LESSON 2. THE IMPORTANCE OF BIOLOGICAL MOLECULES: STRUCTURE, FUNCTION, REACTION AND INTERACTION.

E-mail: herminia.gonzalez@uv.es

Herminia González Navarro 2022

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THE IMPORTANCE OF MACROMOLECULES AND NETWORKS IN BIOCHEMISTRY

MACROMOLECULES ARE THE LARGEST CONSTITUENTS OF CELLS. BUT ISOLATED BIOMOLECULES HAVE NO LIFE CHARACTERISTICS.

INTERACTION BETWEEN BIOMOLECULES IN COORDINATION TO PERFORM THE FUNCTIONS OF LIFE

NUTRITION: extraction of energy from the environment for the maintenance of structures
RELATIONSHIP: adaptation, defense and use of the environment
REPRODUCTION: continuation of life

BIOCHEMISTRY studies the molecular basis of life including the structure of the macromolecules of living matter and the networks that interconnect them**.**

BIOCHEMISTRY STUDIES HOW COLLECTION AND THE GROUPING OF SUCH INANIMATE MACROMOLECULES LEAD TO LIFE

DIFFERENCES BETWEEN LIFE MOLECULES AND ORGANIC MOLECULES OF NON-LIVING MATTER

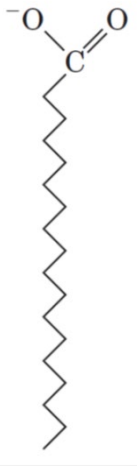
Living organisms are mainly **characterized by the presence of organic compounds.**

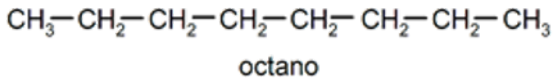
Most compounds found in living things are organic molecules derived from **HYDROCARBONS:** example, hydrocarbon chains of lipids.

The inert matter has molecules with a good structural skeleton but very little functional reactivity.

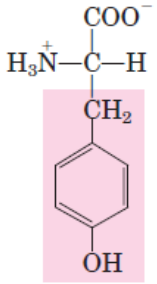
The biomolecules: molecules also contain carbon and hydrogen, oxygen, nitrogen, phosphorus and sulfur.

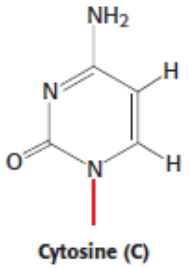
Fatty acid



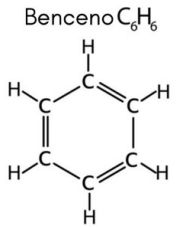


amino acid

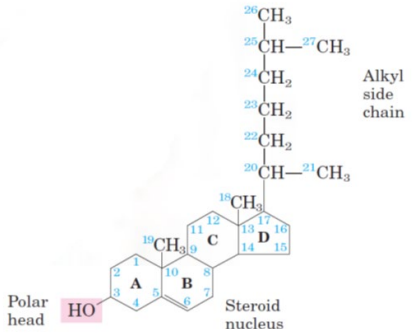




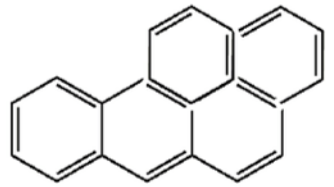
Nitrogen base



Cholesterol



benzopyrene



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LIFE IS A NETWORK OF INTERACTIONS BETWEEN MACROMOLECULES AND METABOLITES

The processes that establish interactions between biomolecules and macromolecules are what characterize living matter.

MACROMOLECULES

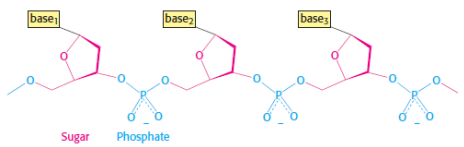
Molecules high molecular weight such as proteins and nucleic acids, lipids. THREE-DIMENSIONALITY, FUNCTIONALITY.

METABOLITES

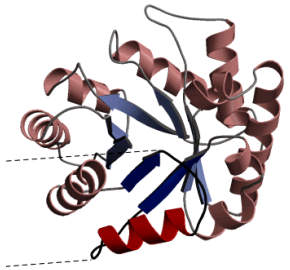
Low molecular weight molecules such as glucose and glycerol.

MACROMOLECULES

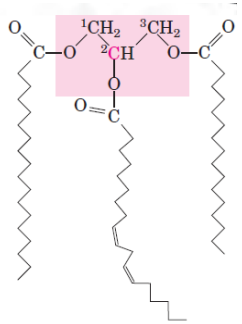
DNA



PROTEIN



TRIGLYCERIDE



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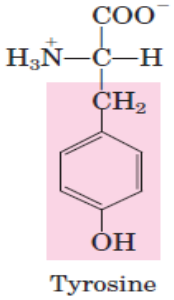
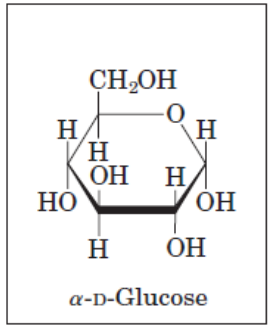
METABOLITES





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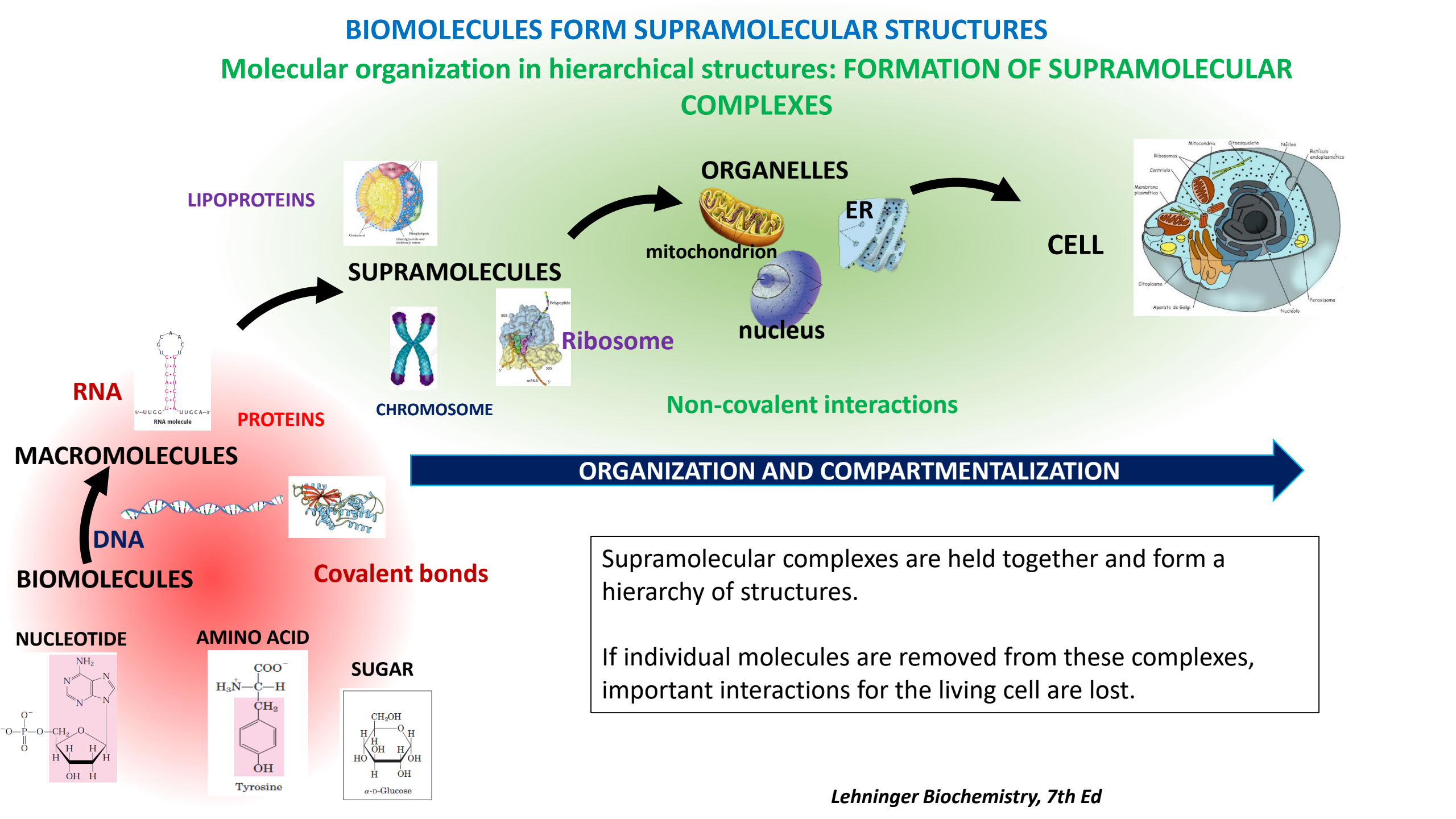
BIOMOLECULES FORM MACROMOLECULES

Molecule	Macromolecule/Polymer	Function
Amino acid	Proteins	Catalysts, receptors, channels, hormones, structures, antibodies,
Sugars	Carbohydrates	Energy source, structural
Fatty acids	Lipids	Energy source, hormones, structural,
Nucleotides	Nucleic acids (DNA, RNA)	Genetic information, transmission of genetic information, protein synthesis

BIOMOLECULES FORM SUPRAMOLECULAR STRUCTURES

Molecular organization in hierarchical structures: FORMATION OF SUPRAMOLECULAR COMPLEXES



Supramolecular complexes are held together and form a hierarchy of structures.

If individual molecules are removed from these complexes, important interactions for the living cell are lost.

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PROPERTIES OF LIVING MATTER THAT DIFFERENTIATE THEM FROM OTHER MOLECULES

1. **High degree of CHEMICAL COMPLEXITY AND MICROSCOPIC ORGANIZATION:** ***chemical units that are repeated*** to form a hierarchy of organizations creating complex systems.

2. Systems with the **ability to EXTRACT ENERGY FROM THE ENVIRONMENT**, transform it and use it for its own use: chemical reactions to perform mechanical, electrical work among others. ***Energy used for the maintenance of complex structures*** as opposed to inert matter that tends to acquire states of lower energy and greater disorder.

3. Capacity for self-replication and self-organization: **COORDINATION BETWEEN MACROMOLECULES AT THE STRUCTURAL AND FUNCTIONAL LEVEL.**

4. **Mechanisms of environmental detection, response development and ADAPTATION:** changes in internal chemistry.

5. Specific functions for each macromolecular component, with the purpose of: **INTERACTION BETWEEN MACROMOLECULES, METABOLITES-MACROMOLECULES,** to make the necessary internal chemical changes.

