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Introduction

complexity of the endocrine system:

- A single endocrine gland may produce multiple hormones
  - The anterior pituitary,
- -Most hormones have multiple actions in their target tissues and are said to have a pleiotropic effect
  - insulin in skeletal muscles
- Some hormones are known to have different effects in several different target tissues
  - testosterone,
  - Vasopressin
- - The same hormone (functionally and chemically) may be secreted by 2 or more endocrine glands
  - Somatostatin
- The same chemical messenger may be either a hormone or a neurotransmitter,depending on its source and mode of delivery to the target cells
  - norepinephrine
- Multiplicity of regulation is also common in the endocrine system
  - For example,1) several different hormones, including insulin, glucagon, epinephrine, thyroid hormone and adrenal glucocorticoids regulate liver glycogen metabolism
    2) Many hormones have the same function, e.g., on the growth,growth hormone doesn't function properly if the insulin isn't present.
- A single target cell may be influenced by more than one hormone
  - For example, liver cells are affected by insulin and glucagon
- 1 Some organs of the endocrine system are exclusively endocrine in function,
  2whereas other organs perform nonendocrine functions in addition to secreting hormones, these organs are called mixed organs
  - 1 Anterior pituitary gland and thyroid gland
  - 2 The testes ,the intestines, the kidneys, the pancreas, the stomach and the heart and the brain. brain has something special

Interactions Between Hormones

- 1- Permissive effect (Permissiveness):
  (0+1=2)
  thyroid hormone & adrenalin (epinephrine) (fatty acid release)
- 2- Synergistic effect (Synergism):
  -(1+1>2)
  -Mammogenic hormones & Lactogenic hormones & Galactokinetic hormones (milk)
- 3 Antagonistic effect (Antagonism):
  -calcitonin (CT),& parathyroid hormone (ca level)
  -Insulin & Glucagon (glucose level)

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Hormone type and mao

Protien hormone

Protein Hormones that use Adenylyl CyclasecAMP 2nd messenger pathway

Adrenocorticotropic hormone (ACTH)	Human chorionic gonadotropin (HCG)
Angiotensin II (epithelial cells)	Luteinizing hormone (LH)
Calcitonin	Parathyroid hormone (PTH)
Catecholamines (β receptors)	Secretin
Corticotropin-releasing hormone (CRH)	Somatostatin
Follicle-stimulating hormone (FSH)	Thyroid-stimulating hormone (TSH)
Glucagon	Vasopressin (V2 receptor, epithelial cells)

Protein Hormones that use the PLC 2nd messenger pathway

Angiotensin II (vascular smooth muscle)	
Catecholamines (α receptors)	
Goadotropin-releasing hormone(GnRH)	
Growth hormone-releasing hormone(GHRH)	
Oxytocin	
Thyrotropin releasing hormone(TRH)	
Vasopressin (v1 receptor, vascular smooth muscle)	

2- Amino acid derived hormones

A. Catecholamines (Epinephrine, norepinephrine, and dopamine) cell surface receptors,

B. Thyroid hormones (lipophilic) intracellular receptors & nuclear receptors

3- Steroid hormones

cytoplasmic receptors & nuclear receptors directly.
Note: Sometimes for rapid action and quick response sex hormones (especially female sex hormones: estrogens and progesterone) bind to receptors on the cell membrane rather than intracellular receptors.

4Other examples

Hormones that follow Tyrosine kinase mechanism, e.g. Insulin

following cGMP mechanism, e.g. NO and ANP receptors

pituatry gland

Physio2

The Pituitary Gland

Posterior pituitary lobe

Two types of nuclei

1- The Paraventricular nucleus mainly produces Oxytocin

2- The Supraoptic nucleus which produces ADH

ADH binds to V2 receptors in distal tubules and collecting ducts of the kidney.
1- Regulates serum osmolarity: by increasing the reabsorption of water in the renal tubules.

