Endocrine system

Biochemistry

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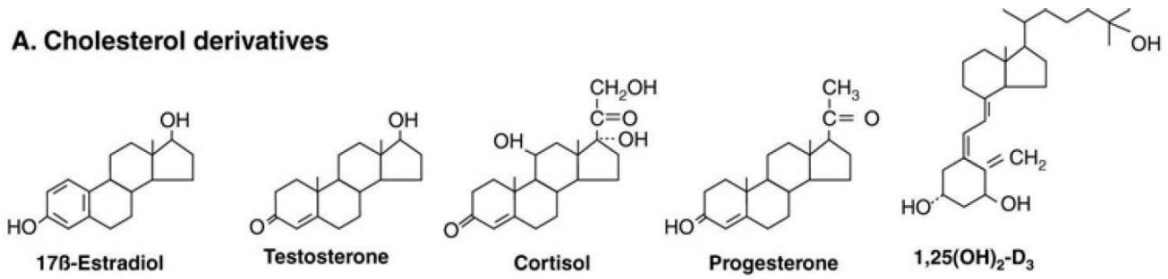
Last lecture we went through the definition of hormones, classification according to effect, interaction with the nervous system, biochemical problems posed on the endocrine system, Kd, receptors, domains, signal amplification, loops to control hormone action, chemical structure classification and mechanism of action.

Examples on Steroids Hormones Families:

Remember:

- **They are cholesterol derivatives (have sterol nucleus consist of 3 six-membered rings and 1 five-membered ring fused together)**
- **Hydrophobic so they need carrier**
- **Slow acting mainly on DNA level**

Sex hormones - are divided into 3 groups	Hormones of Adrenal Cortex
1. Male sex hormones or Androgens 2. Female sex hormones or Estrogens 3. Pregnancy hormones or Progestines	1. Mineralocorticoids: aldosterone. 2. Glucocorticoids: cortisol. 3. Adrenal androgens: male sex hormones mainly dehydroepiandrosterone (DHEA) and testosterone



Non-steroid hormones

A. Peptide and protein hormones

All hypothalamic, pituitary, digestive hormones

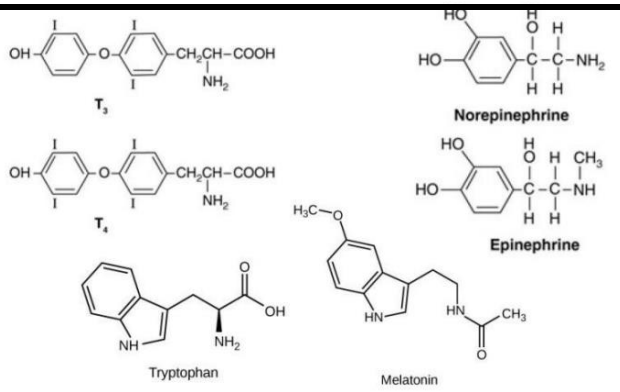
All pituitary hormones are made from short single polypeptide chains

EXCEPT: TSH; FSH; LH (big glycoproteins homodimers (≈ 25 kDa))

B. Amino acid derivatives

Amines - derived from tyrosine (epinephrine, norepinephrine, dopamine, TH) or tryptophan (melatonin, serotonin)

Tyrosine has a phenol group. Addition of another phenol group gives thyroid hormones T3 or T4 (according to the number of iodine ions)



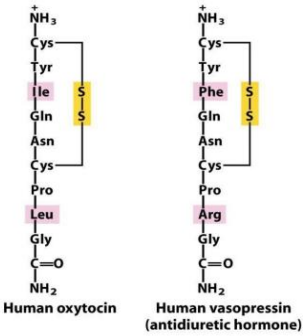
Doctor said that he isn't interested in the exact number of amino acids of each hormone, but you must know some of them like TRH the smallest peptide hormone in our body which is secreted from hypothalamus towards pituitary gland (consists of 3 amino acids only)

Hormone	Structure
GHRH	44
TRH	3
GnRH	10
CRH	41
ADH	9
Vasopressin	9
Angiotensin I	10
Angiotensin II	8
Insulin	51
Glucagon	29

You must know that these hormones are peptides and the general size of them for example insulin is a large peptide hormone

