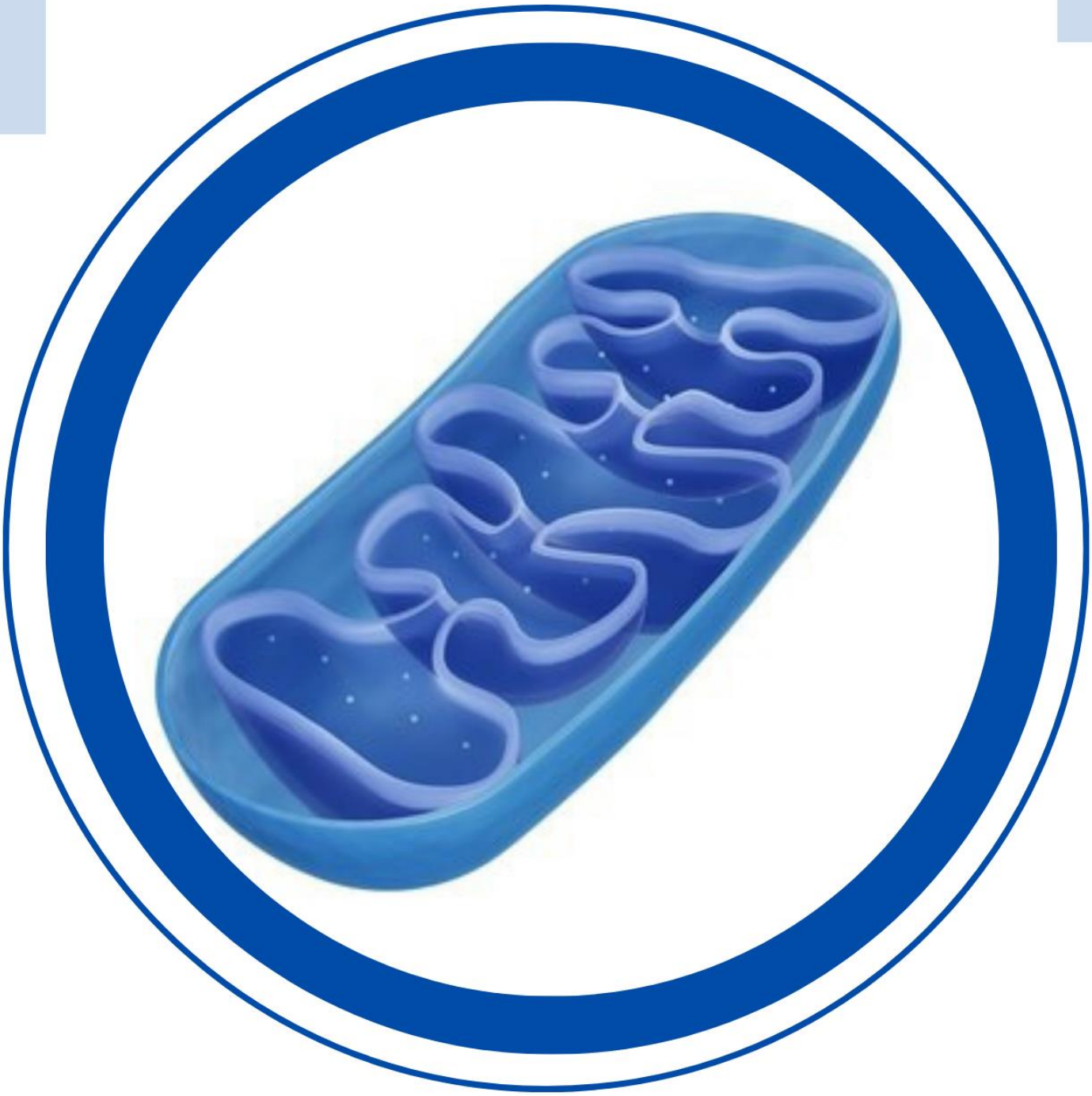
ENDOCRINE

METABOLISM

 # 1



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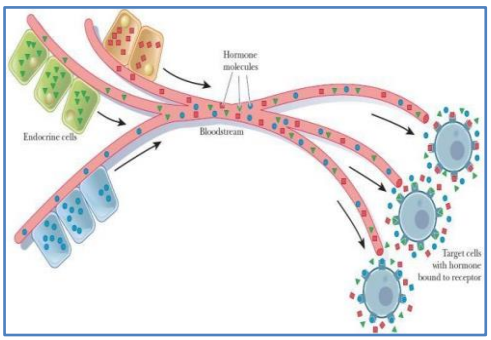
(This gonna be a short & easy lecture, enjoy :))

1.DEFINITIONS

- **What are hormones?**
  - **Exocrine vs. endocrine**
  - **Organic, blood, low amounts, source & target**
  - Ductless secretion unlike exocrine glands.
  - Low amounts as their functions would be disturbed in higher concentrations, similar to enzymes.



  - **Remote Controllers**
  - **Hormao (Greek): excite or arouse**
  - Basically, a hormone is an organic substance that is synthesized in one organ (glands) and transported by the circulatory system (blood) to act on another tissue.

DO ALL FIT THE DEFINITION?!

However, the definition is changed to include:

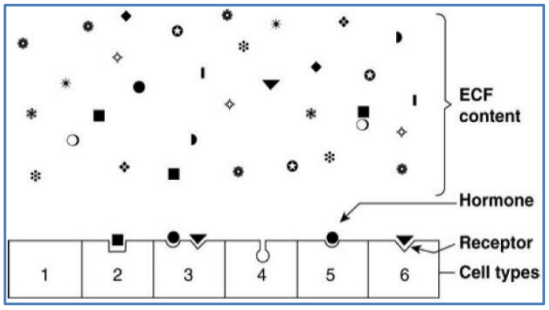
- **Endocrine:** hormones act on distant cells.
- **Paracrine:** hormones act on adjacent cells of DIFFERENT type.
- **Autocrine:** hormones act on the cells from which they were secreted -same cell type in the vicinity-.
- **Neuroendocrine:** neurons secreting hormones, a form of regulation of the endocrine system.
- **Intracrine:** act on the same cell that secreted them.
- **Juxtacrine:** hormones are secreted onto the cell surface, remain on the cell surface, and interact with a receptor on another cell that is bound to the surface of the secreting cell.
- **Phermonal:** volatile hormones acting on distant olfactory cells, mostly found in animals.

-**Remember**: hormones only affect the cells that have their specific receptor.