CELLS ARE THE STRUCTURAL AND FUNCTIONAL UNITS OF ALL LIVING ORGANISMS

1. **Compartmentalization and exterior-interior communication:** remarkably flexible structure, allowing changes in the shape and size of the cell **(relationship).**

2. CYTOPLASM AND CYTOSOL: high concentration of molecules and salts. Metabolites, intermediates, macromolecules, supramolecular structures (ribosomes). **Interaction between them in a coordinated manner for the maintenance of supramolecular structures (nutrition).**

3. Nucleus, nucleolus with genetic material for **self-replication (reproduction).**

INTERACTION BETWEEN BIOMOLECULES IN LIVING MATTER HAS TWO HIGHLY IMPORTANT ELEMENTS:

1) WATER

2) REACTIVITY BETWEEN BIOMOLECULES TO BE ABLE TO INTERACT: CARBON CHEMISTRY

IMPORTANCE OF WATER IN THE MAINTENANCE OF STRUCTURES AND BIOCHEMICAL INTERACTIONS

THE WATER:

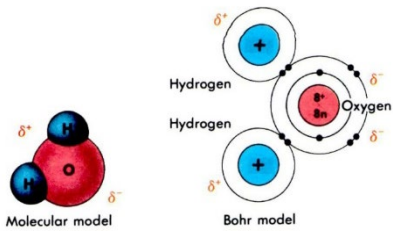
1. Main solvent and matrix in which they take place, sometimes participates and sometimes favors biochemical reactions.
2. Its properties are essential for the formation of macromolecular structures.

TWO PROPERTIES of water are especially relevant:

1. **THE POLARITY OF WATER:** ASYMMETRIC LOAD DISTRIBUTION. Electric dipole. They form an angle
The oxygen nucleus extracts electrons from the two hydrogen nuclei.

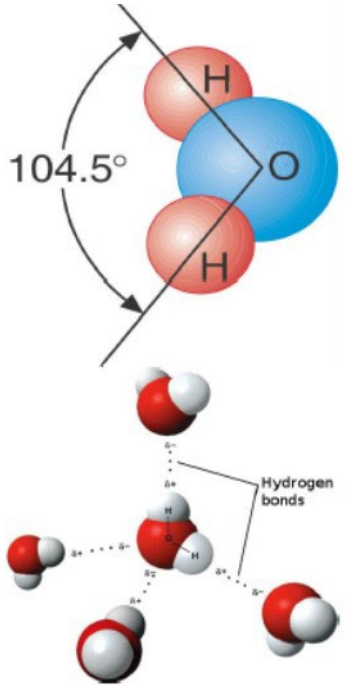
2. **THE COHESIVENESS:** Water molecules interact strongly with each other and with other biomolecules in aqueous solution (the cellular medium) through hydrogen bonds and others. Resistance in cells and tissues and is a mechanical shock absorber.

Solubilization of minerals, proteins, salts, carbohydrates, nucleic acids... Etc. It is also involved in many chemical reactions and cellular respiration.
It allows the mobility of dissolved molecules.



CHARGE DISTRIBUTION

IMPORTANCE OF WATER IN THE MAINTENANCE OF STRUCTURES AND BIOCHEMICAL INTERACTIONS



Due to the polarity and the **ability to form 4 hydrogen** bonds in water:

1. The best **solvent and stabilizer** of biomolecules: DNA, RNA, PROTEINS, AMPHIPATHIC LIPIDS, CARBOHYDRATES. Stabilizes membrane structures in general.

2. It can behave as a **weak acid or base** under certain conditions: it can buffer biological media and can participate in chemical reactions.

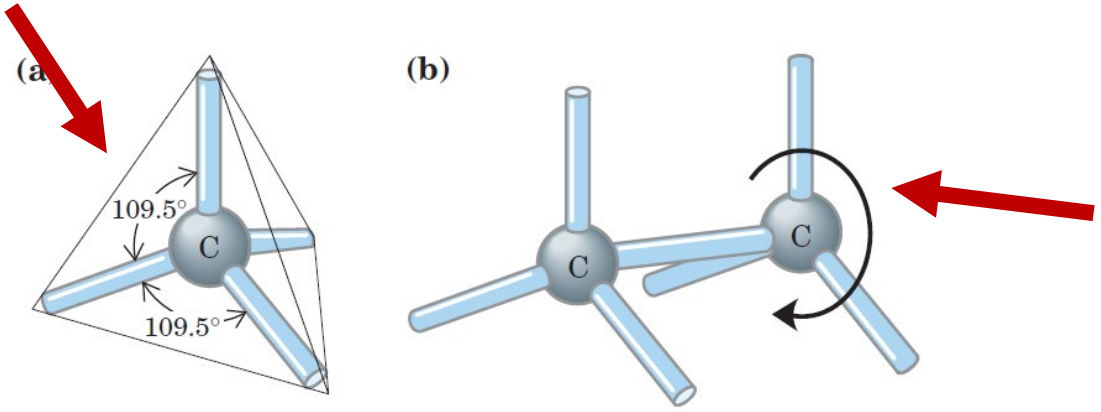
3. Thermoregulation due to its high specific heat.

BIOMOLECULES ARE CARBON COMPOSITES WITH A VARIETY OF FUNCTIONAL GROUPS AND REAGENTS

The chemistry of **living organisms is organized around carbon**.
Forms single and double bonds with oxygen and nitrogen atoms.

CARBON BONDS FOUND IN BIOMOLECULES: C-O, C-N C=O, C=N, C-H, C=H2

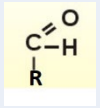
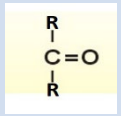
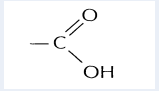
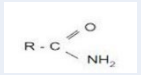
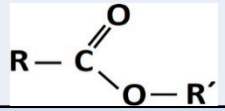
VERY STABLE C-C
Can bind up to 4
carbons



CARBON-CARBON BONDS:
they can share two (or three) pairs of electrons:
they form double (or triple) bonds.

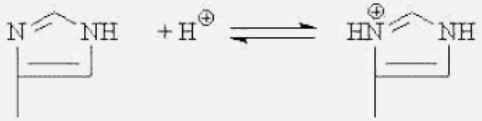
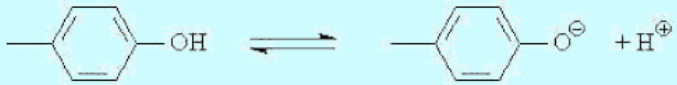
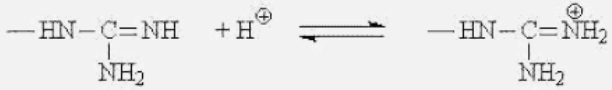
Carbon-based chemistry allows the generation of functional chemical groups of high importance for life.

CHEMICAL GROUPS CHARACTERISTIC OF BIOMOLECULES

CHEMICAL FAMILY	STRUCTURE	NUMBER	CHEMICAL PROPERTIES
ALCOHOL	R-OH	Hydroxyl	Polar and capable of forming H-bonds, it is found in sugars
ALDEHYDES		Carbonyl	Polar and capable of forming H-bonds, it is found in sugars
KETONES		Carbonyl	Polar and capable of forming H-bonds, found in sugars
ORGANIC ACIDS		Carboxyl	Weak acid, can donate an H+ and acquire a negative charge. In fatty acids and amino acids (proteins).
AMINES	R-NH3	Amino	Weak base, acquires an H+ and load +. In amino acids (proteins).
AMIDES		Amida	Polar, forms H bridges and has no charge
TIOLES	R-SH	Thiol	It can be easily oxidized and form -S-S-: covalent bond
ESTERS		Ester	It can be attached to polar or apolar groups. In lipids.
DOUBLE BOND	RCH=CHR	Alkene	It can be found in several molecules and is susceptible to oxidation.

CHEMICAL GROUPS CHARACTERISTIC OF BIOMOLECULES

ACID-BASE PROPERTIES OF AMINO ACID R-CHAINS

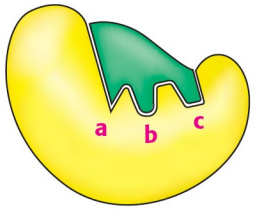
Aminoácido	pK_a	Grupo Funcional	Reacción Acido-Base
Asp, Glu	4.4	Carboxilo	
His	6.5	Imidazol	
Cys	8.5	Sulfidrilo	
Lys	10.0	Amino	
Tyr	10.0	Fenol	
Arg	12.0	Guanidinio	

MACROMOLECULES REQUIRE A THREE-DIMENSIONAL STRUCTURE TO BE FUNCTIONAL

The combination of the chemical groups and their arrangement in the biopolymers as well as the weak interactions that are established determine the functionality.

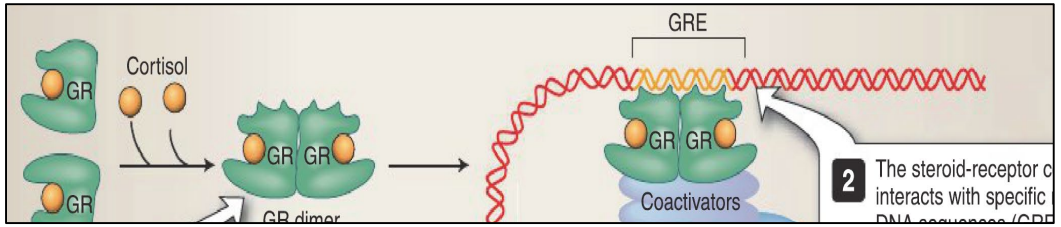
THE THREE-DIMENSIONAL STRUCTURE GIVES FUNCTIONALITY TO THE MOLECULES:

SPECIFICITY AND EFFICACY

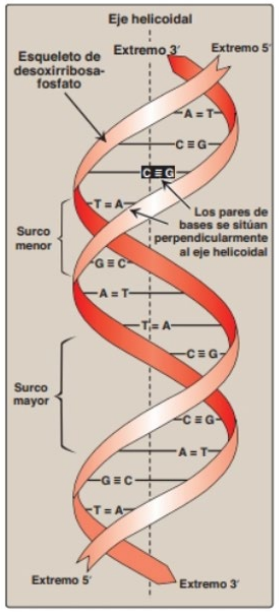


ES complex

DYNAMISM: COMMUNICATION AND SIGNALING

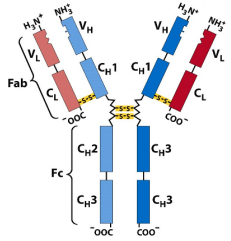


STRUCTURAL STABILITY

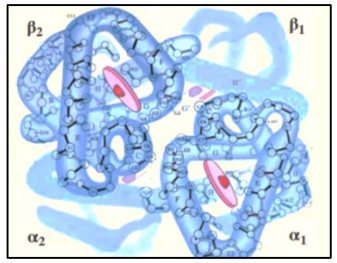


COMPLEMENTARITY

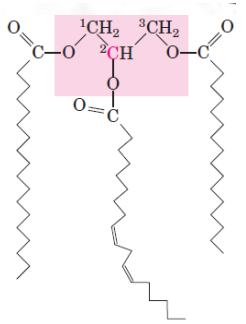
MOLECULAR RECOGNITION

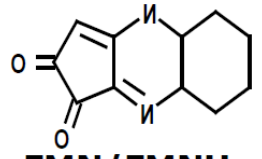


TRANSPORT



REACTIVITY, ENERGY STORAGE OR REDUCING POWER





FMN/FMNH$_2$

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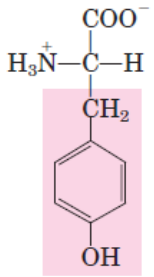
MACROMOLECULES: FUNCTIONAL STRUCTURE IS MAINTAINED BY WEAK INTERACTIONS

