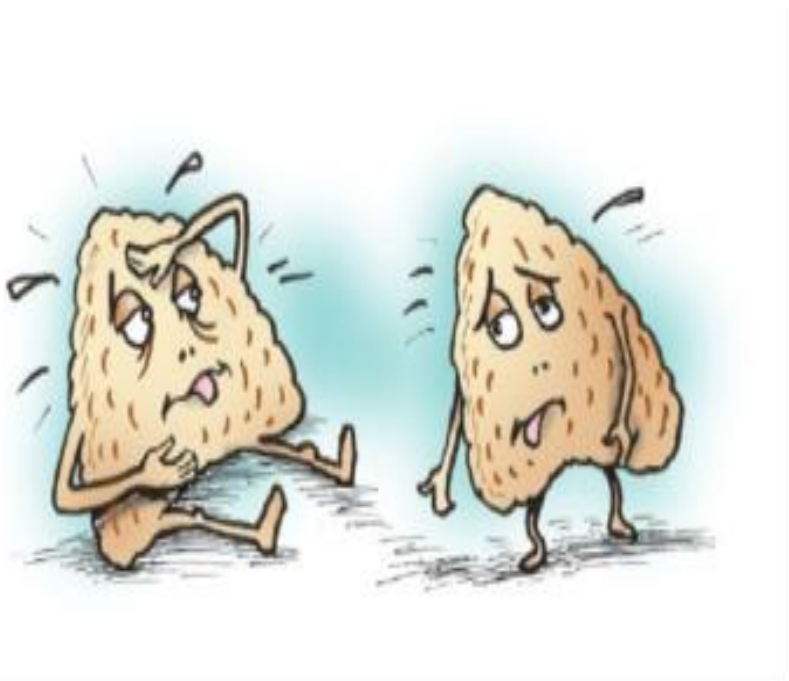
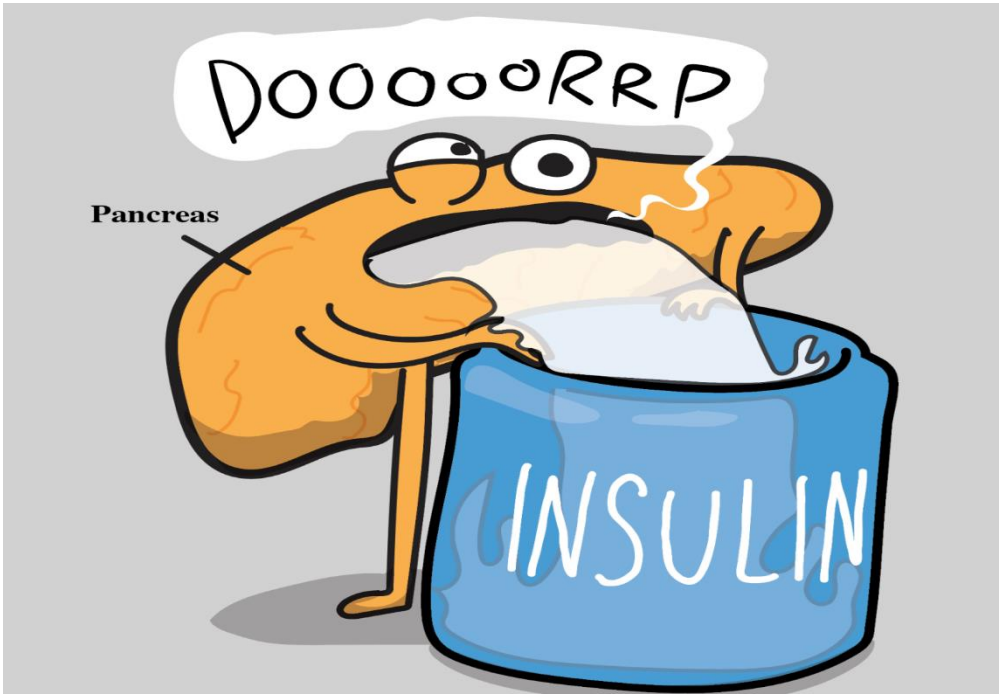
Physiology Revision for Final Exam





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Non-hormonal regulation: for fast exchange which the rapid regulation of ionized (free) calcium, the source of (ca) is amorphous salts (bone fluid).