Vasopressin binds to V1 receptors in blood vessels.
Vasoconstriction

1. Stimulators of ADH
A. Increased serum osmolarity.
B. Decreased extracellular fluid (ECF) volume.
C. Stress-related factors: nausea, pain, vomiting, nicotine, opiates (analgesic drugs like morphine), and hypoglycemia.
D. Anti-neoplastic drugs.
2. Inhibitors of ADH
A. Ethanol.
B. α-Adrenergic Agonists.
C. (ANP) Atrial natriuretic peptide—hormone secreted from the atria of the heart.
D. Decreased serum osmolarity.

- ADH and Oxytocin
They differ from each other in just two amino acids:
NH3-Gly-Tyr- X -Gln-Asn-Cys-Pro- Y -Gly-N
In Oxytocin → X represents Ile // Y represents Leu
In ADH → X represents Phe // Y represents Arg

Anterior Pituitary lobe

Cells of Anterior Pituitary

Table 76-1 Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Action
Somatotropes	Growth hormone (GH) (somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of insulin-like growth factor-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH) (corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH) (thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing (LH) hormone	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes-Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

1. Cells that release Tropic hormones stain basophilic.

Corticotropes: cells release Adrenocorticotropic hormone ACTH (corticotropin) / About 20%

Thyrotropes: cells release Thyroid stimulating hormones TSH

Gonadotropes: cells release both Follicle-stimulating hormones FSH and Luteinizing hormones LH

2. Cells that release non-tropic hormones

Somatotropes: cells release somatotropin (also known as growth hormones GH) / acidophilic./ 30-40%

Lacotropes (mammotropes): cells release Prolactin.
****Note:The mammary glands are exocrine glands not endocrine which are the target of prolactin,*****

Note: GH is a single chain polypeptide that is homologous with prolactin.

Hypothalamic Hormones that stimulate or inhibit the secretion of the pituitary hormones:

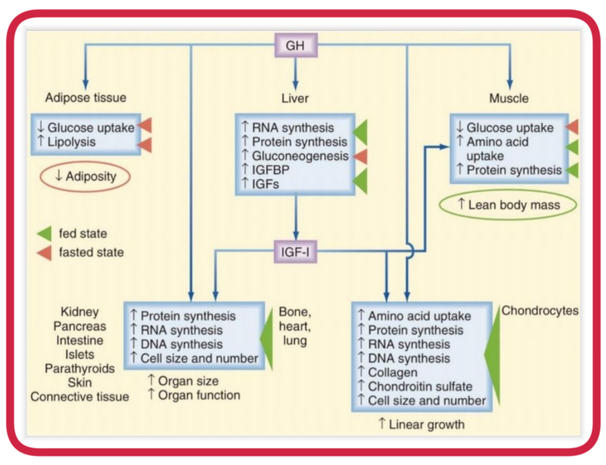
✓ Corticotropin Releasing Hormone (CRH) that stimulate corticotropes to release ACTH.
✓ Thyrotropin Releasing Hormone (TRH) -a polypeptide of 3 amino acids- that stimulate thyrotropes to release TSH.
✓ Growth Hormone Releasing Hormone (GHRH) that stimulate Somatotropes to release GH
✓ Growth Hormone Inhibitory Hormone (GHIH/Somatostatin) that inhibit the release of GH from Somatotropes.
✓ Gonadotropin Releasing Hormone (GnRH) that stimulate Gonadotropes to release LH and FSH.
✓ Prolactin inhibiting hormone (PIH/Dopamine)
**Note :All the hypothalamus hormones are peptides except dopamine (a catecholamine)
** Growth hormone has stimulatory and inhibitory hormones, while other hormones have only stimulatory hormone as they are regulated by a feedback mechanism.
**There may be a stimulatory hormone for prolactin but the inhibitory hormone exerts more function & control

growth hormone

Hormones functioning with growth hormone
o Multiple hormones, including growth hormone (GH), insulin – like growth factors 1&2 (IGF-I and -II) ,insulin ,thyroid hormones, Glucocorticoids, androgens & estrogens contribute to the growth process in humans
INSULIN AND GROWTH HORMONE
** GH and insulin function synergistically

