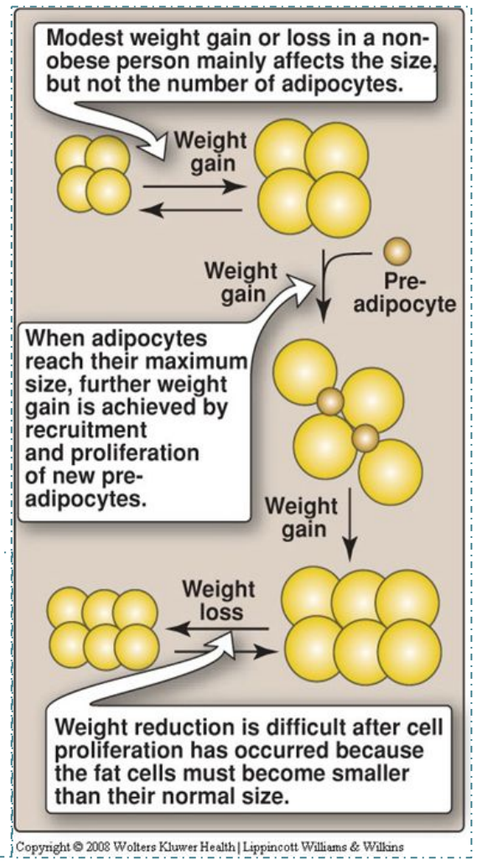
- Thus obesity is due to a combination of increased fat cell size (hypertrophy) and number (hyperplasia)
- Fat cells, once gained, are never lost. Fat cells have lifespan = 10 years
- Reduction in weight causes adipocyte to reduce in size but not in number

Ectopic fat

- Excessive calories that cannot be stored in adipose tissue "spill over" into other tissues such as muscle and liver. In liver, this is called **Non-Alcoholic fatty liver disease (NAFLD).**



- It is called "ectopic fat" that is strongly associated with **insulin resistance**.



Dr's notes:
When you gain weight the cell will increase in size (hypertrophy), and when you lose weight the cell will return to the normal size without change in number of cells. But when the amount of fat is beyond the storage capacity of the cell, a new adipocytes will be formed (hyperplasia) which will make it hard for the person to lose weight because the cells should be smaller than normal since these cells are never lost.
People who lose weight will easily regain it because the (hyperplasia) is already there and that's why weight is much easier controlled in early stages (hypertrophy) before (hyperplasia) starts.
When adipocytes aren't enough to store all the fat then the fat spread out to other regions in the body(rather than adipose tissue) such as liver and muscles and they become fatty .

Factors contributing to obesity

Genetic

Familial tendency

Polygenic disease

Environmental and behavioral

Sex : women more susceptible
Activity : lack of physical activity
Psychogenic : Emotional deprivation/depression
Alcohol : problem drinking
Smoking : cessation of smoking

Drugs

E.g. tricyclic derivatives

Diseases

Hypothyroidism and Cushing's syndrome

Causes of weight gain

Every body has a **set point** tries to maintain

More in and less out = **weight gain**

More out and less in = **weight loss**

Hypothalamus : control center for hunger and satiety

Endocrine disorder : hormonal imbalance

Energy imbalance : calories consumed not equal to calories used over a long period of time due to <u>combination of several factors</u> :

- Individual behaviors
- Social interaction
- Environmental factors
- Genetics

Over long period of time set point will increase or decrease

Hypothalamic hormonal control

1

Appetite is influenced by :
- Afferent neural signals.
- Circulating hormones.
- Metabolites.

Appetite is mainly controlled by Hypothalamus

2

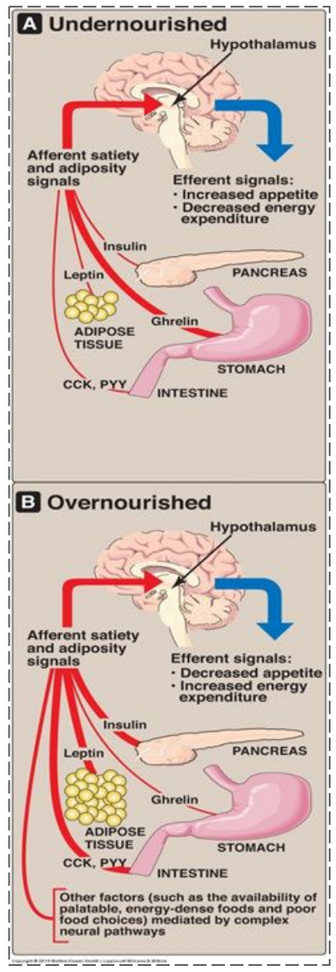
These signals cause the release of hypothalamic peptide and activate efferent neural signals.