Hormonal regulation: provide high capacity long term regulation of plasma calcium and phosphate concentrations. The source is hydroxyapatite crystals intestine and DCT in the kidney according to which hormone is regulating

PTH (parathyroid gland)

- Mechanism of action: 2nd massager cAMP.
- Secreted in response to LOW plasma calcium.
- Functions :
  - Kidney:

↑ ca++ and Mg ions absorption.

↓ Phosphate absorption.

In other words it increases renal excretion of phosphate an decease renal excretion of calcium

Activation of active VitD (stimulates α hydroxylase)

  - Bones: induce bone resorption by:

1- ↓ Osteoblastic activity

2- ↑ Stimulating osteoclastic activity and number.

  - Intestinal tract: indirectly by stimulating the formation of active Vit D

Vit D

- Active VitD is catalyzed by α hydroxylase enzyme.
  - PTH
  - Prolactin
  - Low Ca++ ions

All stimulate α hydroxylase

- Functions:
  - Intestinal tract:
    - ↑ Calcium absorption
    - ↑ Phosphate absorption
  - Renal:
    - ↑ Calcium absorption
    - ↑ Phosphate absorption
  - Bone:

Bone resorption.

  - Stimulates differentiation of immune cells.
- Important note:
  - If VitD is taken in smaller quantities:

Induce bone calcification by

1- Increasing calcium and phosphate absorption from the intestine.

  - If VitD is taken in a large amounts:

Induce bone resorption by:

1- facilitating PTH action on bones
2- Stimulating osteoclastic activity and number.

Calcitonin (c cells of thyroid gland)

- Rapid action.
- Secreted in response to High plasma calcium.
- Other stimulants : Estrogen, gastrin, glucagon, secretin,CCK and β adrenoceptor stimulation
- Functions :
- Kidney:

↓ Calcium absorption.

↑ Calcium and phosphate excretion.

- Bones:

↑ calcium deposition of bones

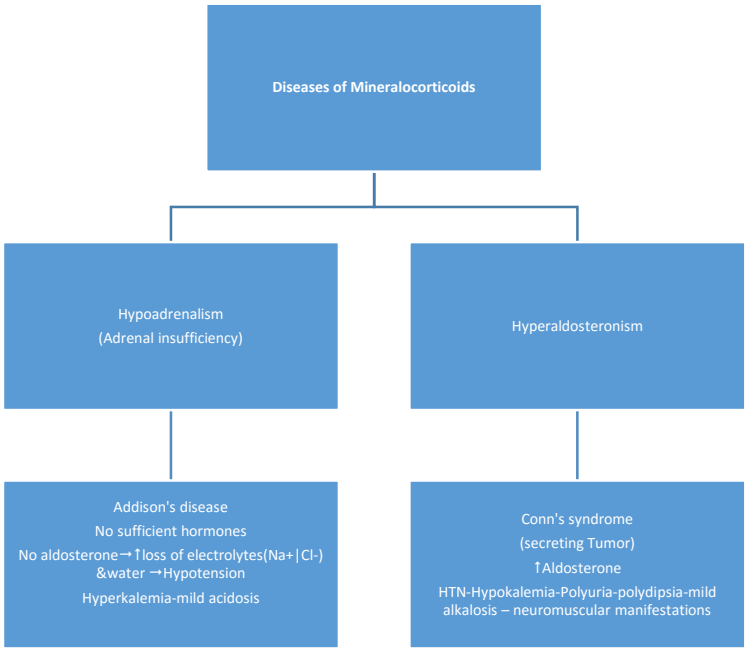
↓ bone resorption

↑ Calcium ↓ Phosphate	↑ Calcium ↑ Phosphate	↓ Calcium ↓ Phosphate

VitD Deficiency		Osteoporosis	Disorders of parathyroid hormone secretion	
Rickets	Osteomalacia		Hyperparathyroidism	Hypoparathyroidism (rare)
• In children • Bone composition: Collagen > mineralized bone. • Features: -low plasma calcium and phosphate -weak bones -tetany: low plasma Ca++ causes CNS excitability and vice versa. • Events: -early stages: normal plasma ca++. There is no tetany. High PTH to cover vitD action. -then the bones become exhausted of calcium, plasma calcium levels drop rapidly. - when blood calcium drop below 7 mg\dl : • Tetany signs (positive Chvostek's sign) • Eventually death because of tetanic respiratory spasm. • Treatment: supplying - adequate calcium and phosphate in the diet - Administering large amounts of vitamin D.	• Adult rickets. • Rare. • Bone composition: Collagen > mineralized bone. • Features: -Low plasma Calcium and Phosphate. -Causes bone disability. -rarely cause tetany. • Causes: -steatorrhea: inability to absorb fats and vitD is a fat soluble vitamin. - Osteomalacia-"Renal Rickets: Chronic renal disease→ vitD activation failure. (↓ 1,25(OH) – D3 synthesis)	• Osteoporosis is the most common of all bone diseases in adults, especially in old age. • Bone composition: Bone mass is reduced so both collagenous and mineralized bone are affected. • Mechanism of development: - the osteoblastic activity in the bone is usually less than normal so the rate of bone osteoid deposition is depressed. - excess osteoclastic activity. (estrogen decreases the osteoclastic activity so that's why female after menopause are more liable to develop osteoporosis) • Causes : (1) lack of physical stress (2) malnutrition (3) lack of vitamin C (4) postmenopausal lack of estrogen (5) old age (6) Cushing's syndrom	• Primary: High PTH , High Ca++. Hypophosphemia Hypercalciuria Demineralisation of bone High Alkaline phosphatase • Secondary: occurs as compensation to low calcium levels. High PTH , Low Ca++ • Causes : 1) Low calcium diet 2) Pregnancy 3) Lactation 4) Rickets 5) Osteomalcia 6) Chronic renal failure ↓ 1,25(OH) – D3 synthesis	• Causes : -parathyroid gland injury -autoimmune. • Low PTH,Low ca++ • Symptoms: Hypocalcemia Tingling in the lips Dry hair Muscle cramps Cataracts on the eyes Malformations of the teeth Loss of memory Headaches Tetany latent or ovret Chvostek's sign Trousseau's sign Delayed cardiac repolarization with prolongation of the QT interval • Treatment : Calcium carbonate and vitamin D supplements

Normal plasma calcium levels: 9-10.5 mg\dl

Steroidogenesis: the conversion of cholesterol into steroid hormones, by the enzyme cholesterol Desmolase to form pregnenolone



RAAS (Renin-Angiotensin-Aldosterone system)

When blood pressure is decreased *renin* will be released from the Juxtaglomerular cells → it will change angiotensinogen (synthesized by the liver) to Angiotensin 1 → ACE in lungs will change angI to ang II → Ang|| will acts on zona glomerulosa to stimulate aldosterone synthesis via increased intracellular cAMP which will decrease Na excretion.

JGA (Juxtaglomerular apparatus)

Is a specialized collection of two cell types:

1- Macula Densa cells

Specialized **chemoreceptor** cells in the wall of the distal convoluted tubule, respond to changes in solute concentration (especially Na levels) in tubular fluid.

Information is conveyed to juxtaglomerular cells which will adjust their output of renin accordingly

2- Juxtaglomerular cells

Specialized smooth muscle cells which act as **mechanoreceptors** , They are stretched in response to increases in the blood pressure of the afferent arteriole. They synthesize and secrete Renin

L9-Mineralocorticoids

- Aldosterone is an essential steroid hormone secreted from Zona Glumerulosa .
- Aldosterone exerts 90% of mineralocorticoids action while cortisol exerts only 10%.
- Parallel to cortisol rhythm, Aldosterone levels are high in the morning and low during night.