GH effects on body tissues

Directly:
1. Adipose tissue:
2. Liver cells
3. Muscle cells:



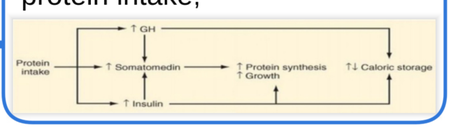
Indirectly:
By somatomedins (Insulin like Growth Factor (IGF-I)) its 6 types
They increase organs size and function

METABOLIC EFFECTS OF GROWTH HORMONE

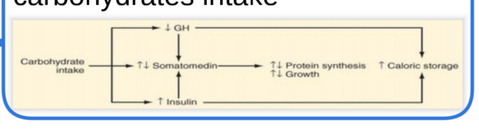
●Net effect: GH enhances the body protein, uses up the fatty stores and conserves carbohydrates.
●Can cuase diabetogenic effect , this effect can be achieved by at least three hormones other than GH, Including Adrenocorticotropin (ACTH), Thyroid-stimulating hormone (TSH) and Prolactin.
●Can cause ketogenic effect

Diets

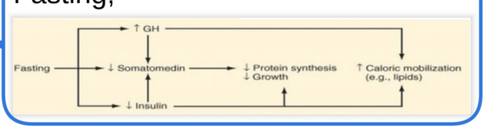
protein intake,



carbohydrates intake



Fasting,



1 Negative feedback control of GH release:
& 2 FEEDBACK MECHANISMS FOR CONTROL OF FOOD INTAKE

1 • GHRH inhibits its own secretion directly. (ultra-short loop).
• By stimulating the secretion of somatomedin which stimulates somatostatin secretion (which in turn inhibits the release of GH)
• by stimulating the secretion of somatostatin directly

2 - Stretch receptors
- Peptide YY ,CCK (cholecystokinin) & insulin>satiety
-Ghrelin >hunger - Leptin >satiety

Factors that stimulate or inhibit GH secretion

Stimulate GH secreation	Inhibit GH secreation
Decreased blood glucose	Increased blood glucose
Decreased blood free fatty acids	Increased blood free fatty acids
Increased blood amino acids (arginine)	Aging
Starvation or fasting, protein deficiency	Obesity
Trauma, stress, excitement	GH inhibitory hormone (somatostatin)
exercise	GH exogenous
Testosterone, estrogen	Somatomedins (IGF'S)
Deep sleep (stage II & IV)	
Growth hormone-releasing hormone	
ghrelin	

HORMONES OF PUTITARY

ANTERIOR LOBE	POSTERIOR LOBE
Tropic :ACTH,FSH,LH,TSH	Oxytocin
NON Tropic: MSH,GH &Prolactin	ADH (Vasopressin)

Abnormalities

Hypofunction secretion:

1. Panhypopituitarism
Deficiency in all hormone

2. Severe anterior pituitary deficiency:

3. Moderate anterior pituitary deficiency:
deficiency in all anterior pituitary hormones except STH (GH) ,it is normal.
MSH&ACTH are partially deficient, Gonadotropin &TSH are deficient.

4. Mild anterior pituitary deficiency
only Gonadotropins hormones (FSH& LH) are deficient,

GH over secretion

Gigantism:
before adolescence
(genetic – not tumor)

acromegaly:
(the adult form of the disorder)
(tumor after adolescence)

adrenal gland

Adrenal gland

two major parts

1. The adrenal medulla:
secretes the catecholamines (epinephrine and norepinephrine)

2. The adrenal cortex:
-secretes adrenocortical steroid hormones, synthesized from cholesterol.
- has 3 zone:

A. zona reticularis (23%)
produce androgens and estrogens

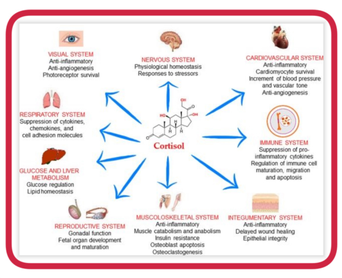
B. Zona fasciculata
secrete glucocorticoids (mainly cortisol) which function in metabolism of glucose,