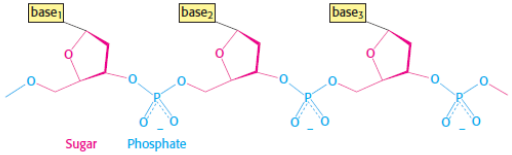
BIOMOLECULES → **MACROMOLECULES** → **FUNCTIONAL MACROMOLECULES** — **ACTIVITY**



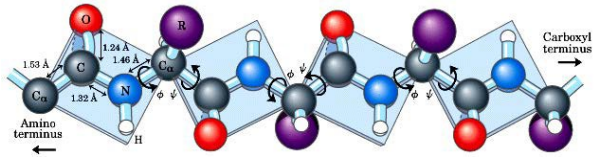
Tyrosine

AA

COVALENT BONDS

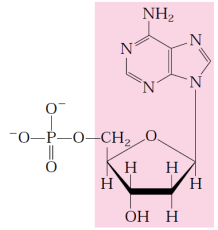


Nucleic acid chain



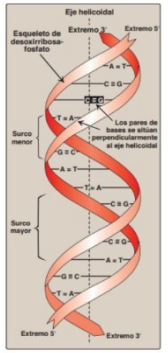
Extended polypeptide

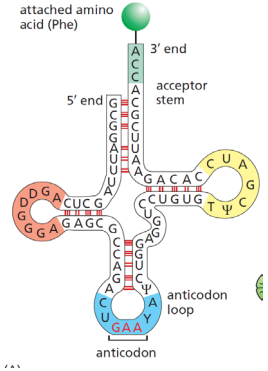
REPEATED MONOMERS: DNA, AMINO ACID CHAIN



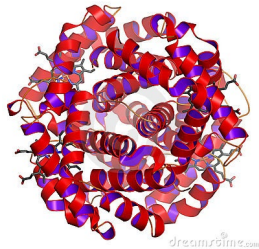
NUCLEOTIDES

WEAK LINKS





3D STRUCTURE



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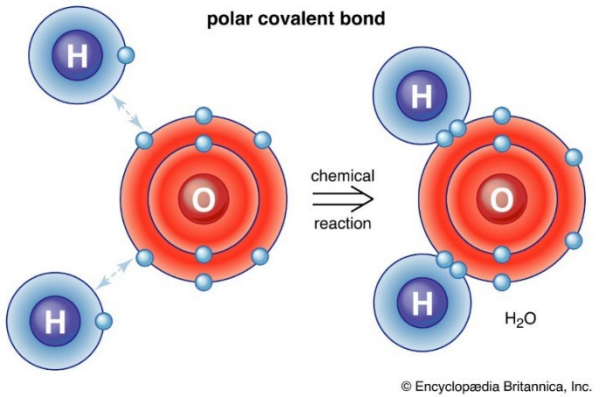
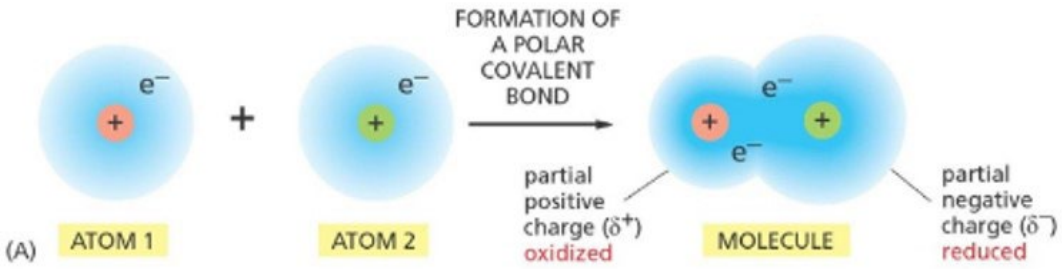
MACROMOLECULES: COVALENT BONDS

Covalent Bonds

They involve sharing pairs of electrons between atoms. Available electrons are **shared** to achieve more stable electronic configurations.

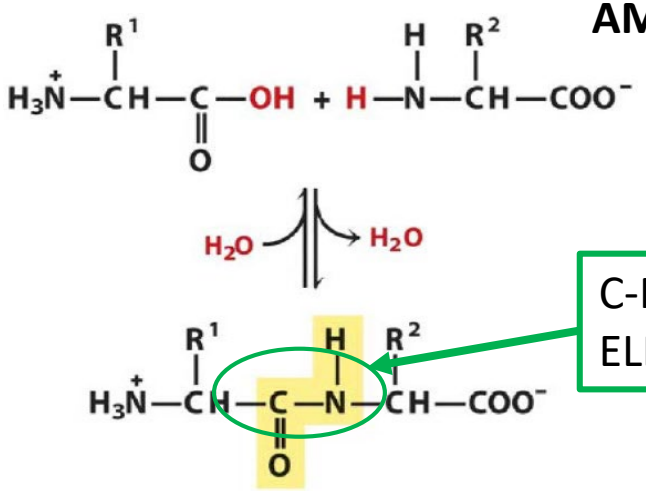
Covalent bonds contain high energy. The water molecule needs 470 kJ/mol for rupture





BIOMOLECULES

AMINO ACIDS



C-N SHARE ELECTRONS

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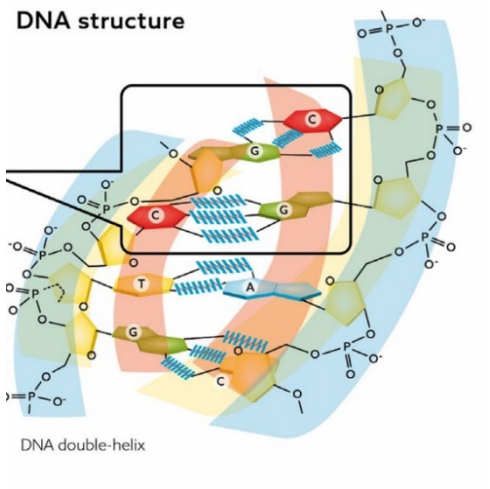
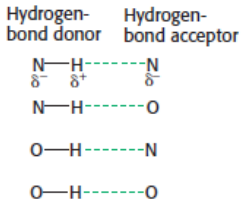
MACROMOLECULES: FUNCTIONAL STRUCTURE IS MAINTAINED BY WEAK INTERACTIONS

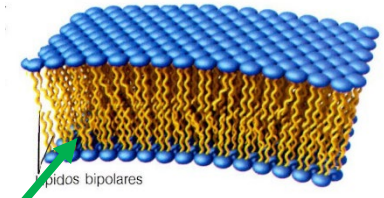
Weak Bonds

ENERGY OF WEAK INTERACTIONS: low or very low 23 kJ/mol a hydrogen bridge.
CRITICAL IN THE MAINTENANCE of the functional structure and for the interactions between molecules.

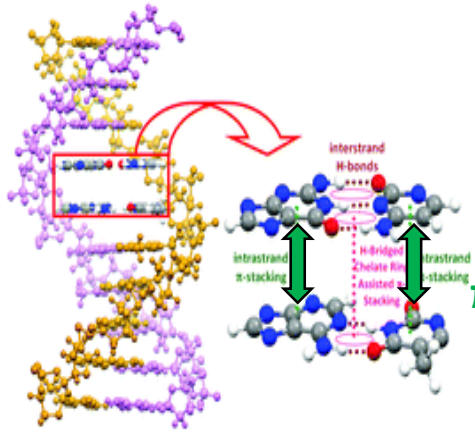


Hydrogen bonds



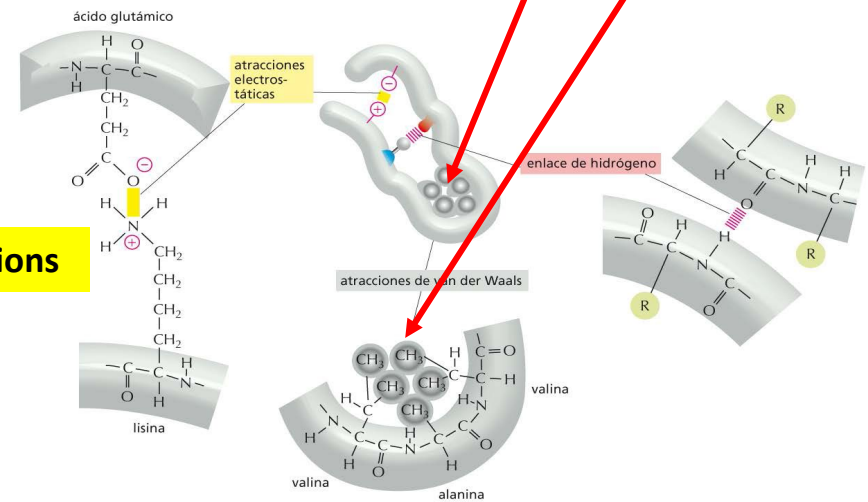


Hydrophobic interactions



Van der Waals interactions: the weakest; induced by electrical interacctions of very close molecules.

Ionic interactions



π-π stacking interactions: aromatic rings; dipolo-dipolo

The large number of weak interactions between macromolecules in supramolecular complexes stabilize these assemblies, producing their unique structures.

LESSON 15. CELL SIGNALING (I): RECEPTORS AND SIGNAL TRANSDUCTION

E-mail: herminia.gonzalez@uv.es

Herminia González Navarro 2022

INDEX

PRINCIPLES OF CELL SIGNALING AND TRANSDUCTION

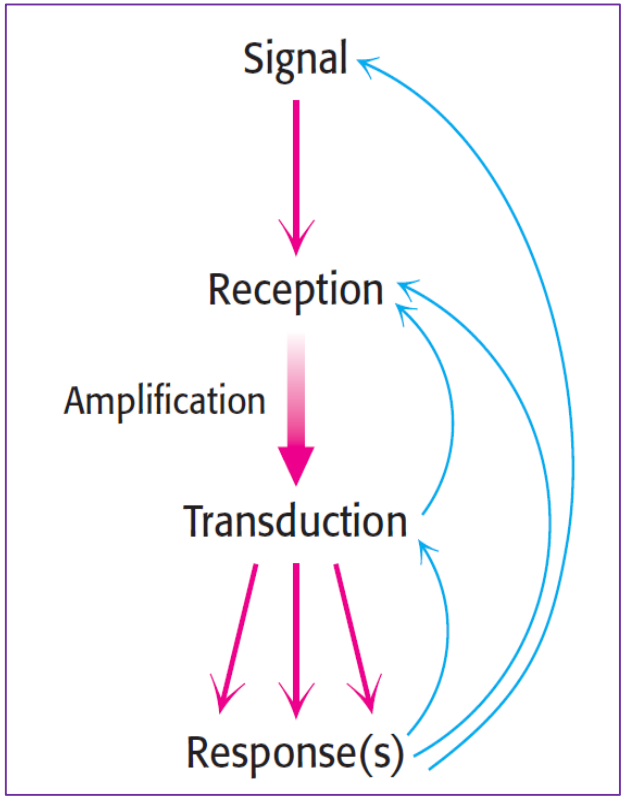
Cells receive signals of different origins that are interpreted to prepare a response.
Signaling pathways affect ALL metabolic circuits and cellular functions.