Diagnosic tests for Primary Aldosteronism

Test	Range
• Plasma supine aldosterone at 0800h	> 15 ng/dl
• Urinary aldosterone metabolites -18-Monoglucuronide -Tetrahydroaldosterone	 > 20 ug/24h > 65 ug/24h
• NaCl infusion/suppression test	> 10 ng/dl

Actions of Mieralcorticoides :

Stimulates synthesis of Na/K-ATPase pumps, which results in :

- Increase the reabsorption of sodium in the principal cells of the convoluted tubules and collecting ducts.
- Increase the reabsorption of sodium in sweat , salivary and intestinal cells .
- Increase the excretion of pottasium and hydrogen ions from distal tubular cells to the urine .

As a net result it will maintain the extracellular volume

Regulation of Aldosterone

Direct Stimulators	*Indirect stimulators*	*Inhibitors*
High plasma potassium levels	Ang II (RAAS)	ANP
ACTH		

Main glucocorticoids in humans are:

- Cortisol
- Corticosterone

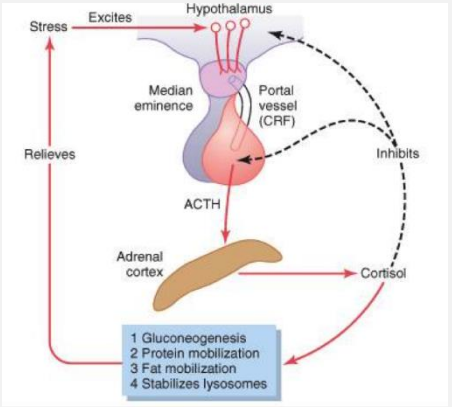
- Cortisol is produced more than corticosterone
- 90-95% is bound to plasma protein
- Under control primarily by **ACTH**

Effects

1. ↑ Blood glucose levels
2. Protein catabolism EXCEPT in liver
3. Lipolysis & redistribution of body fat
4. Anti-inflammatory
5. Immune system suppression

Regulation

Stress and circadian rhythm induce CRH release → ACTH → cortisol



Functions

1. Maintains body fluid volumes & vascular integrity
2. Mineralocorticoid effect (less potent than aldosterone
3. Permissive action on NE
4. ↓ capillary permeability
5. Maintains normal renal function
6. CNS –ve feedback & emotions
7. Anti-vitamin D
8. ↑ HCl
9. Permissiveness of fetal organ maturation
10. Surfactant synthesis
11. ↓linear bone growth

Natural episodic secretion rhythms:

- Cortisol appears 15-30 mins after ACTH gets produced
- There are 7-15 episodes per day
- Major burst is in **the early morning** before awakening

Cortisol excess

Exogenous: Mostly by steroid therapy (prednisone)
Endogenous: ACTH independent or ACTH dependent

Transport

Bind to plasma protein carriers: (because they're steroid hormones)

- Cortisol binding globulin (CBG) (transcortin)
- Albumin

Unbound steroid hormones are the active form
Significance of binding:
1. Acts as reservoirs 2. Ensure a uniform distribution to all