-For further clarification check this video .

2.MAJOR CHALENGES

- There are many biochemical challenges concerning the concept of hormones, these challenges may include:
- **200 types of differentiated cells in humans.**
- **Only a few produce hormones! (<50 known hormones).**
- **All of 75 trillion cells in a human are targets to one or more.**
- **One hormone → several cell types.**
- **One cell type → several hormones.**
- **One hormone → several effects** on different cells' types.
- **Concentration: Atto- to nano-molar range (10^{-15} to 10^{-9} mol/L) vs. Structurally similar molecules (sterols, amino acids, peptides, and proteins): micro- to milli-molar (10^{-6} to 10^{-3} mol/L) range.**



- Hormones are secreted in low concentrations (diluted) to perform several functions on several cell types.
- Chemical similarity: hormones are classified into 3 different classes according to their chemical structures ((proteins, polypeptides, peptides), amino acid derivatives and steroid), moreover, some hormones differ in only one carbon unit, just like the case of testosterone (19C) & estrogen (18C), yet they have different function, receptors, etc...
- Extra note from the book to understand the figure: Target cells must not only distinguish between different hormones present in small amounts but also between a given hormone and the 10^{-6} to 10^{-9} fold excess of other similar molecules. This high degree of discrimination is provided by cell-associated recognition molecules called receptors.
- **Desensitization: response fades up upon continuous release** -lack of signaling-.