Note: Angiotensin I (which is released from kidneys) is converted to Angiotensin II by ACE enzyme in the lungs by cleavage of two amino acids, it works as artetiolar vasoconstricter

Also you must be familiar with posterior pituitary gland hormones: vasopressin (ADH) and oxytocin



They are nonapeptide
They differ in the 3rd and 8th amino acids (which is responsible for function difference)

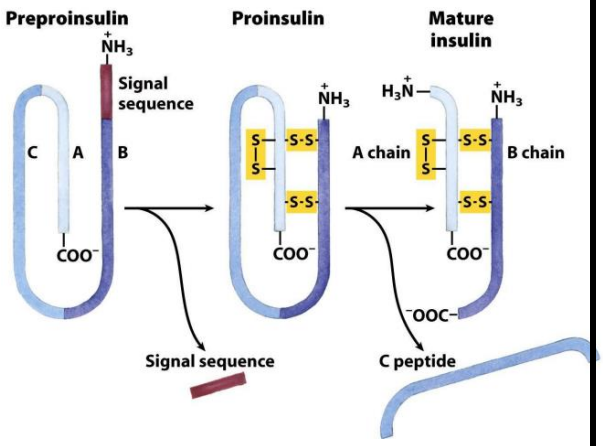
Synthesis of peptide hormones

1. **from precursor gene**

ex. vasopressin (ADH) and oxytosin
Synthesis in separate cell bodies of hypothalamic neurons (supraoptic nucleus, paraventricular nucleus) from related genes then stored in posterior pituitary

2. from precursor preprohormones ex. insulin

Certain gene will be transcribed and translated to amino acids sequence (preproinsulin) then number of amino acids known as signal sequence (in insulin they are 23 AA) will direct it to the ER then is removed in ER resulting in what is called proinsulin which provides the conformation necessary for the proper and efficient formation of the 3 disulfide bridges, the structure of proinsulin is B chain— connecting (C) peptide—A chain.
C peptide is removed by certain enzymes results in mature insulin (A and B chains only)

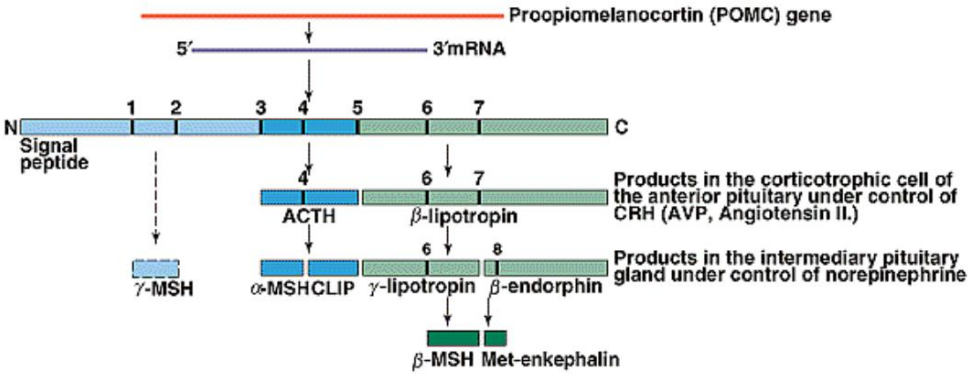


3. from precursor polypeptide such as

We can have large mRNA which is translated to a large peptide which can be cleaved at many sites depending on specific enzymes that are present in the tissue

So one gene may code more than one hormone and the cleavage site depends on availability of specific enzymes

For clarification this peptide in the lungs will be cleaved at point X producing two active hormones while in the heart it will be cleaved at point Y (due to enzymes variation in different tissues) producing another 2 active hormones with different functions ex. proopiomelanocortin (POMC)



Pro: not mature

Opio: analgesic (opioid related)

Melano: melanine related

Cortin: cortisol related

Similar to above concept, it can be converted from another active compound ex. Angiotensin I is cleaved to become Angiotensin II

TARGET CELLS INTERACTIVE EFFECT:

Hormones interacts at target sites, if a cell is affected by more than one hormone there might be interaction between these hormones on the cell.