C. zona glomerulosa
secretes mineralocorticoids (mainly aldosterone), they control the metabolism of minerals

Note :The adrenal cortex hormones are essential for life because they:
1- Control Na+, k+ and H2O metabolism (ECF volume).> (Mineralocorticoids).
2- Control carbohydrate, fat and protein metabolism and mobilization for energy.
3- Participates in responses of stresses of various kinds.(cortisol)
Note : no hormones stored in the adrenal cortex

Glucocorticoids (Cortisol)

Functions:
1- Production of glucose from non-carbohydrate sources (gluconeogenesis).
2- Facilitates fat mobilization.
3- Increases the response of blood vessels to catecholamines.
4- Modulates CNS function.
Note:* cortisol & glucagon > (permissive effect). (glycogenolysis)
*in the kidney "hydroxysteroid dehydrogenase" that inactivates cortisol.



Cortisol binding:
90% >> bound to corticosteroid-binding proteins.
6% >> bound to albumin.
4% >> "free" >> This is the only amount that is functional

: There are natural as well as synthetic glucocorticoids:
1. Cortisol: natural,
2. Corticosterone: natural
3. Cortisone: synthetic, almost as potent as cortisol.
4. Methylprednisone: synthetic, five times as potent as cortisol.
5. Dexamethasone: synthetic, 30 times as potent as cortisol.

Adrenocorticotropic Hormone (ACTH) in Regulating Cortisol:
-Adrenocorticotropic hormone ACTH, an anterior pituitary hormone
- CRH and ADH are the main stimuli for ACTH secretion
- ACTH has extra-adrenal actions like lipolysis and MSH-like action.

The Synthesis of the Adrenal Cortical Hormone

Mineralocorticoids (Aldosterone)

Function
controlling the balance of water and salts in the kidney by keeping sodium in and releasing potassium from the body and finally increasing the blood pressure

Bindind:
20% bound to corticosteroid binding proteins (transcortin).
40% bound to albumin.
40% free

Types:
1. Aldosterone: (natural)
2. Deoxycorticosterone: (natural)
3. Corticosterone: slight mineralocorticoid activity.
4. 9-alpha-Fludrocortisone: synthetic
5. Cortisol: very slight mineralocorticoid activity, but a large quantity is secreted.
6. Cortisone: slight mineralocorticoid activity.

Stimulating factor:
1. Angiotensin II from the renin angiotensin system. (the strongest effect)
2. High potassium & low sodium in blood.
3. ACTH from the anterior pituitary gland (the weakest effect).

The Renin Angiotensin System (RAS)

Steps :
1 convert the precursor prorenin into renin
2. Plasma renin convert angiotensinogen (released by the liver) into Angiotensin I.
3. Angiotensin I is subsequently converted to angiotensin II by the angiotensin converting enzyme (ACE) found in the lungs.
4. Angiotensin II is a potent vasoconstrictor , stimulates the secretion of the hormone aldosterone from the adrenal cortex.
5. Aldosterone causes the renal tubules to increase the reabsorption of sodium and water into the blood, while at the same time causing the excretion of potassium

Aldosterone mechanism of action:
يعمل داخل النواة

Aldosterone induces the transcription of new membrane transport proteins (Sodium channels, potassium channels and sodium potassium pumps), all these contribute to enhance the secretion of potassium from the blood to the urine, and enhances the reabsorption of sodium from urine back to the blood. Water will follow the concentration of the sodium (to the blood), so the final result will be an increase in blood pressure.