SIGNALS COME FROM: the environment or near or distant cells or are internal.

INFORMATION: on cellular homeostasis, the organism, external threats, the availability of nutrients.

SIGNAL TRANSDUCTION: a multi-step process that amplifies the signal, allows interaction with other pathways, and generates multiple responses.

RESPONSE: metabolic or cellular changes and adjustments in response to chemical signals from the environment.



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STAGES OF CELL SIGNALING:

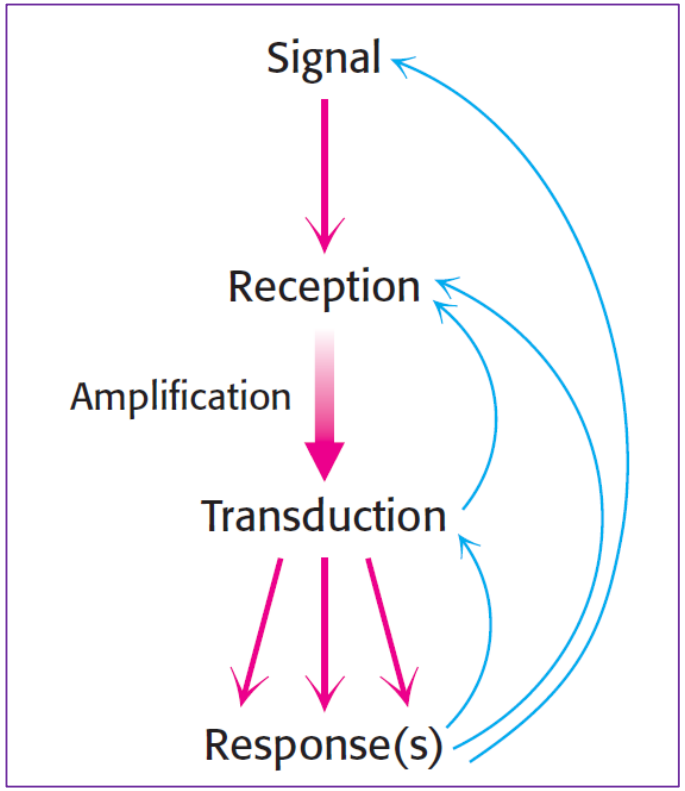
1. PRIMARY MESSENGER RELEASE: a SIGNAL from the extracellular or intracellular environment in response to a physiological change (food).

SMALL MOLECULES: **LIGANDS**

2. PRIMARY MESSENGER RECEPTOR: located on the cell surface or internally (protein in nature), this receptor binds to the signal. **RECEPTOR-LIGAND INTERACTION**.

RECEPTOR ACTIVATION→ TRIGGERS SIGNAL TRANSDUCTION

CHANGES in structural proteins, channels/transporters, or enzymes that will amplify the signal.



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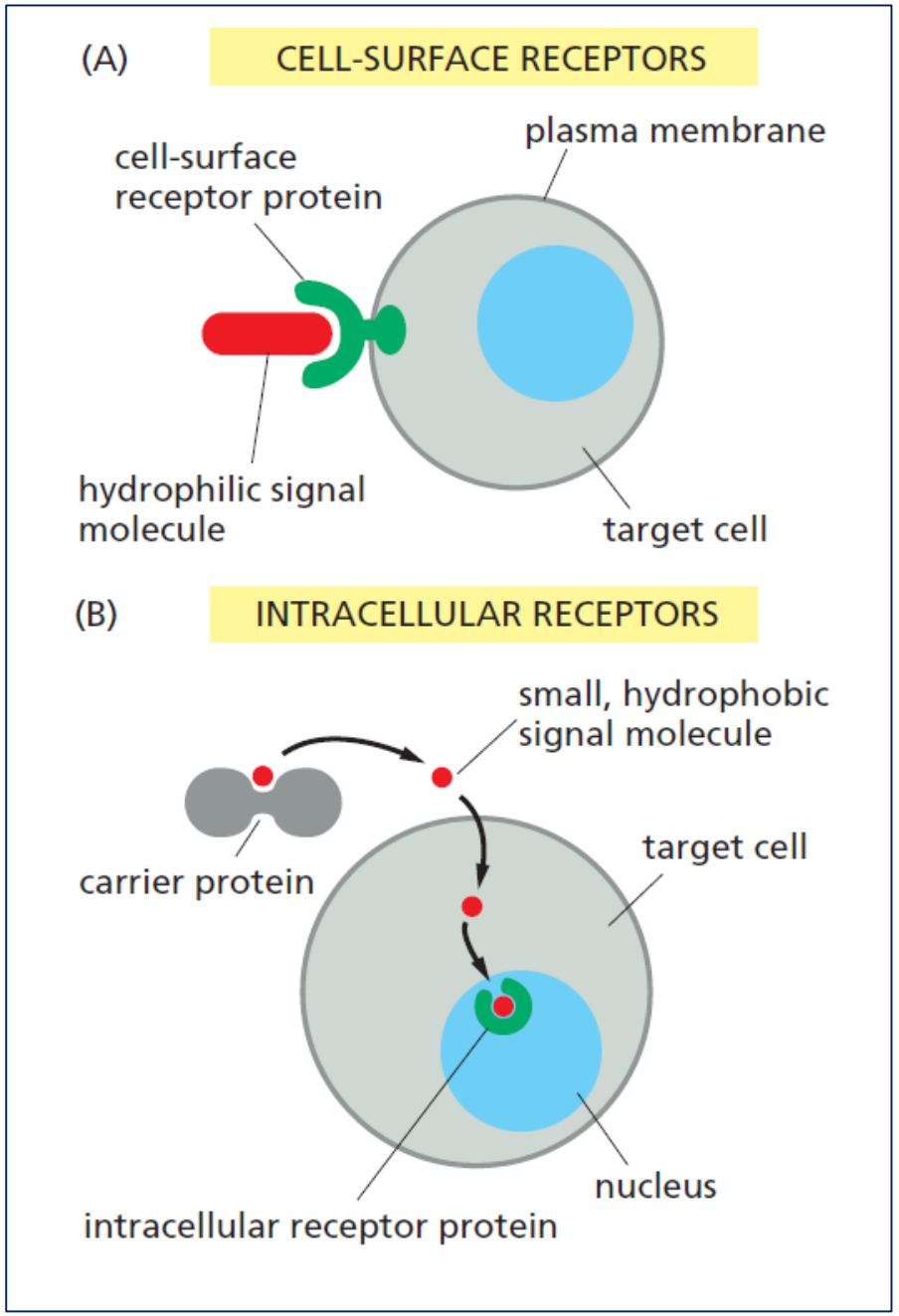
2. PRIMARY MESSENGER RECEPTOR:

Cell surface receptors: signals that cannot enter the cell.

Intracellular receptors: signals that can enter the cell.



Alberts, 6th edition, Molecular Biology of the Cell

STAGES OF CELL SIGNALING

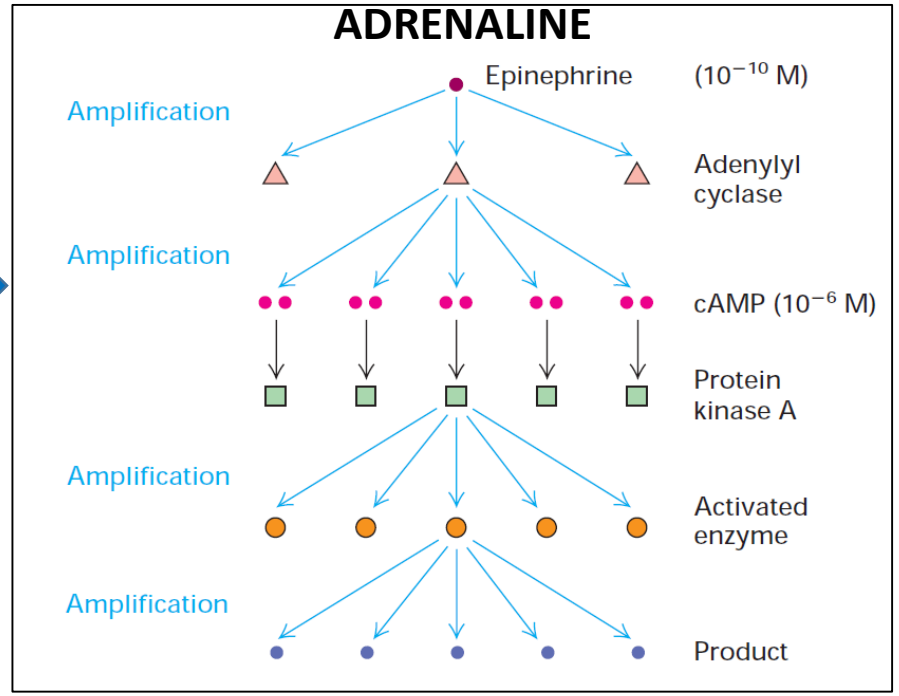
3. TRANSDUCTION: TRANSMISSION AND AMPLIFICATION of the signal with SECOND MESSENGERS: intracellular messenger generated AND/OR activated by the receptor binding to the ligand.

WHAT ARE SECOND MESSENGERS?

Small intracellular molecules that change concentration **in response to ligand-receptor interaction**.
Cyclic AMP (cAMP) or GMP (cGMP), Calcium, inositol 1,4,5-triphosphate (IP3) or DAG (diacylglycerol).

Second messengers amplify the signaling with chemical reactions, protein kinase cascades, or parallel signaling pathways.

AMPLIFICATION OF SIGNALING BY INTERACTION WITH OTHER PATHWAYS.



Lodish et al., Freeman, Molecular Cell Biology, 5th ed.

AMP: ADENOSIN MONOPHOSPHATE
GMP: GUANOSIN MONOPHOSPHATE

STAGES OF CELL SIGNALING

4. END OF TRANSDUCTION: ACTIVATION OF EFFECTORS THAT MODULATE THE PHYSIOLOGICAL RESPONSE.

CHANGES IN channels, pumps, enzymes, transcriptional factors that directly control metabolic pathways, gene expression, and membrane permeability.