Types of these interactions

Permissive effects: one hormone enhances the effect of a later, first hormone is a requirement for the second work, so if I put the second one before, it will not work. (most common way that first hormone stimulates surface receptors synthesis of the cell at the gene level, so it becomes able to respond)

- **Estrogen up-regulates progesterone receptors in uterus**
- **Thyroid hormone increases the effect of epinephrine on breakdown of triglycerides in adipocytes**

Integrative effects: hormones have the same, complementary effects but with no potentiation (the first hormone is doing an action the second is doing the same action so either you will have this or that)

- **PTH and calcitriol increase ECF calcium**

Synergetic effect: both of them share the action in a way that produces a much stronger effect than each one together. (1 + 1 > 2).

Antagonist effect: effect of hormone opposed by another hormone.

- **Insulin and glucagon**

Transduction of the signal:

Transduction: conversion of one form of a signal to another so as cells can produce many kinds of responses in different ways.

Why amplification is A MUST??

1-There is Low concentrations of hormones but high affinity, so we achieve the effect in short duration.
2-Regulation is better because we can easily inhibit little number of receptors.

3-Energy conservation

4- بزبطش احط عخلية مليون ريسبتور عشان هرمون واحد ما بوسع

Signal (polar, large) should bind receptors:
Receptors of hormones are Intrinsic membrane proteins non-integral

side note: Both intrinsic and integral proteins present in cell membrane both are transmembrane, but the difference is that if we removed intrinsic protein, the membrane will be destructed and the cell dies, so it is more attached, so its movement is hard and restricted and they are few in numbers

Second messengers

Some general characteristics of the second messengers:

- Ability to diffuse to other cellular compartments
- Amplification of the signal by:
  - Enzyme activation
  - Membrane channels
- Some second messengers are common in multiple signalling pathways (≈ 30 hormones uses cAMP!!!)

  Permits fine tuning but can pose problems
- Types of 2nd messengers:
  - Small molecules: cAMP,cGMP,Ca+2
  - Phosphorylation through kinases

How signal transduction ends up??

Firstly, we must terminate the action because it keeps cells responsive to new signals. Also, failure of termination may cause problems like cancers and overgrowth.

HOW IS IT ACHIEVED??

1-Detachment of the hormones when concentration decreased (no more saturation of receptors).

2-Desensitization of the signal. (Decreased number or affinity of receptors)

3-Degradation of the second messengers.

4-Oppose the actions (dephosphorylate the phosphorylated proteins).

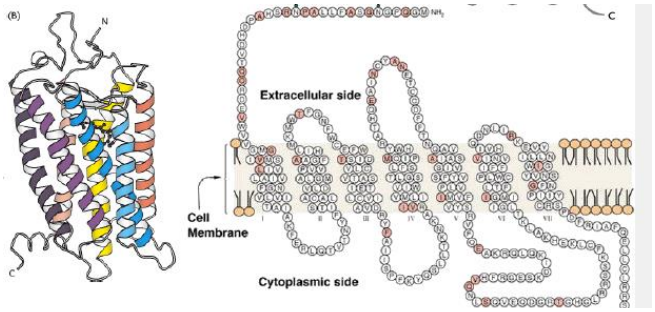
Membrane associated receptors 7 transmembrane helix receptors (7 TM)

7 alpha helices spanning the membrane have outside and inside parts, the bind the membrane with H bonding, rigid.

They are hydrophilic in nature because there is hydrogen bonding between backbone of amino acids as it is secondary structure. Although, they are stable inside the hydrophobic membrane due to the extensive Hydrogen bonding which prevents it from being able to bind with outside (no place left), so it becomes hydrophobic.

Signal induces conformational change, so it makes an action at cytoplasmic side.

Cytoplasmic side is rich in serine and threonine mainly which give it's the ability to become phosphorylated



Biological Functions Mediated by 7TM

- Examples:
- Smell, Taste, Vision
- Neurotransmission
- Hormone Secretion
- Chemotaxis
- Exocytosis
- Cell Growth, Development
- Viral Infection

All these receptors share the same basic structure; however, they differ in their specificity and effects

7 transmembrane helices are bound to G proteins (GPCR), trimeric protein (alpha, beta, gamma) attached to the membrane by fatty acids, one to alpha subunit and one to gamma subunit that are one subunit.