HORMONE-RECEPTOR INTERACTIONS

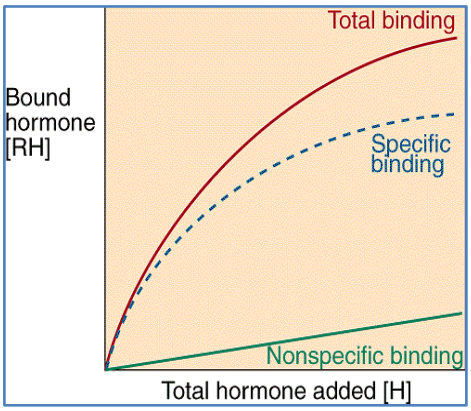
All these challenges and others can be beaten by high **AFFINITY!**

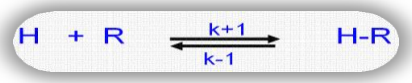
(Unfortunately, this makes the dissociation of hormones from the receptors much harder, which we absolutely don't want. However, this problem is solved by conformational changes at the level of the receptor).

- **Should be specific: displaceable by agonist or antagonist.**
- **Should be saturable.**
- **Should occur within the concentration range provided.**

  Again, all these points refer to high affinity.

- **Dissociation constant K_d**
- **K_d = {[H] X [R]} / [H-R]**
- **20X dissociation constant is enough to saturate the receptor.**
- **K_d values for many hormones range from 10^{-9} to 10^{-11} M** (implies high affinity- low dissociation over high association).