Drug inhibit action of aldesteron:
-Amiloride (inhibit the reabsorption of sodium from sodium channels)
-Spironolactone (bind to MR protein).

The mechanism of action of Angiotensin II

1. DIRECT effect on renal tubules by:
A. stimulating the sodium potassium ATPase pump (basolateral membrane)
B. stimulates sodium-hydrogen exchange in the luminal membrane
C. Angiotensin II stimulates sodiumbicarbonate co-transport in the (basolateral membrane)

2. INDIRECT effect on renal tubules by constriction of the peritubular capillaries

Note: Aldosterone functions are not on the renal tubules only but also on other glands like salivary glands, intestines, as well as on the sweat glands, so it reabsorbs sodium in all these organs

Comparison between aldosterone and cortisol

Notes :
-Secretion rate : cortisol is secreted at a much higher rate than aldosterone
-the relative contribution of cortisol as a mineralocorticoid is much more than that of aldosterone as a glucocorticoid; because cortisol has a higher secretion rate.

Androgens & Estrogens
-Weak androgens:
• dehydroepiandrosterone • androstenedione
- Strong androgens:
• Testosterone • Dihydrotestosterone (the strongest)
- Estrogens:
• Estradiol • Estrone • Estriol
Androgens Function
• In males → Secondary sexual characteristics & Spermatogenesis
• In females → pubic & axillary hair, libido

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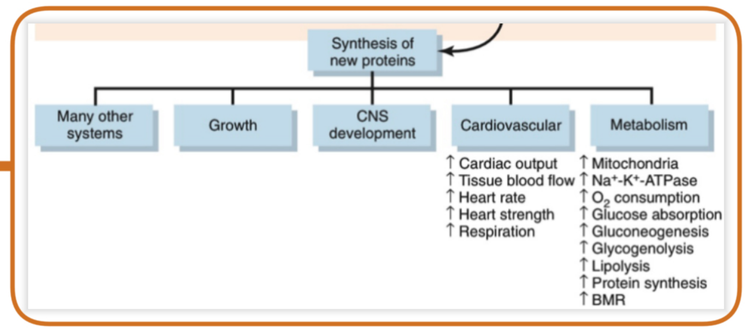
Thyroid gland

Thyroid Hormone Secretion

Function



↑ metabolism

Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors
TSH	I⁻ deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I⁻ intake (Wolff-Chaikoff effect)
	Perchlorate; thiocyanate (inhibit I⁻ pump)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

➢ TRH from Hypothalamus
➢ TSH from Anterior Pituitary
Note: ➢TSH stimulated by TRH and inhibited by cortisol, growth hormone, dopamine and somatostatin

Hormone interaction

• Thyroxine at normal concentrations has a permissive effect on the action of GH on protein

Dissorder

Hypothyroidism
Childs: Cretins (Cretinism).
Adult :Myxoedema.

Hyperthyroidism
1- Exophthalmos
2- Goiter
3- Graves' Disease
Types of Goiter:
1- T3, T4 are low (Benign non-toxic goiter) ? hypothyroidism
2- T3, T4 are High (malignant toxic goiter) ? hyperthyroidism

Important note
➢ Thyroid Gland
• By 12 weeks of gestation the gland produces hormones that are essential for normal development of the nervous system and skeletal during the fetal life
•Secretes thyroid hormone and calcitonin
➢ TSH composed of two peptides subunits: Alpha (α) subunit & Beta (β) subunit:
➢ some enzymes used in synthesis of Thyroid Hormones:
• Sodium-iodide symporter
• chloride-iodide ion counter-transporter molecule (pendrin)
•Thyroglobulin •peroxidase •proteases
➢ Thyroid hormones are essential in normal amounts for growth; excess does not produce overgrowth as with GH, but causes increase catabolism of proteins & other nutrients