3

Adipocyte also function as endocrine cells.

4

They release many regulatory molecules :
- Leptin
- Adiponectin
- Resistin Antagonize the Insulin



Hormones

- **Adipocyte**
  - **Leptin**
  - **adiponectin**
  - **resistin**
- **Ghrelin**
- **Cholecystokinin**
- **Insulin**

Link to reference article that the figures were taken from.

leptin

- A protein hormone produced by adipocytes

Secretion	-Suppressed in starvation (depletion of fat stores). Leads to ↓ in energy and ↑ in appetite -Enhanced in well-fed state (expansion of fat stores).
Function	-Required to keep the body weight under control. -Signals the brain about fat store levels. -Regulates the amount of body fat by controlling appetite (-ve control) and energy expenditure (stimulating effect) -Leptin causes overweight mice to lose weight and maintain weight loss.

Leptin signaling (hypothalamic leptin action)

Dr's notes :

- The function of leptin is to make feel full, it decreases your appetite.
- The amount of leptin in the body is proportional to the amount of fat levels and adipose tissue, so it levels will increase in obese people and after meals, but when you are hungry your fat levels will decrease so there's NO action of leptin on the hypothalamus.

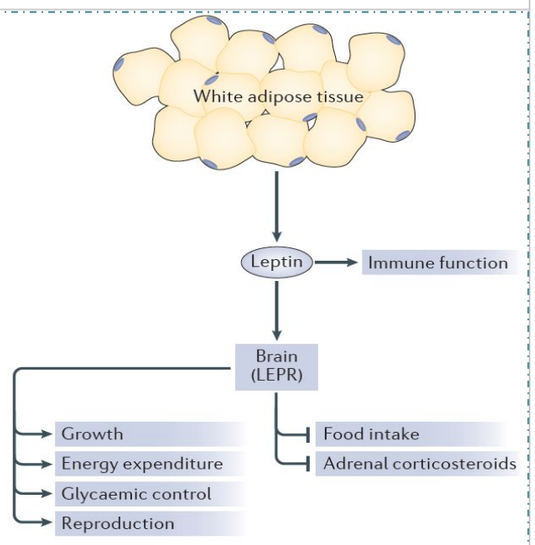


Figure 1 | **Leptin action.** Cells of white adipose tissue secrete leptin in approximate proportion to their triglyceride content. Circulating leptin binds to the long form of the leptin receptor (LEPR) in the brain and, in doing so, promotes growth, energy expenditure, glycaemic control and reproduction.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

Leptin signalling and mechanisms that mediate its inhibition In individuals with normal body weight