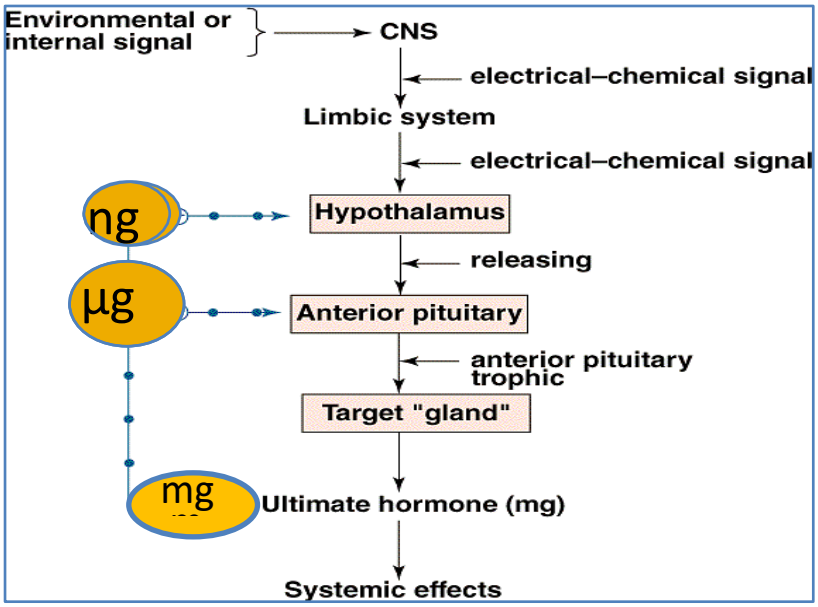


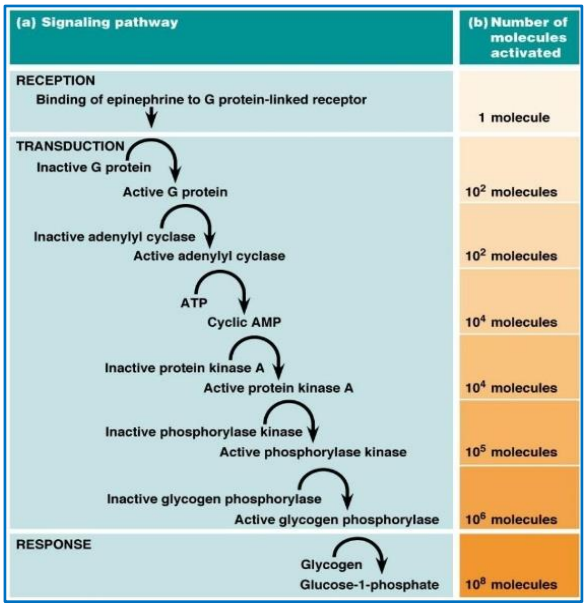


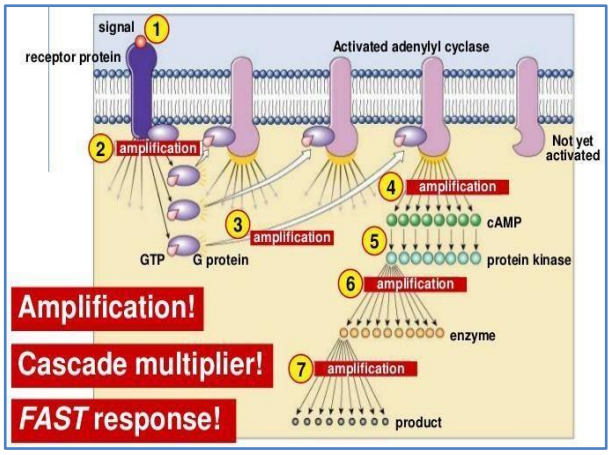
Non-specific binding refers to the binding of unintended molecules (molecules that have similar structure) to the receptor other than the hormone as-a-result-of the affinity defect (which is already found to permit the dissociation).

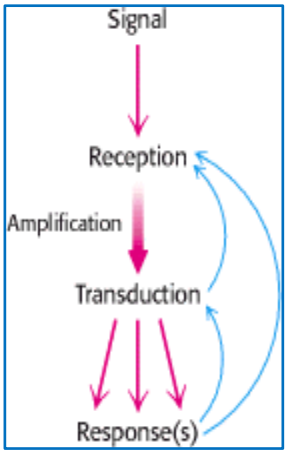
SIGNAL AMPLIFICATION

Another way by which the cells overcome the low concentration issue.



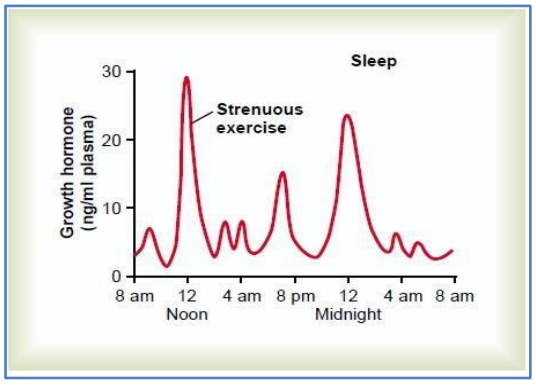


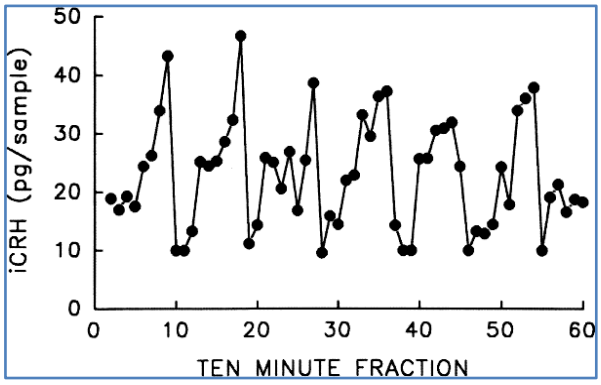




PULSATILE MANNER

- **Coordinated with concentration and rate of clearance from plasma**
  - Refers to the secretion of hormones in bursts or pulses and a lag period in between these pulses, otherwise desensitization would occur.
  - Hormones differ from each other in their secretion pattern, for instance, oxytocin during delivery, GH during the day and CTRH.