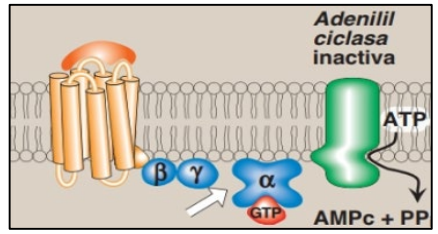
GLUCOSE DEFICIENCY SIGNAL: GLUCAGON

EFFECT: GLUCOSE PRODUCTION BY GLYCOGEN BREAKDOWN

GPCR

G PROTEIN

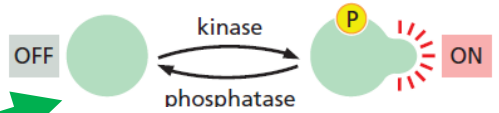
Adenylate cyclase



D. Ferrier, Lippincott IR, Bioquímica, 7th ed.

cAMP

PKA activated by cAMP



ACTIVATED EFFECTOR PROTEIN: Glycogen phosphorylase

GLYCOGEN BREAKDOWN

GLYCOGENOLYSIS

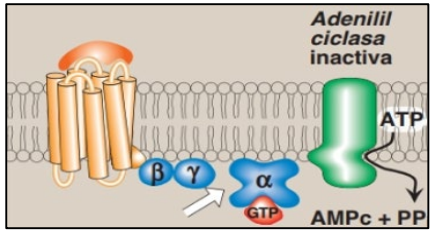
STAGES OF CELL SIGNALING

5. SIGNAL TERMINATION: after the effects are executed, there is a need for mechanisms that repress/stop the activated events.

EXAMPLES OF SIGNALING TERMINATION

G PROTEIN

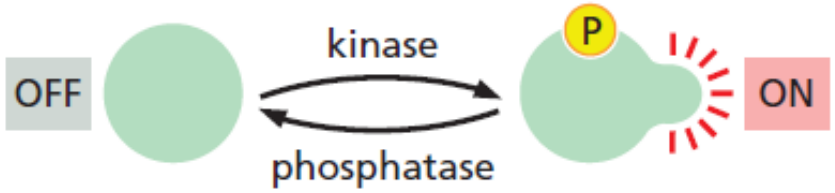
D. Ferrier, Lippincott IR, Bioquímica, 7th ed.



TERMINATION: GTPase SELF-INACTIVATION

G PROTEINS NEED GTP TO BE ACTIVATED. As they are GTPases self-inactivate and lead to the termination of signaling.

DEPHOSPHORYLATION



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SIGNAL CHARACTERISTICS

INTERNAL OR EXTERNAL

Internal signals can propagate external signals, **require an intracellular receptor** (cytoplasm/nuclear), and originate intracellularly.

External signals require a **receptor on the membrane** or cross the membrane and bind to **an internal/nuclear receptor.**

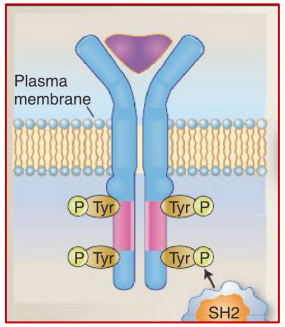
CANNOT CROSS THE MEMBRANE

Aas and derivatives: **adrenaline** (TYR)
Peptides: oxytocin, vasopressin
Proteins: metabolic hormones such as insulin, glucagon.
Glycoproteins: **pituitary hormones**

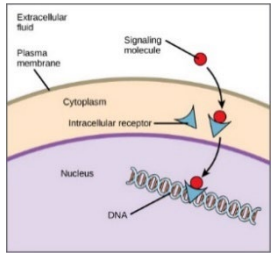
CAN CROSS THE MEMBRANE: HYDROPHOBIC MOLECULES

Physical signals (Photons) and Gas (Nitric Oxide)

Cholesterol-derived steroid hormones: cortisol, estradiol, fat-soluble vitamins, vitamin A, long-chain fatty acids and derivatives (eicosanoids, prostaglandins and leukotrienes), hydrophobic aas derivatives, **thyroid hormone derivatives**



Chandar and Viselli, Cell and Molecular Biology, Lippincot, 2nd ed. (2019)



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CHARACTERISTICS OF THE SIGNALS: TYPES DEPENDING ON THE DISTANCE OF THE TARGET TISSUE

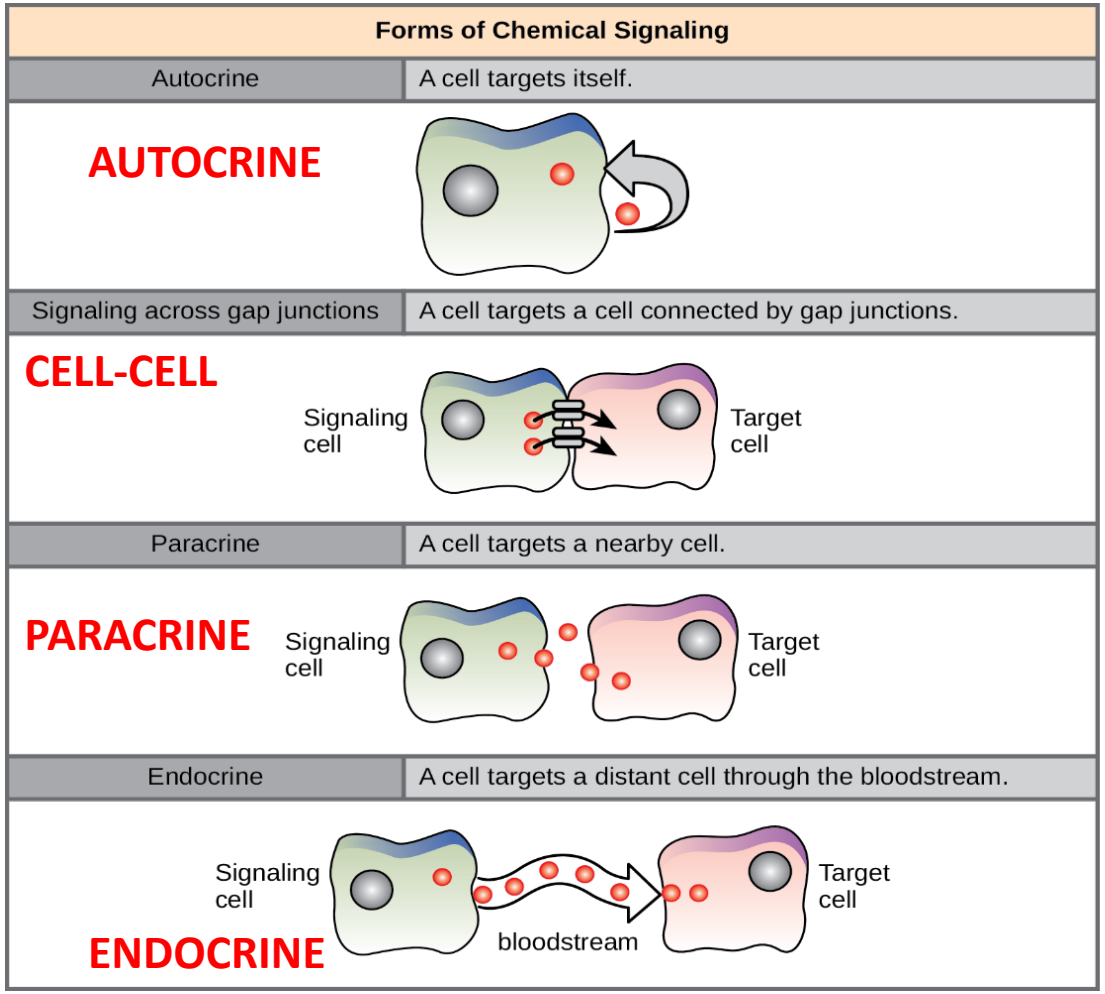
In animals, the signals can operate at different distances. They can also be:

ENDOCRINE signaling: these are hormones that act on various endocrine organs. Origin in a distant cell, e.g., insulin, glucagon

PARACRINE signaling: Signals that act on neighboring neurotransmitter cells (between neurons, neuron-muscle). Growth factors during development (form gradients).

AUTOCRINE signaling: signals produced by the cell itself. Common tumor cells or cells in culture (growth factors).

CELL-CELL CONTACT signaling: Direct contact with another cell or with the extracellular matrix.



Freeman Molecular Cell Biology, 5th ed.

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CHARACTERISTICS OF PHYSIOLOGICAL RESPONSES

THERE ARE TWO TYPES OF RESPONSE:

Quick and/or transient responses

-Ionic changes: depolarization of the membrane by ATP (-), K+ channels in the beta cell.

-Immediate **regulation of metabolic pathways**: energy use production

-Cell movement

GPCR

↓

G PROTEIN

↓

Adenylate cyclase

↓

cAMP

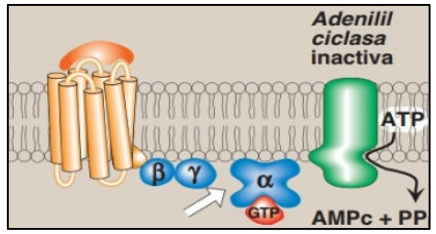
↓

PKA activated by cAMP

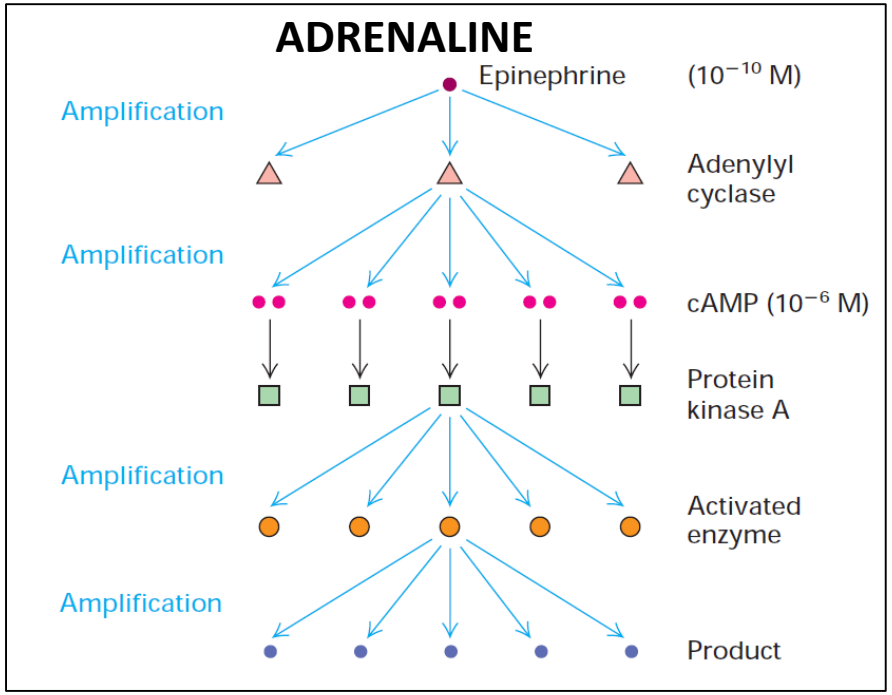
↓

ACTIVATED glycogen phosphorylase

GLYCOGENOLYSIS



D.Ferrier, Lippincott IR, Bioquímica, 7th ed.