L10-Glucocorticoids

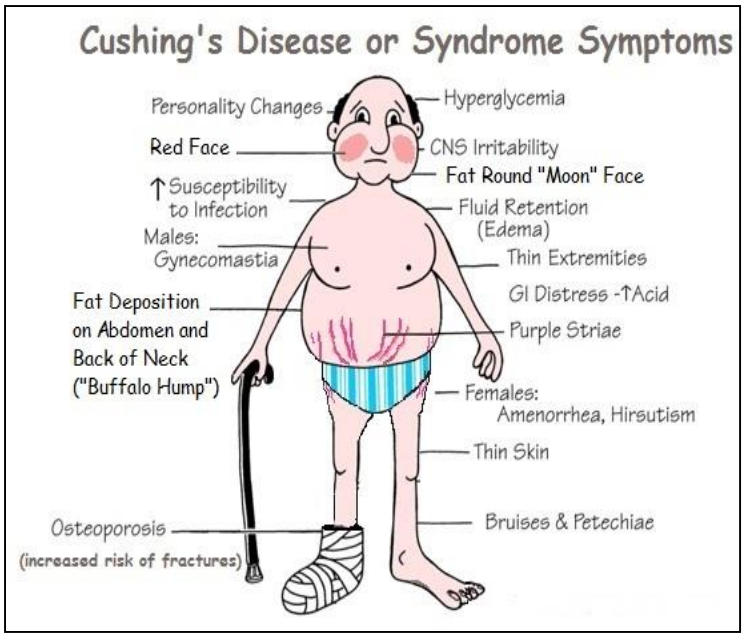
Cushing's

- Excessive amounts of cortisol in the body lead to cushing's syndrome
- Both exogenous & endogenous cortisol excess show manifestations of Cushing's disease

What happens when there's cortisol excess?
Carbohydrates: ↑blood glucose & ↓ sensitivity to insulin may lead to "adrenal diabetes"
Proteins: proteolysis → muscle atrophy & thin skin
Bone matrix & mass losses which may lead to osteoporosis
Fat: ↑trunk & face fat deposition ↓ extremities fat (lemon on sticks appearance)

S Y M P T O M S

Buffalo torso, Moon face, Acne & hirsutism, Striae (due to lack of collagen)



Stimuli

Stimuli releasing cortisol:

- Physical trauma
- Infection
- Extreme heat & cold
- Exercise to the point of exhaustion
- Extreme mental anxiety
- stress

Metabolism

Metabolized in liver by reductases & conjugated to glucuronides & excreted by kidney
Free cortisol → excreted in urine

Note that: Cushing's syndrome is the general term while Cushing's
Disease is caused by a tumor in the pituitary gland that secretes excess ACTH

11/ Adrenal Medulla

Epinephrine 80% More Beta → cardiac stimulation
Norepinephrine 20% more alpha → constrict BV
They are stored and released in response to stimuli.

1

Hormones affect (Fight or Flight)

Metabolism :Glycogenolysis
Cardiovascular: increased HR + BP
Respiration: increased O2 consumption

2

Pheochromocytoma

- Catecholamine-secreting tumor of chromaffin cells in adrenal medulla.
- Classic triad: 1-Resistant hypertension
  2-Headache
  3-Sweating
- Other signs: Palpitation ,Chest pain,Anxiety, Glucose intolerance (DM),encrease metabolic rate.

Diagnosis:
High catecholamines → in plasma
increased metabolites of catecholamines → in urine

Treatment:
Surgical resection

3

12/ Adrenal Androgens

Androgen:

- Masculinizing effect
- Promote anabolism and growth
- Zona reticularis,ACTH (hormone control)
- Target tissue → general body

1

- Most active androgen is testosterone
- Testosterone converted in male to estrogen in adipose tissue.
- In females androgen is produced as intermediate step in estrogen production.(some is released in blood)

2

Effect of adrenal androgen:
1-Growth of pubic & axillary hair
2-pubertal growth spurt.
3-Development and maintenance of female sex drive.

3

Dehydroepiandrosterone (DHEA)

- Steroid hormone
- primary precursor of estrogen.
- most abundant.

Androstenedione:

- Important source of estrogen in men and postmenopausal women.
- Used in Athletic or body building supplement.

4

Congenital adrenal hyperplasia:
Cause: Lack of an enzyme 21- hydroxylase.

- Block of synthesis of cortisol and aldosterone → abnormal feedback →more androgen synthesis

Hyper-secretion: **Adrenal Congenital syndrome**
Males: Prepubertal → rapid development of secondary sexual characters.
Females: causes Beard growth,deeper voice,body hair and clitoris that resembles a penis.