Parathyroid and ca+2

Parathyroid Gland + Calcium metabolism

Calcium
- Normal levels ≈ 10-11 mg/dL

Function
- Maintains normal Na permeability
- Involved in exocytosis process (like Ach)
- Important for muscle contraction
- Serves as intracellular messenger
- Important for enzymes activity
- Require for blood clotting
- Constituent of the bones
- Required for proteins secretion (or hormones secretion like insulin)

2 forms
- (non-diffusible)
- Diffusible

Calcium Regulators
- PTH
- vit d
- Calcitonin

Phosphate

Function
- Part of intracellular buffer system
- Constituent of the bone (85% of the bone)
- Important constituent of variety of macromolecules such as (nucleic acids, phospholipids, metabolic intermediates and phosphoproteins)

Parathyroid Glands Give PTH

two types of cells
1. Chief cells: produce PTH
2. Oxyphil cells

Funtion
- [1] Bone
  Increase bone resorption
- [2] Kidneys
  Increase Ca+2 reabsorption and Phosphate excretion
  Stimulates Vit D activation
- [3] Intestines
  Increase Ca+2 absorption

Regulation
- ↑ Phosphate
- ↓ Calcium
- ↓ Magnesium

Disorders
- 1^ Hyperparathyroidism
  Ca level will increase above 16 mg/dL
  - Osteitis fibrosa cystica
  - Hypercalcemia (bones, stones, groans, and psychic moans)
  - conistipation
- Hypoparathyroidism
  lower than 6mg/Dl
  - Hypocalcemia (increased excitability (tetany))

Vitamin D

Types
- Vitamin D2 [ergocalciferol](from vegetables)
- Vitamin D3 [Cholecalciferol] (made in the body
  1,25(OH)2D > 24,25(OH)2D > 25-(H)-D

1,25(OH)2D **stimulated by**
Prolactin/ GH/insulin/pTH/deficiency of vitD, ca or phosphate

Effects
- [1] Bones
  - Effect is similar to PTH , promoting its function - synergism -
  - Plasma Ca and phosphate level will increase to the normal limit
  has a role in bone mineralization and remodeling
- [2] Intestines
  Increases Ca and phosphate absorption
- [3] Kidney
  Increases Ca and phosphate reabsorption

Calcitonin
- Functions
- It decreases Ca levels (antagonizes PTH)
- It decreases Phosphate level
- Calcitonin is less important than other calcium regulators (easily compensated)

Disorders of vitD deficiency And bone disease
1. Rickets
2. Osteomalacia “Adult Rickets”
3. Osteoporosis

Pancreas + Glucose level

Pancreas,

insulin

- Mixed Gland
- Exocrine (acinar cells)
- Endocrine (islets of Langerhans) 2% Hormones

Cell Type	Percentage	Hormone
Alpha cells	20%	Glucagon + Proglucagon
Beta Cells	75%	Insulin + C peptide + Proinsulin + amylin
Delta Cells	3-5%	Somatostatin
F cells	<2%	Pancreatic Polypeptide
Epsilon Cells	<1%	Ghrelin

Functions :

i. Activation of glucose transporters, for the entry of glucose to cells.
ii. Insulin produces two other second messengers IP3 and DAG, these mostly play a role in the entry of amino acids as well as minerals(potassium , phosphate and magnesium)
iii. Stimulates protein synthesis.
iv. Stimulates fat synthesis.
v. Inhibits gluconeogenesis
vi. Promotes growth and gene expression (remember that growth does not occur in the absence of insulin even if GH is present).