Lodish et al, Freeman Molecular Cell Biology, 5th ed.

CHARACTERISTICS OF PHYSIOLOGICAL RESPONSES

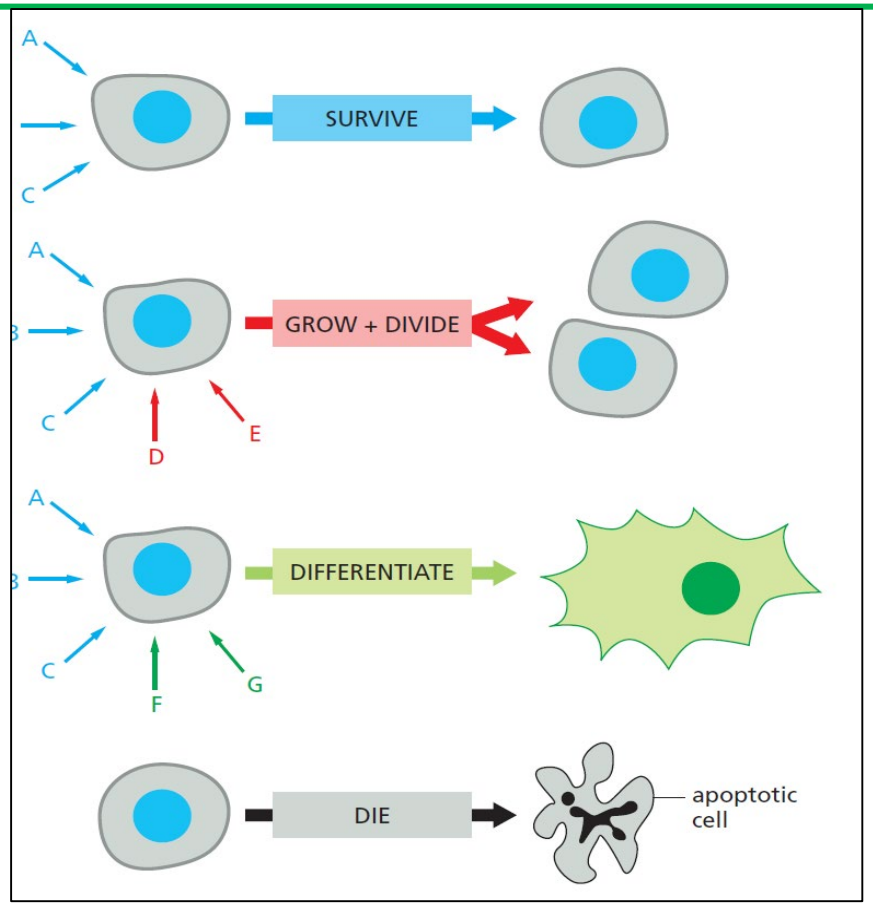
THERE ARE TWO TYPES OF RESPONSE:

Slow and/or sustained responses

Regulation of:

GENE EXPRESSION: translation or transcription

PERMANENT EVENTS: differentiation, proliferation (growth) and cell death



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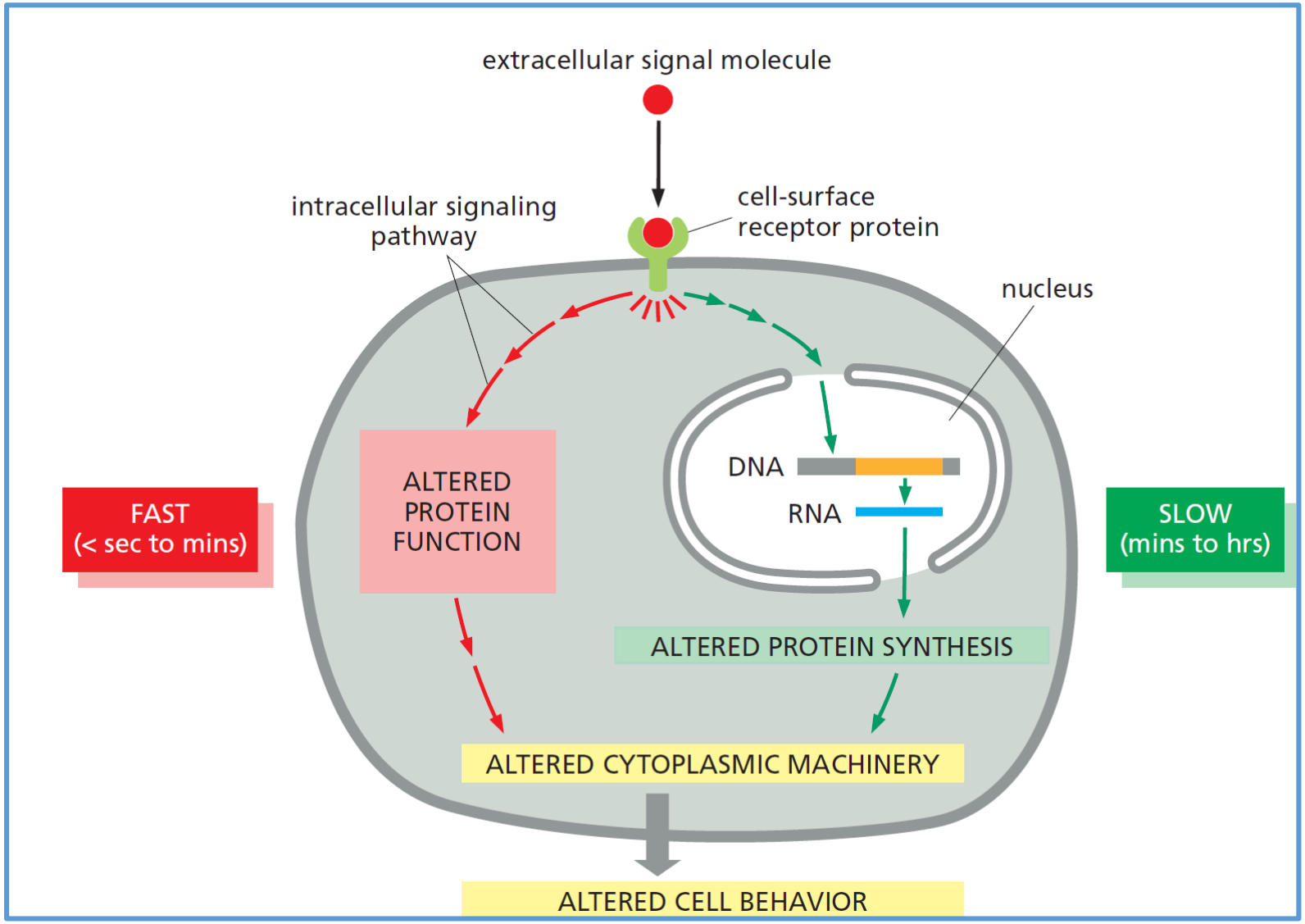
TYPES OF RESPONSE

Rapid response: activation of specific enzymes.

Changes in a metabolic pathway.



Slow response: activation of nuclear factors

Changes in cellular events: cellular mitosis

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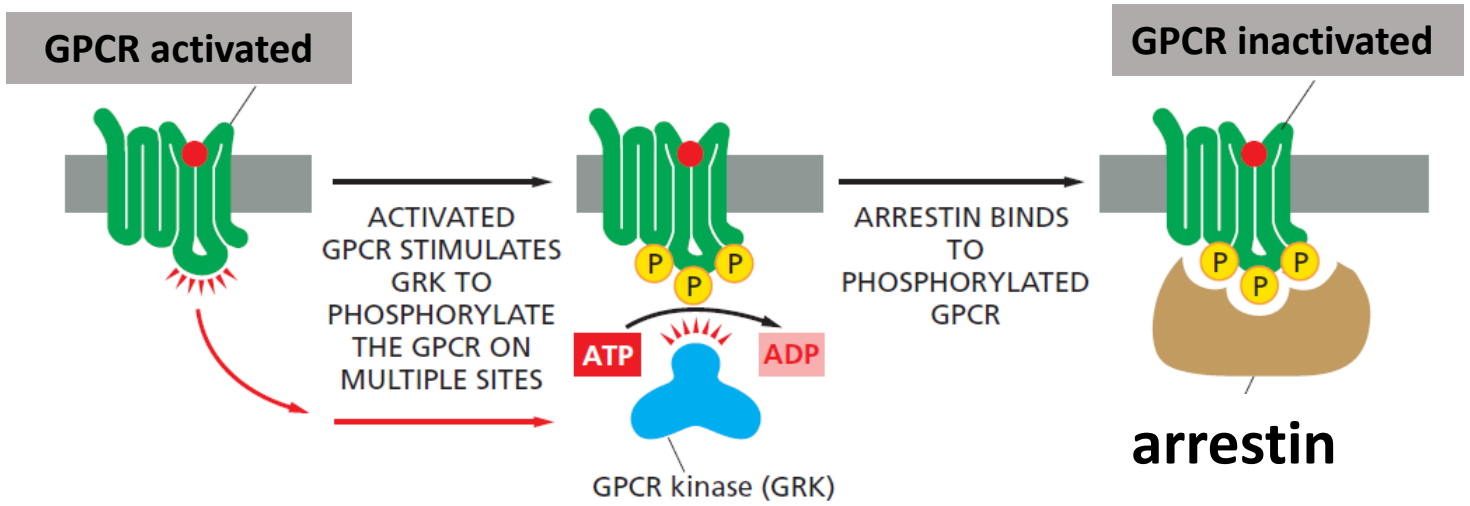
SIGNAL TERMINATION MECHANISMS

TERMINATION: after the effects are executed, mechanisms are necessary to repress/stop the activated events.

INTERACTION WITH PROTEINS



GPCR is activated by phosphorylation, and the signal transduction ends when this is blocked by the binding of a protein to the phosphates.

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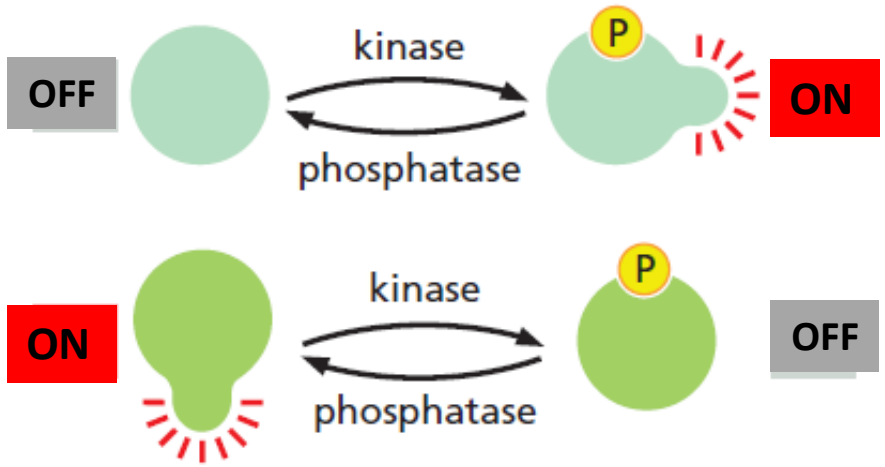
SIGNAL TERMINATION MECHANISMS

TERMINATION: after the effects are executed, mechanisms are necessary to repress/stop the activated events.