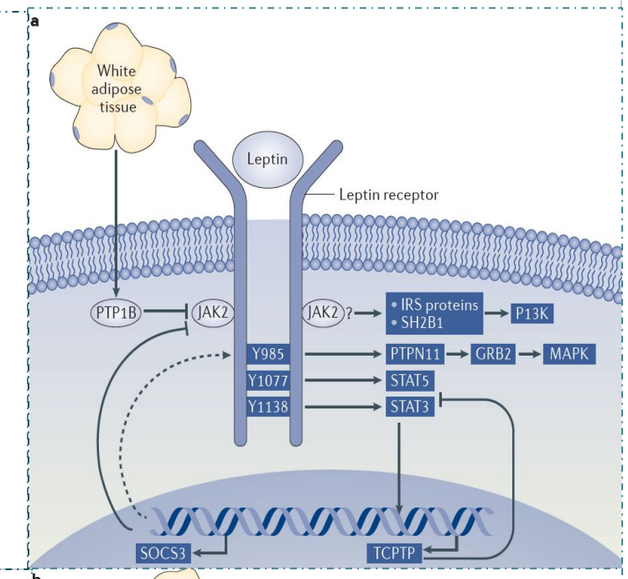
The LEPR-STAT3 pathway : IMPORTANT

- Leptin + Receptor (LEPR) → Activates JAK2 → Phosphorylation of LEPR tyrosine residues (Y985, Y1077, Y1138).
- Y1138 → Activates STAT3 transcription factor → Gene expression → Control of energy balance. And change the BMR
- STAT3 → activates suppressor of cytokine signaling 3 (SOCS3) → Binds to Y985 → Inhibits leptin signaling (by inhibiting JAK2 and Y985).
- PTP1B from WAT and TCPTP → dephosphorylate JAK2 and STAT3.

- Leptin Receptor (LEPR)
- White adipose tissue (WAT)
- Janus kinase 2 (JAK2)
- Signal transducer and activator of transcription 5 (STAT5)
- Suppressor of cytokine signalling 3 (SOCS3), inhibits **JAK2** and **Y985**
- PTP1B (Protein tyrosine phosphatase 1B), inhibits **JAK2**
- TCPTP (T cell protein-tyrosine phosphatase), inhibits **STAT3** and **STAT5**

Dr's notes :

- Leptin binding to his receptor, which is present in the hypothalamus, will phosphorylate (activate) a phosphorylating enzyme (**JAK2**) then it will phosphorylate (activate) the **tyrosine residues** (Y985, Y1077, Y1138), after the activation they will activate transcription factors to act on certain genes resulting in effects on energy control .
- **TCPTP** : a gene involved in growth and glycemic control



Leptin and obesity

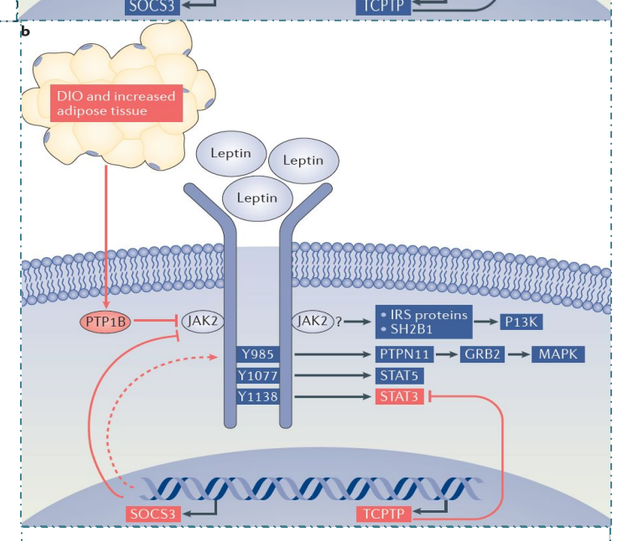
- Leptin increases metabolic rate and decreases appetite in humans.
- Plasma leptin levels are in proportion to adipose tissue mass.
- Two mechanisms by which this leptin-adiposity balance is lost:

1. Leptin resistance:

- The receptor for leptin in the hypothalamus (Arcuate nucleus) 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. (One of the reasons of diet failure)
  - Reducing metabolism, stimulating appetite.

2. Defect in leptin signaling.

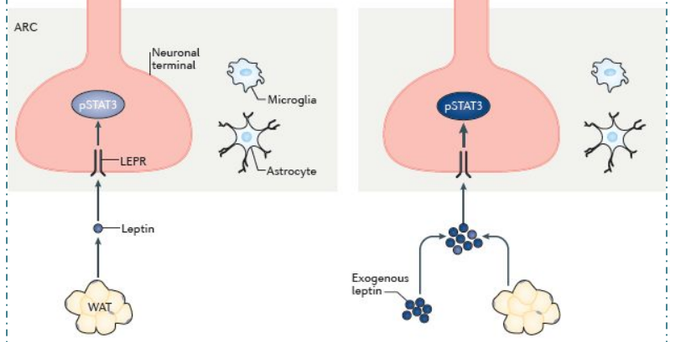
<u>Leptin signalling and mechanisms that mediate its inhibition In Individuals with diet-induced obesity (DIO) :</u>
- Increased adipose mass →increases leptin levels → high LEPR signaling → increased expression of SOCS3, TCPTP and PTP1B → Decrease the amplitude of leptin response.