- Factors affecting Insulin secretion:

- Factors affecting Insulin secretion:

Stimulatory Factors	Inhibitory Factors
1) Increased glucose concentration 2) Increased amino acid concentration 3) Increased fatty acid and ketoacid 4) concentration 5) Glucagon 6) Cortisol 7)Glucose-dependent insulinotropic peptide (GIP) 8) Potassium 9) Vagal stimulation;acetylcholine 10) Sulfonylurea drugs (e.g.,tolbutamide, glyburide) 11) Obesity	1) Decreased blood glucose 2) Fasting 3) Exercise 4) Somatostatin α-Adrenergic agonists 5) Diazoxide

Regulation of Plasma Glucose

- Short term regulation (Insulin vs Glucagon and others)
- Insulin is the only hormone that LOWERS plasma glucose
- Glucagon is the most important hormone that INCREASES glucose
- Cortisol, Catecholamines, Thyroid hormone, and GH also INCREASE plasma glucose (but more long-term)

Summary of Glucose-Counterregulatory Controls

	Glucagon	EPI	Cortisol	GH
Glycogenolysis	X	X		
Gluconeogenesis	X	X	X	X
Lipolysis		X	X	X
(Inhibition) Blockade of Glucose Uptake			X	X

Important note:

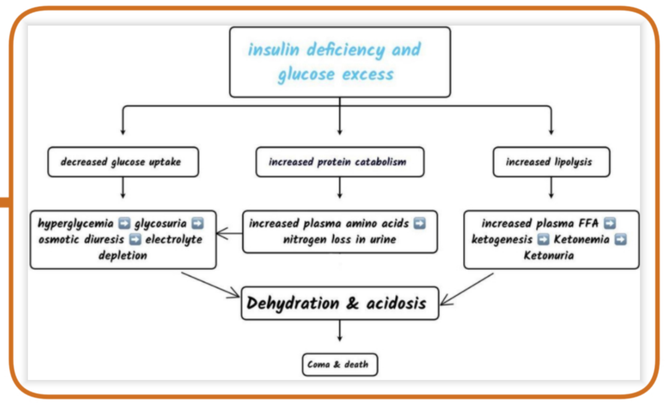
- Amylin acts as a neuroendocrine hormone that complements the action of insulin (synergism) in postprandial glucose homeostasis
- Insulin :Composed of two chains (connected by disulfide bridges)
A chain >composed of 21 amino acids
B chain >composed of 30 amino acids
- Cortisol has permissive action with glucagon in stimulating gluconeogenesis.
- Adrenaline has permissive hormonal interaction with glucagon in stimulating lipolysis
- cortisol is more potent and stronger than GH in providing glucose.
- Some tissues uptake glucose without insulin (Brain, kidney tubules, intestinal mucosa, RBCs)

Pancreas disease

effects of insulin deficiency

on fat metabolism
- Hormone-sensitive Lipase (HSL) in fat cells becomes strongly activated
- Hydrolysis of Triacylglycerols → FA + Glycerol
- FA → Ketoacids (β-hydroxybutyrate, acetoacetate, acetone)
- Acidosis
- Na+ replaced by H+

On protein metabolism
- Decrease protein synthesis
- Increase protein degradation
- Amino acids are then used for energy or gluconeogenesis
- Increased urea
- Weakness



cause coma
- Hyperglycemia
- Hypoglycemia (<40)
- Hyperosmolar state
- Lactic acidosis
- Brain edema (due to ketoacidosis)

DM 1
- Insulin-dependent diabetes mellitus IDDM
- Antibodies against Beta cells → Decrease in insulin production
- Usually young age, low to normal weight
- Treated by insulin injections

DM 2
- Non-insulin-dependent diabetes mellitus (NIDDM)
- Decrease insulin sensitivity
- Usually old age, obese, sedentary lifestyle
- Treated by
- Insulin sensitizers in the liver cells (biguanides)
- Insulin sensitizers in the peripheral tissues (glitazones)
- Insulin secretagogues (sulfonylureas)
- Drugs the decrease carbohydrates absorption (α-glucosidase inhibitors)
- Drugs the increase glucose excretion (SGLT2 inhibitors)

Glucagon
- Ingestion of proteins appears to be the major stimulus to the secretion of glucagon
- Mainly affects the liver as well as other tissues
- Stimulates gluconeogenesis, ketogenesis, glycogenlysis

Done by:
Abdulla halawa