- Problem: How does the same hormone affect cells in different ways?
  - Cells have different patterns of protein expression, and this is what makes them different although they all have the same DNA.
- Problem: How many hormones have we discovered until now?
  - Less than 50; however, 30 of them use the same second messenger which is cAMP, even though they should result in different effects, this creates a challenge for biochemistry. However, this challenge can be beaten by different protein expressions.

3. THE TARGET CELL CONCEPT

- What affects target cells?

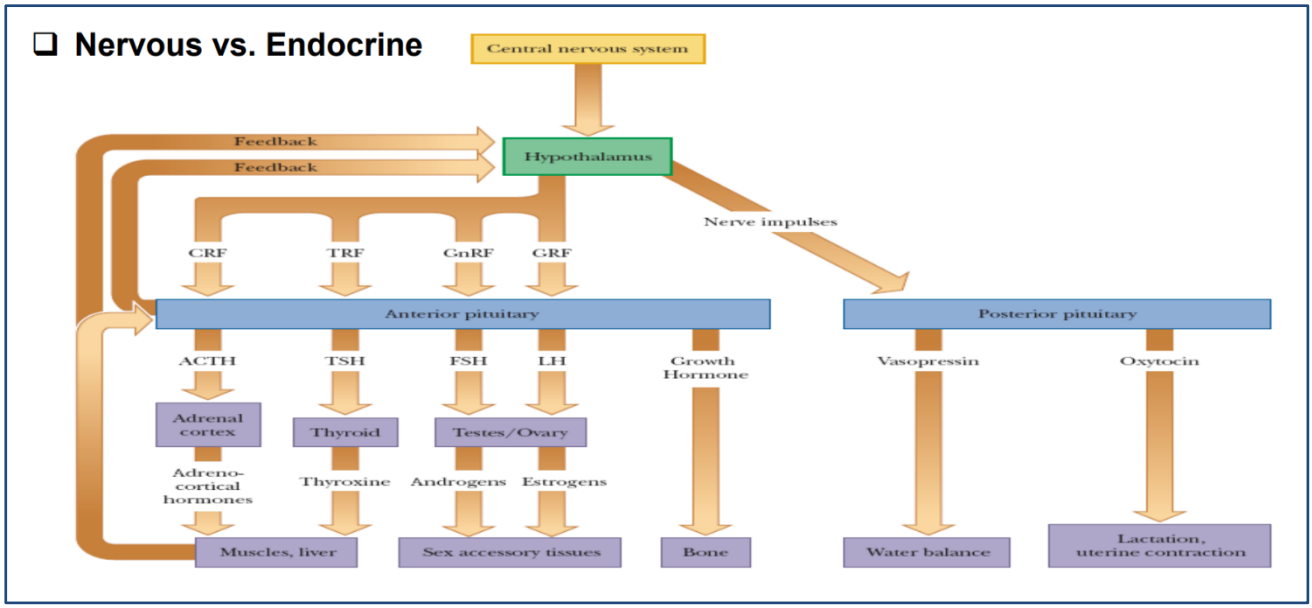
Factors affect the concentration of the hormone at the target cell
✓ The rate of synthesis and secretion of the hormone
✓ The proximity of the target cell to the hormone source (dilution)
✓ The K_d of the hormone – receptor complex
✓ The rate of conversion of inactive form to the fully active form
✓ The rate of clearance from the plasma

  - The cell itself and the changes that happen inside it.
  - The level of hormone that reaches this cell.
  - Distance of hormones from target cell (that's why they're usually anatomically close, eg: pancreas and liver are close to prevent dilution effect).
- What affects response at target cells? If all these cells have the same level of hormone, what makes their responses different?