Beta, gamma is always attached as a dimer

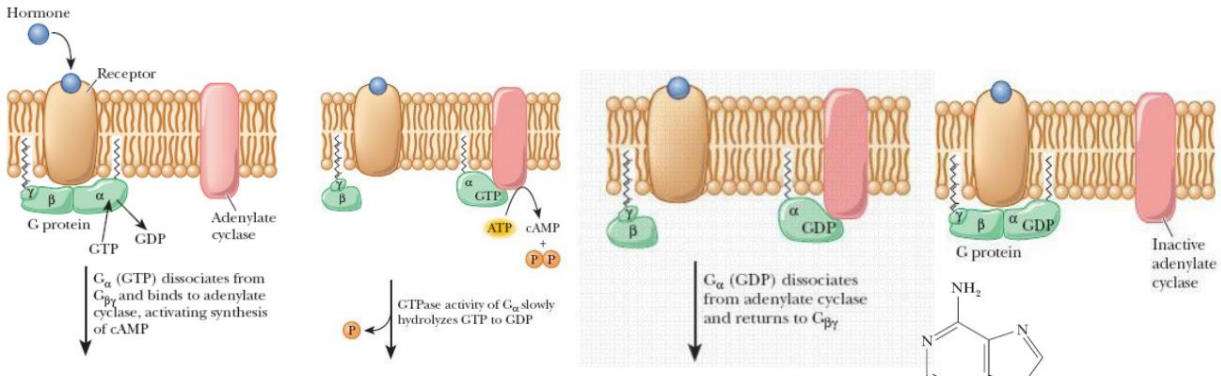
First pathway: cAMP PATHWAY

cAMP is small and heat stable molecule

G protein in the rest state is bound to GDP

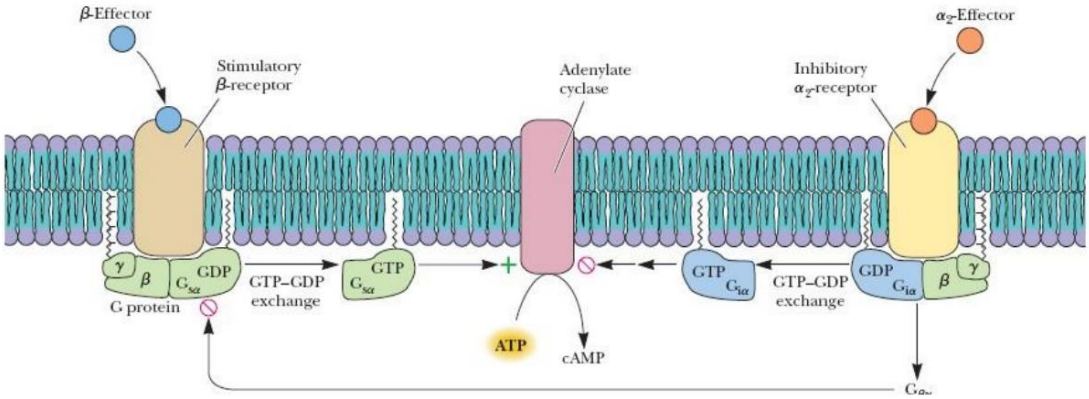
Hormone binds receptors, conformational change, GDP will be exchanged by GTP, affinity between alpha and (beta gamma) is decreased, alpha detaches from beta gamma dimer, go turn on adenylyl cyclase which converts ATP to cAMP, consequently activating protein kinases that will phosphorylate proteins to produce an action.

Alpha subunit has GTPase enzymatic activity which converts GTP to GDP. Now alpha subunit gets back attached to beta gamma dimer (high affinity to it again).



Signal sometimes excitatory sometimes inhibitory depends on:

- **G protein types (there is nine types like G αs, G αi)**
- **Nature of receptors also affect if it is stimulatory or inhibitory action (β1 and β2 receptors are stimulatory. α2 is inhibitory)**
- **The hormone**



G proteins receptors are more than 100 known GPCR and more than 20 known G proteins.

Can be activated by combination of hormones (Epinephrine and glucagon act via stimulatory G proteins in the liver)

Other 2nd messengers: Phospholipase C . Ion channels .