Dr's notes :
- Obese individuals will have higher levels of Leptin, initially they will have its effects, but it will stop quickly because of the strong activation to the inhibitory process , resulting in almost NO effect.
- **Negative feedback inhibition** on the leptin receptor signaling (PTP1B, TCPTP and SOCS3)

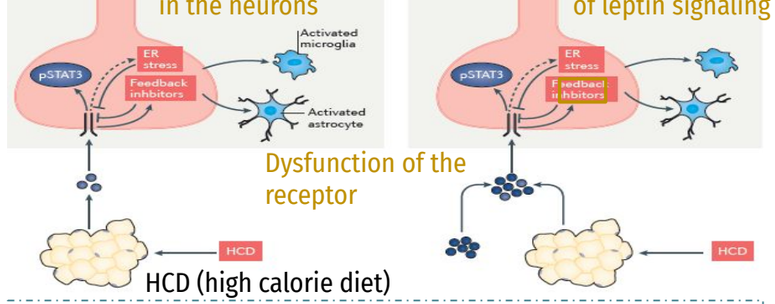
Hypothalamic leptin action and changes during diet-induced obesity.

- **In lean individuals:**



- ↑The expression and weight will be managed
- Exogenous leptin will potentiate the response

- **In obese individuals:**



No benefits of giving them exogenous leptin because the inhibition will increase as will

Adiponectin

- A protein hormone exclusively and abundantly secreted by adipocytes.

Function	-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	-Adiponectin levels are inversely correlated with body fat percentage and parallels with HDL levels. -Low levels are seen in metabolic syndrome and diabetes mellitus.

Ghrelin

- A peptide hormone secreted by stomach.

Secretion	• Secretion increases just before meals and drops after meals. • The body steps up ghrelin production in response to weight loss. • Levels in dieters are higher after weight loss. It recommended to start dieting gradually with small goals • The higher the weight loss, the higher the ghrelin levels.
Function	• Stimulates appetite. • Increases food intake. • Decreases energy expenditure and fat catabolism.

Cholecystokinin

- Peptides released from the gut after a meal
- Sends satiety signals to the brain and slows the gastric emptying

Insulin

- Promotes metabolism

Metabolic Changes in Obesity

Adipocytes send cytokine (Pro-inflammatory) **signals to liver and other organs causing:** Called adipokines

- Dyslipidemia
- Glucose intolerance
- Insulin resistance

Benefits of weight loss in obesity

Weight loss decreases risk factors for obesity leading to:

1. **Lower** blood pressure
2. **Lower** blood glucose levels
3. **Decreased** mortality
4. **Decreased** energy requirements
5. **Decreased** serum TAGs
6. **Increase** in HDL in levels
7. **Beneficial** changes in BMR
8. Slow weight loss is more stable

Treatment options

Lifestyle modification

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 and the amount of the absorbed fat

Surgery

- Surgical procedures are designed to reduce food consumption in patients with BMI >40. Or 35 if they have comorbidity like DM & Hypertension
- Used when other treatment options fail