Factors affecting the target cell response
✓ The number, relative activity, and state of occupancy of receptors
✓ The metabolism (activation / inactivation) of the hormone in the target cell
✓ The presence of factors within target cell necessary for the response
✓ Up- or down-regulation of the receptors upon interaction with ligand ✓ Post-receptor desensitization of the cell

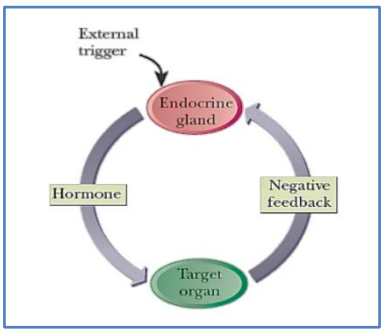
4. MAJOR REGULATION OF THE BODY'S HOMEOSTASIS

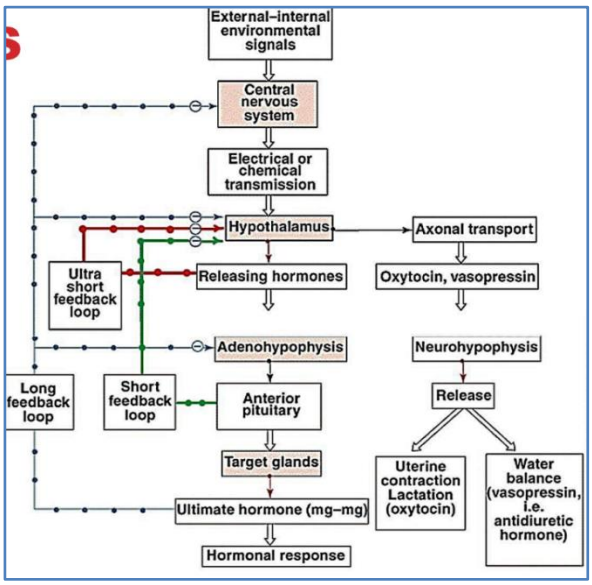
- How is body homeostasis controlled?
  - Nervous and endocrine systems. They control the whole body and control each other. The control mainly comes from the feedback manner.



4. MAIN REGULATION OF THE ENDOCRINE SIGNALS

Feedback loops can be:





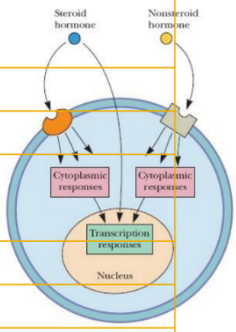
- **Ultrashort loop**
- **Short loop**
- **Long loop**
- The type of the loop depends on which cell is being regulated (the same cell that is secreting the hormone, distant cell that regulate the hormone releasing cells, etc...), however, all cells are regulated.

5. CLASSIFICATION

- **Solubility → transport** (lipid soluble vs water soluble)
- **Chemistry**
- **Processing and modification**
- **Synthesis**
- **Mechanism of action**
- Binding
- Clearance

5.1 SOLUBILITY

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast
Solubility	**Lipophilic**	**Hydrophilic**
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs .– days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor- hormone complex	cAMP, cGMP, Ca^{2+}, kinase cascades, metabolites of phosphoinositols



Solubility- few notes for further explanation:

- Water soluble:
  - They are transported in blood on their own, they don't need a transporter.
  - Easier to enter cells (the doctor said enter but I believe he meant affect -the writer).
  - Rate of clearance from body is faster.
  - They perform their functions quicker.
  - All are present in the free form.
  - Bind to cell surface, receptors on cell surface.
  - Need cascades within the cells to transduce their messages.
- Lipid soluble:
  - Their solubility in blood isn't high.
  - They need proteins in blood to transport them (specific globulins).
  - They have 2 forms: free and bound.
  - Slower rate of clearance, their effect remains longer.
  - Can pass through membrane.
  - Receptors can be either cytoplasmic or inside the nucleus.
  - Have direct effect without the need of 2nd messengers, concentration needs to be higher as there are no second messengers to amplify their action.

5.2 CHEMISTRY

- **Peptides, polypeptides, and proteins:**
  - **Pituitary hormones; Hypothalamic releasing hormones; Insulin, Growth factors…**

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

Numbers you need to know-only -:

- TRH: smallest one, 3 amino acids.
- Ang 1 and 2: a decapeptide (Ang 1) that is converted to an octapeptide (Ang 2).
- Oxytocin and ADH are both nonapeptides that are exact in 7 amino acids and different in 2. (The Dr actually compared between ADH and vasopressin rather than oxytocin; however, he probably meant oxytocin since ADH and vasopressin are the same).
- Insulin and glucagon are proteins; they are not small peptides (you don't need to memorize the numbers here).