5

Secretion of Insulin:

1. **Glucose enters B cell by facilitated diffusion via GLUT-2**
2. **Glucose is phosphorylated to glucose-6-phosphate by Glucokinase *((rate limiting enzyme)).**
3. **Oxidation of glucose-6-phosphate generates ATP. (by glycolysis).**
4. **ATP acts on ATP-sensitive K+ channel, closing it. (sulfonylurea drug for diabetics works by closing this channel → ↑ insulin)**
5. **Reduced exit of K+ depolarizes membrane.**
6. **Depolarization opens voltage-gated Ca+2 channels.**
7. **Ca+2 enters B cell.**
8. **Ca+2 triggers exocytosis of insulin vesicles.**
9. **Insulin is secreted**

- Insulin synthesis is stimulated by glucose or feeding and decreased by fasting
- Threshold of glucose-stimulated insulin secretion is 100 mg/dl.
- Glucose rapidly increase the translation of the insulin mRNA and slowly increases transcription of the insulin gene
- Glucose is the primary stimulator of insulin secretion!

Glucagon Actions:

Its major target is liver:

Glycogenolysis
Gluconeogenesis
Lipid oxidation (fully to CO2 or partially to produce keto acids "ketone bodies").
Release of glucose to the blood from liver cells
It also acts on adipose tissue but does NOT act on muscles.

Action of insulin on Adipose tissue:

(+) glucose entry
(+) fatty acid synthesis
(+) glycerol phosphate synthesis
(+) triglyceride dep0sition
(+) lipoprotein lipase
(-) of hormone-sensitive lipase
(+) K uptake

Action of insulin on Muscle:

(+) glucose entry
(+) glycogen synthesis
(+) amino acid uptake
(+) protein synthesis in ribosomes
(-) protein catabolism
(-) release of gluconeogenic amino acids
(+) ketone uptake
(+) K uptake

Action of insulin on Liver:

(-) ketogenesis
(+) protein synthesis
(+) lipid synthesis
(-) gluconeogenesis,
(+) glycogen synthesis,
(+) glycolysis.

Diabetes is characterized by the polytriad:

Polyuria (excessive urination).
Polydipsia (excessive thirst).
Polyphagia (excessive hunger).

L13,14-Endocrine Pancreas

Actions of Insulin:

1-Rapid (seconds):

(+) transport of glucose, amino acids, K+ into insulin-sensitive cells.

2-Intermediate (minutes):

(+) protein synthesis
(-) protein degradation
(+) of glycolytic enzymes and glycogen synthase
(-) phosphorylase and gluconeogenic enzymes

3-Delayed (hours):

(+) mRNAs for lipogenic and other enzymes

Glucose Transport:

Name	Location
GLUT 1	**erythrocytes, brain** *Insulin independent
GLUT 2	**liver, pancreas, small intestines, kidney** *insulin independent
GLUT 3	**Brain** *Insulin independent
GLUT 4 *	**muscle, adipose tissue * insulin sensitive transporter**

Insulin Receptor:

-the insulin receptor is a transmembrane receptor
-belongs to the large class of tyrosine kinase receptors
-Made of two alpha subunits and two beta subunits

table 7-7 Comparison of Insulin and Glucagon

	Stimulus for Secretion	Major Actions	Overall Effect on Blood Levels
Insulin (tyrosine kinase receptor)	↑ Blood glucose ↑ Amino acids ↑ Fatty acids Glucagon GIP Growth hormone Cortisol	Increases glucose uptake into cells and glycogen formation Decreases glycogenolysis and gluconeogenesis Increases protein synthesis Increases fat deposition and decreases lipolysis Increases K^+ uptake into cells	↓ [glucose] ↓ [amino acid] ↓ [fatty acid] ↓ [ketoacid] Hypokalemia
Glucagon (cAMP mechanism)	↓ Blood glucose ↑ Amino acids CCK Norepinephrine, epinephrine, ACh	Increases glycogenolysis and gluconeogenesis Increases lipolysis and ketoacid production	↑ [glucose] ↑ [fatty acid] ↑ [ketoacid]

table 7-9 Regulation of Glucagon Secretion

Factors that Increase Glucagon Secretion	Factors that Decrease Glucagon Secretion
↓ Blood glucose	↑ Blood glucose
↑ Amino acids (especially arginine)	Insulin
CCK (alerts alpha cells to a protein meal)	Somatostatin
Norepinephrine, epinephrine	Fatty acids, ketoacids
ACh	

ACh = acetylcholine; CCK = cholecystokinin