Extra Summary

obesity	What is obesity?	• A disorder of body weight regulatory systems • Causes accumulation of excess body fat • More than >20% of normal body weight
	Body mass index (BMI)	• BMI is an indirect measure of obesity • Correlates height , weight and amount of body fat in an individual
	Obesity is associated with a high risk of :	• Mortality , Diabetes mellitus, Hypercholesterolemia, High plasma triglycerides, Hypertension, Heart disease , Cancer, Gallstones, arthritis and gout
	Anatomic difference in fat deposition	**1. Android :** • (**Apple shaped**) or upper body obesity • Excess body fat deposited in the central abdominal area • **Associated risk factors are :** hypertension , coronary heart disease, dyslipidemia, diabetes and insulin resistance **2. Gynoid :** • (**Pear shaped**) or lower body obesity. • Fat deposited around the hips or gluteal region • Associated risks are lower
	Biochemical differences in fat deposits	**1. Abdominal Fat :** Smaller cells, More responsive to hormones (Both visceral and subcutaneous), Release substance via portal vein to the liver **2. Gluteal Fat :** Larger cells, Less responsive, Release substance to circulation with no effect on the liver
	Adipocytes	• Triacylglycerols (Fats) are deposited in adipocytes (fat cells) Which can increase in size up to a limit • Fat cells, once gained, are never lost. • Reduction in weight causes adipocyte to reduce in size but not in number
	Factors contributing to obesity	• Genetic • Environmental and behavioral (women, lack of physical activity, depression, ..etc) • Drugs (tricyclic derivatives)
	Causes of weight gain	**Energy imbalance** : calories consumed not equal to calories used over a long period of time due to combination of several factors : individual behavior, social interaction, environmental factors and genetics
	Metabolic changes in obesity	**Adipocytes send cytokine signals to liver and other organs causing:** Dyslipidemia, Glucose intolerance and Insulin resistance
	Treatment options	• Physical Activity combined with healthy diet decreases level of obesity • Dieting • Drugs • Surgery

Hormones	Leptin	• Suppressed in starvation (depletion of fat stores).
		• Enhanced in well-fed state (expansion of fat stores)
		• Required to keep the body weight under control
		• Regulates the amount of body fat by (Controlling appetite and energy expenditure)
		• Two mechanisms by which this leptin-adiposity balance is lost:
		  ○ 1. Leptin resistance.
		  ○ 2. Defect in leptin signaling.

	Adiponectin	• Promotes uptake and oxidation of fatty acids and glucose by muscle and liver. • Blocks the synthesis of fatty acids and gluconeogenesis by hepatocytes. • Adiponectin levels are inversely correlated with body fat percentage and parallels with HDL levels. • Low levels are seen in metabolic syndrome and diabetes mellitus.
	Ghrelin	• Secretion increases just before meals and drops after meals. • The body steps up ghrelin production in response to weight loss. • Stimulates appetite. • Increases food intake. • Decreases energy expenditure and fat catabolism.
	Cholecystokinin	• Peptides released from the gut after a meal • Sends satiety signals to the brain
	Insulin	• Promotes metabolism

Take Home Messages

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

MCQs

1- Leptin:			
A- increases metabolic rate and decreases appetite	B- increases metabolic rate and increases appetite	C- decreases metabolic rate and decreases appetite	D- decreases metabolic rate and increases appetite
2- Orlistat:			
A- inhibits pancreatic proteases	B- stimulate lingual lipase	C- inhibits gastric lipase.	D- inhibits pancreatic amylase.
3-Phosphorylated Y1138 activates:			
A-SOCS3	B- PTPN11	C-STAT5	D-STAT3
4- Gynoid body type is shaped like :			
A- Apple	B- Pineapple	C- Pear	D- none
5- One of the genetic factors contributing to obesity :			
A- Familial tendency	B- Drugs	C- Depression	D- Smoking
6- Appetite is influenced by :			
A- Afferent neural signals	B- Metabolites	C- Circulating hormones	D- All of them

Answers key

1- A 2- C 3- D 4- C 5- A 6- D

SAQs

1- list the Benefits of weight loss in obesity

Answer :
slide 10

2- List 3 Hormones released by adipocytes:

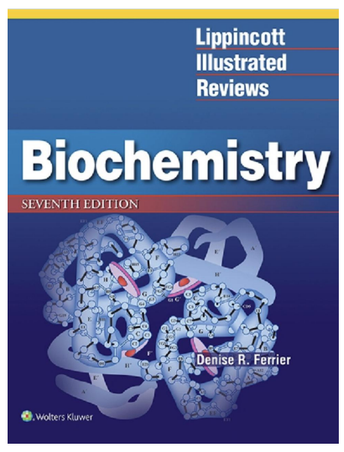
Answer:
1- Leptin.
2- Adiponectin.
3- Resistin.

3- what factors contributing to obesity?

Answer :
slide 6

Resources

Click on the book to download the resource



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Special thanks to Fahad AlAjmi for designing our team's logo.