5.2 CHEMISTRY

- **Amino acid derivatives:** modified amino acids, without peptide bonds
  - **Adrenalin, Thyroid hormones**
- **Steroids:** cholesterol derivatives
  - **Sex hormones, Hormones of Adrenal Cortex**
- **Eicosanoids:** 20 carbon unit molecules
  - **Prostaglandins, Leukotrienes, and Thromboxanes**
- **Gases**
  - **NO**

5.3 PROCESSING AND MODIFICATION

- **Secreted in final active form.**
  - **Aldosterone, hydrocortisone, estradiol, catecholamines**
- **Modified directly in target tissues.**

- Insulin, POMC

➢ **Modified indirectly in non-target tissues.**

- T4 to T3 (liver)
- D3 to active D (liver and kidneys)

5.4 SYNTHESIS

➢ **Peptide and proteins**

- Alternative splicing
- Post-translational modification
- Preprohormones

➢ **Steroids**

➢ **Amines**

➢ **Eicosanoids**

5.5 MECHANISM OF ACTION

➢ **Hormones that bind to cell surface receptors (According to second messenger)**

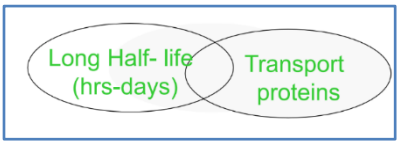
- cAMP (β adrenergic factor, glucagon, ACTH)
- cGMP (atrial natriuretic factor, Nitric oxide)
- Calcium or phosphatidyl inositol (oxytocin, TRH)
- **Kinase or phosphatase cascade (insulin, GH)** ex: tyrosine kinase

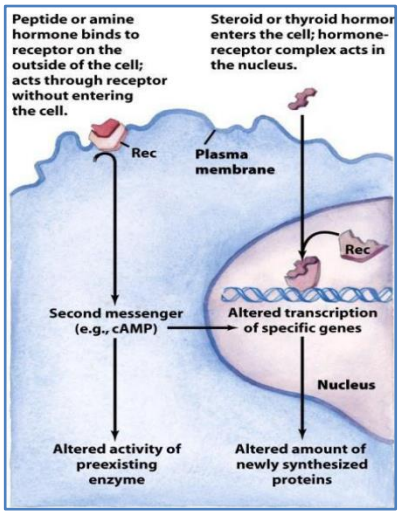
5.5 MECHANISM OF ACTION

➢ **Hormones that bind to intracellular receptors**

- Cytoplasmic vs. nuclear
  - HSP vs. corepressors (dimerization)
- Steroids
- Thyroid hormones
- Calcitriol, retinoic acid

➢ Hormone receptors that bind inside cells are initially inactive and become active by dimerization.





1. Hormone receptors in cytoplasm are usually inactive and are bound to heat shock proteins (HSP), they then separate from HSPs, bind to hormones instead and dimerize actively. The hormone- receptor complexes get translocated into the nucleus and finally exert their effect on DNA.
2. Hormones' receptors in the nucleus usually bind repressors. After the binding of hormones, these repressors are replaced by activators which will activate the transcription factors.

   -For further clarification check this video

FREE VS. BOUND!

- The free form is the active form. In lipid soluble hormones, the free form and the bound form are present in equilibrium; so, when some hormones in the free form leave to the target tissue, others in the bound form get released. This is what determines the half life of each hormone; it depends on the binding affinity of each hormone to globulins that carry it and its clearance from the blood.