COVALENT MODIFICATION



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PROTEIN KINASES AND PROTEIN PHOSPHATASES

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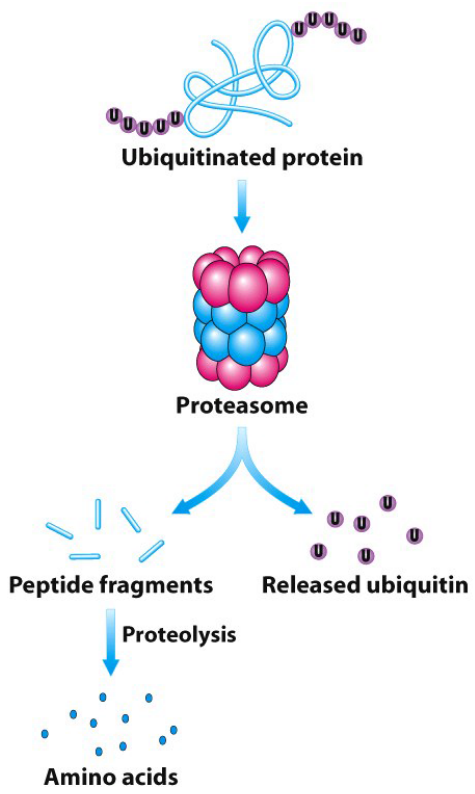
SIGNAL TERMINATION MECHANISMS

PROTEASOME DEGRADATION OF THE EFFECTOR PROTEINS

UBIQUITINATION



UBIQUITIN AND PROTEASOME COOPERATE TO DEGRADE PROTEINS

PROTEASOME

Protease complexes digest proteins that are labeled with UBIQUITIN (Ub).

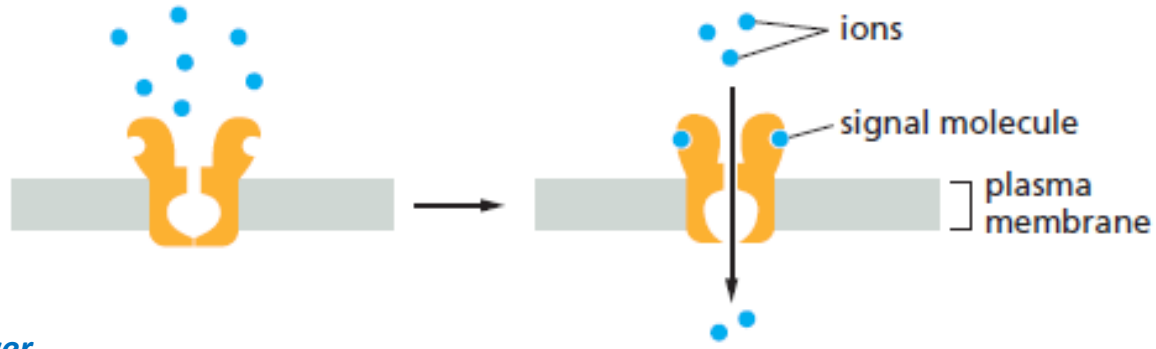
UBIQUITINE

This is a small protein added as a signal/mark.

It is a marking system for protein degradation.

CONFORMATIONAL CHANGES

Open/closed CANAL



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TYPES OF RECEPTORS: SIGNALING MEDIATED BY SURFACE RECEPTORS. CHARACTERISTICS.

BINDING TO THE RECEPTOR LEADS TO:

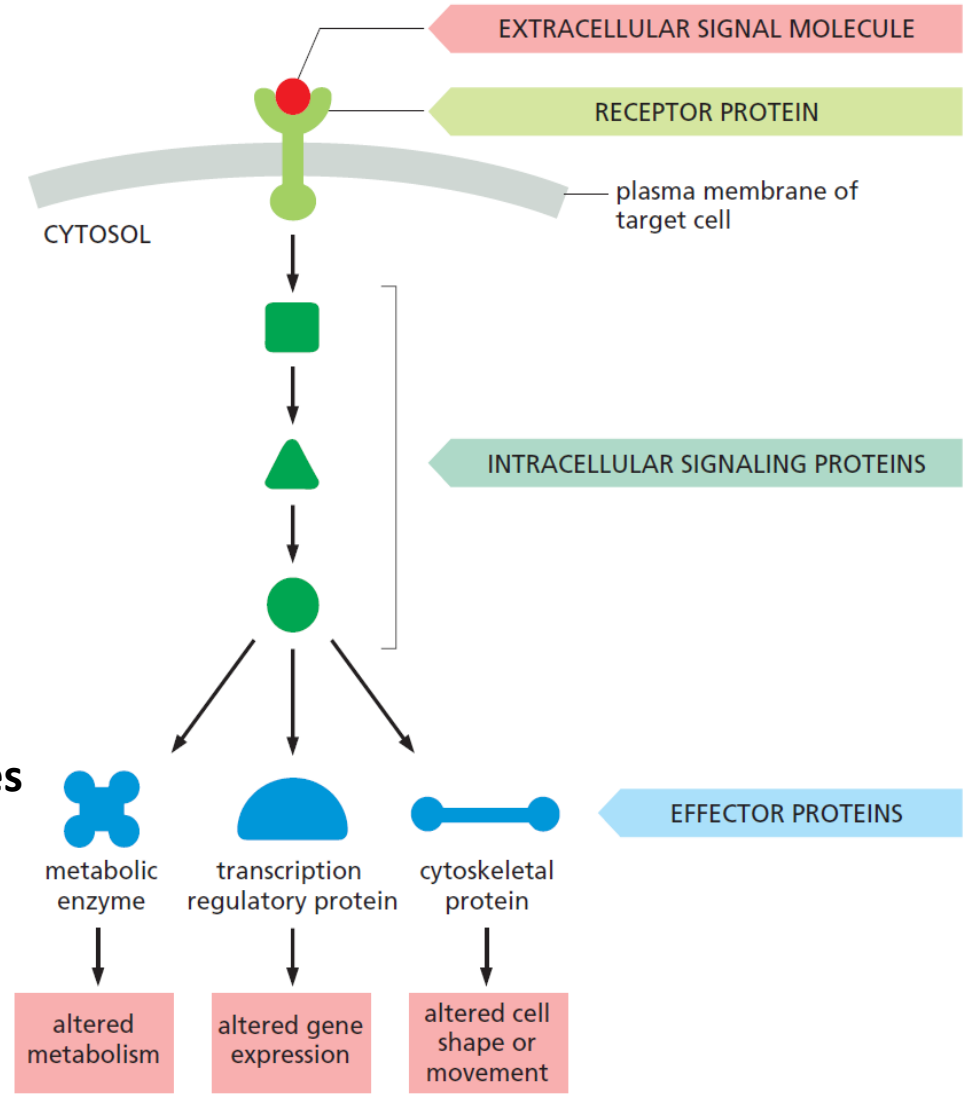
1. Recruitment of ASSOCIATED PROTEINS to the receptors:
Molecular adapters (Shc, IRS) or GTP-binding proteins (G PROTEINS). Protein kinases.

2. SECONDARY MESSENGER Generation:
Enzymatic (Adenyl cyclase, Guanyl cyclase, Phospholipase): cAMP, cGMP, Inositol triphosphate (IP3), Diacyl glycerol (DAG)
Channel changes: Ca_{2+}, Na_{+}, K_{+},
OTHERS: nitric oxide

3. Activation of **INTRACELLULAR PROTEIN KINASES:**

General protein kinases: PKA, PKB (Akt), PKC, Mitogen-activated MAP kinases
Cytokine-activated: JAK kinases.

4. Changes in **THE ACTIVITY OF PROTEINS** that act in the metabolism or **NUCLEAR TRANSCRIPTION FACTORS:** STAT, SMAD, NFAT, Jun, Fos, NF-Kβ



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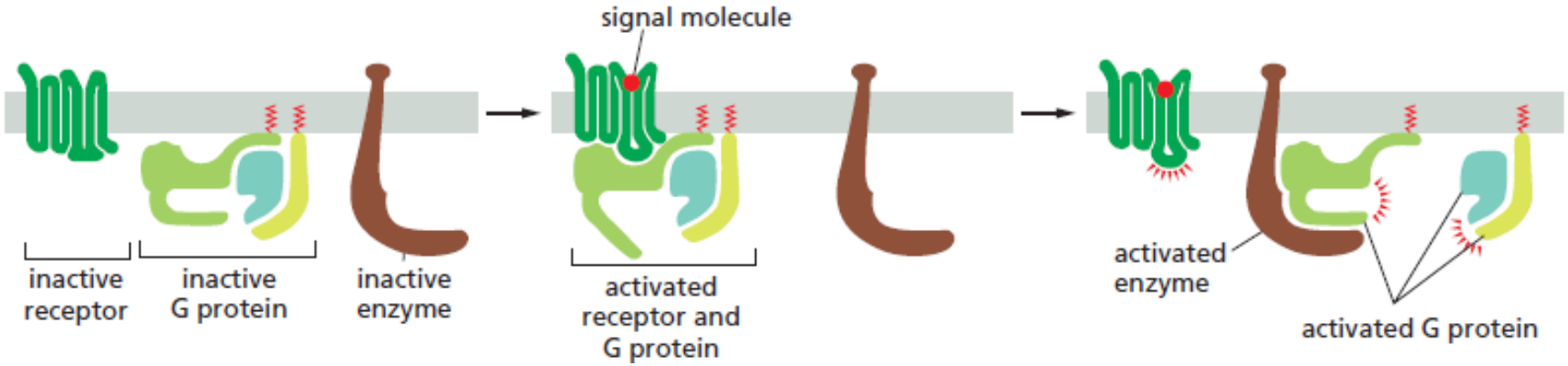
CELL SURFACE RECEPTORS: CHARACTERISTICS AND TYPES

These extend along the membrane and have 3 DOMAINS: **EXTRACELLULAR, TRANSMEMBRANE AND INTRACELLULAR.**

TRANSMEMBRANE DOMAIN: ligand recognition and induction of a conformational change that activates the receptor.

ACTIVATION OF THE RECEPTOR THAT WILL **TRANSDUCE THE SIGNAL** THROUGH THE INTRACELLULAR DOMAIN.