6. TARGET CELL INTERACTIVE EFFECTS

- **Permissive effects – one hormone enhances the effect of a later hormone** (one is allowing the other to work)
  - **Upregulation of receptors or enzyme synthesis**
  - **Estrogen up-regulates progesterone receptors in uterus**
  - **Thyroid hormone increases the effect of epinephrine on breakdown of triglycerides in adipocytes**
- **Integrative effects – hormones produce complementary effects on different tissues** (both are doing the same job)
  - **PTH and calcitriol increase ECF calcium**
- **Synergistic effects** (together they have larger effect)
  - **Both FSH and estrogen necessary for normal oocyte development**
  - **FSH and testosterone together increase spermatogenesis**
- **Antagonistic effects:** (oppose each other in effect)
  - **Insulin and glucagon**

GOOD LUCK ☺

PAST PAPERS

1. **If you know that the dissociation constant Kd equals to 30ng, at which concentration the receptors will be saturated?**
    a. 300 ug
    b. 0.6 ug
    c. 0.03 ug

Answer: B

2. **Best definition of permissive:**
    a. One hormone is precursor to the other
    b. One hormone antagonizes the other
    c. One hormone is needed to have a larger effect
    d. Both hormones have the same action

Answer: C

3. **The hormone with the longest half-life:**
    a. Insulin
    b. Epinephrine
    c. Glucagon
    d. Progesterone

Answer: D

4. **Regardless of how a signal is initiated, the ligand-binding event is propagated via 2nd messengers or protein recruitment. What is the ultimate or final outcome of these binding effects:**
    a. A protein at the bottom of an intracellular signaling pathway is activated.
    b. A protein at the top of an intracellular signaling pathway is activated.
    c. A protein at the top of an extracellular signaling pathway is activated.
    d. A protein in the middle of an intracellular signaling pathway is activated.
    e. A protein at the top of an intracellular signaling pathway is deactivated.

Answer: A

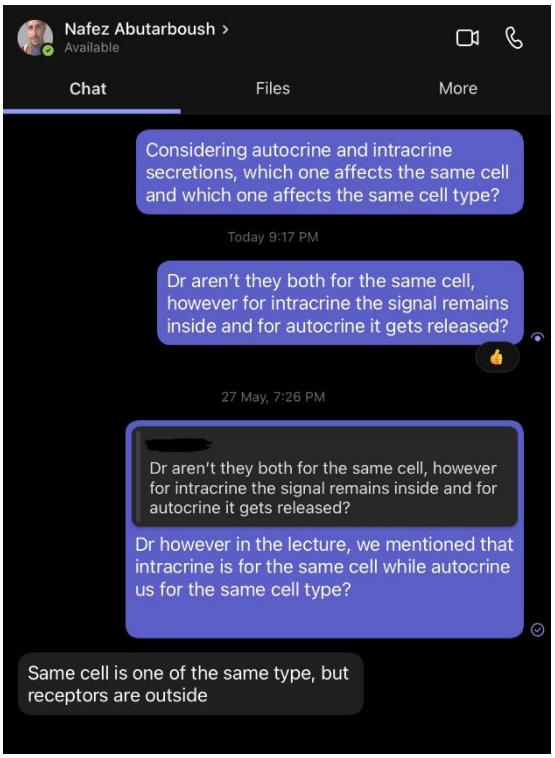
V2

Check the highlighted text please.

V3

Page 2:

- **Juxtacrine:** hormones are secreted onto the cell surface, remain on the cell surface, and interact with a receptor on another cell that is bound to the surface of the secreting cell. (The Dr didn't talk about the highlighted point; however, many resources mention it, we just added it for clarification).
- After further negotiations with the Dr, this is the conclusion we have come up to regarding intracrine and autocrine secretions:
  - Autocrine: hormones act on the same type of cells from which they were secreted including the secreting cell. Now here, notice that the hormone leaves the cell and acts on cell surface receptors.
  - On the other hand, for intracrine secretions, hormones only act on the same secreting cell and do not leave the cell but rather act on intracellular receptors.



Page 9: Insulin and glucagon are proteins; they are not small peptides (you don't need to memorize the numbers here).