1. Receptors without kinase activity: G-protein-associated receptors, GPCR (G-coupled protein receptors)



7 TRANSMEMBRANE DOMAINS (GPCR)

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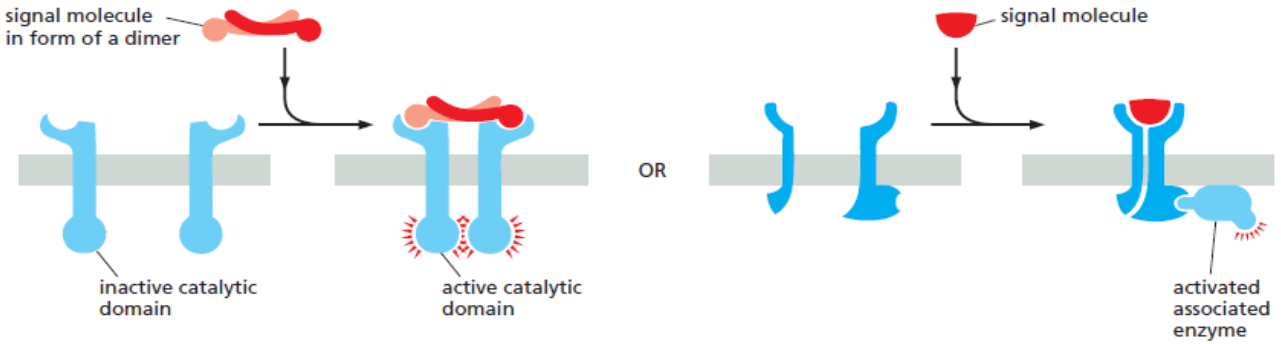
2. Surface receptors with catalytic activity (kinase):

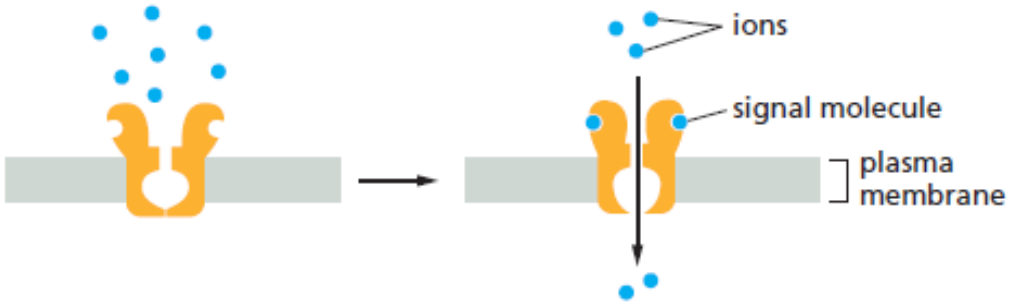


INTRINSIC TYR-KINASE activity: INSULIN RECEPTORS

RECRUIT TYR-KINASE: JAK cytokine receptors

Associated with PROTEINS SERINE/THREONINE KINASE

3. RECEPTORS coupled to ion channels:



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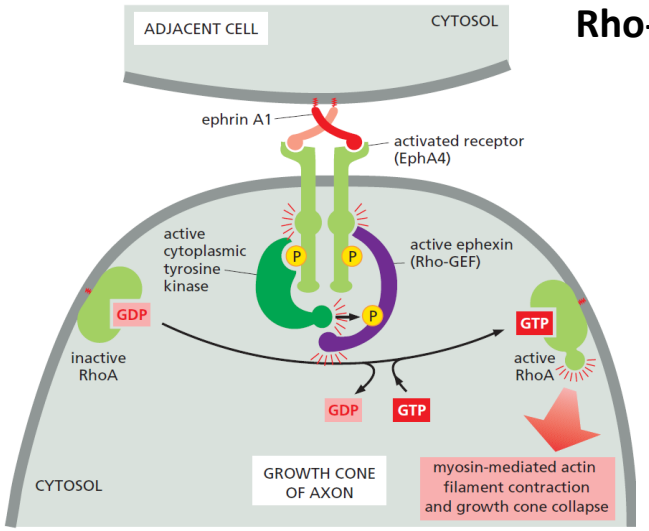
4. Contact CELL-CELL receptors



Rho-GTPase coupled receptors

1. G-PROTEIN-COUPLED RECEPTORS (GPCR, G-PROTEIN-COUPLED RECEPTOR)

RECEPTOR:

-7 transmembrane and G-protein-coupled domains

-Hormone receptors: glucagon receptor and GLP1 receptor, and neurotransmitter receptors, β/α-adrenergic receptors.

G-PROTEINS ASSOCIATED WITH THE RECEPTOR:

- have 3 subunits and are located on the inside of the membrane. They bind GTP and have GTPase activity.

Protein G regulates a membrane-associated enzyme, which generates the second messenger that amplifies the signal.

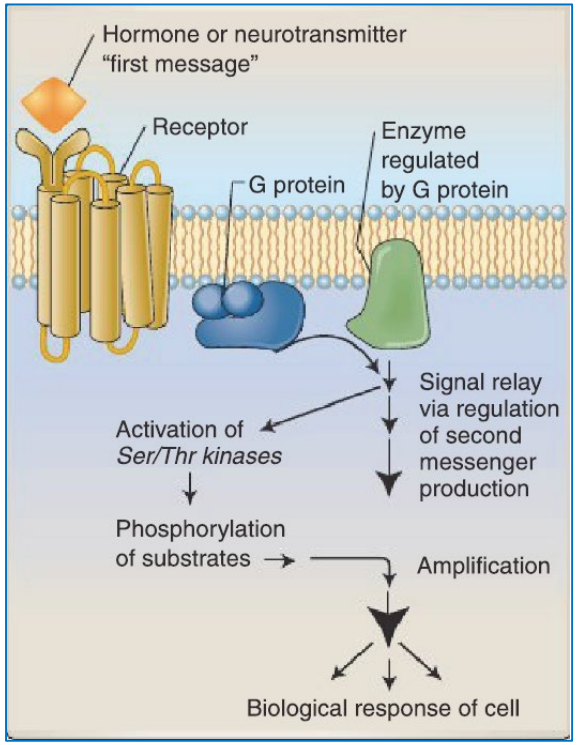
ASSOCIATED ENZYMES AND SECOND MESSENGERS:

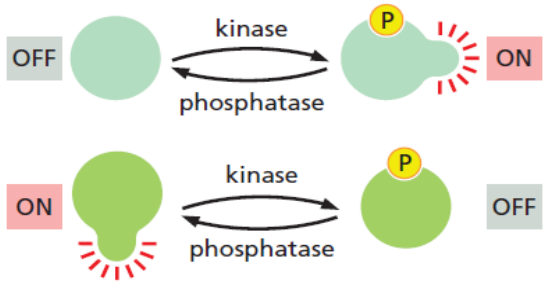
PHOSPHOLIPASE C AND ADENYLATE CYCLASE

PHOSPHOLIPASE C: DAG, PI3, Ca2+ as second messengers.

ADENYLATE CYCLASE: cAMP(s) as second messengers.

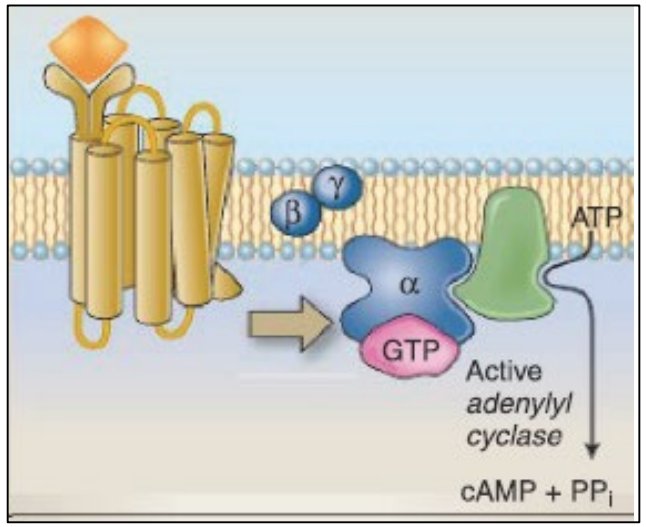
The second messenger activates SER/THR protein kinases that activate/repress enzymatic activities by phosphorylation.





Chandar and Viselli, Cell and Molecular Biology, Lippincot, 2nd ed. (2019)

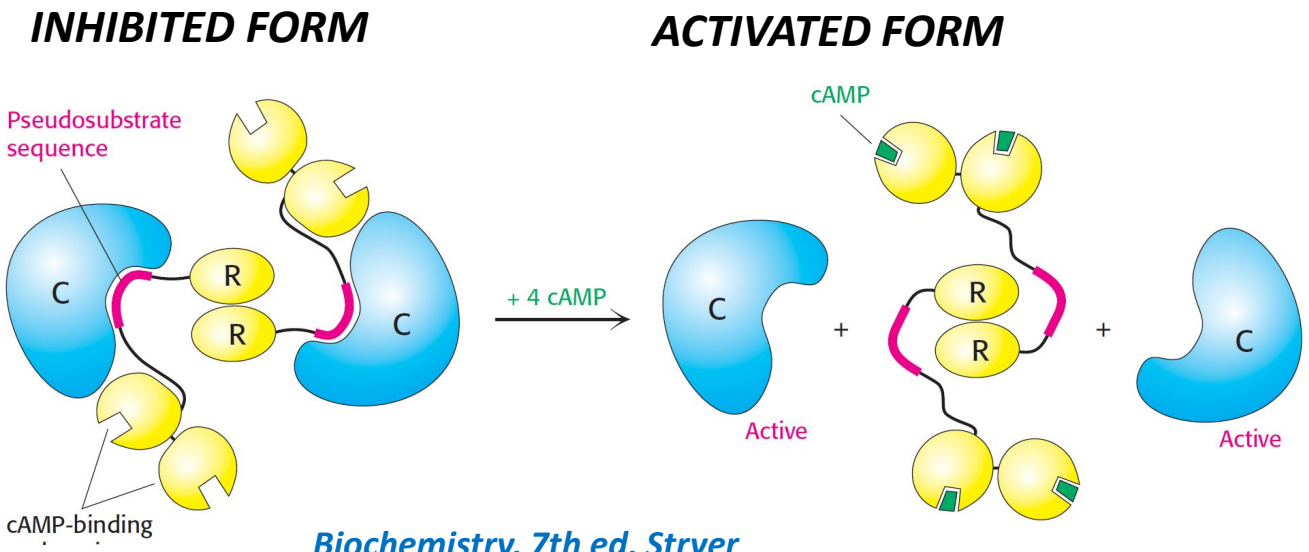
G-protein-coupled receptors (GPCR): SECOND MESSENGER EXAMPLES



ADENYLATE CYCLASE and CYCLIC AMP (cAMP)

Catalyzes the conversion of ATP to cAMP, and pyrophosphate. cAMP activates a specific protein kinase, the PKA.

PKA ACTIVATION OF PKA BY cAMP



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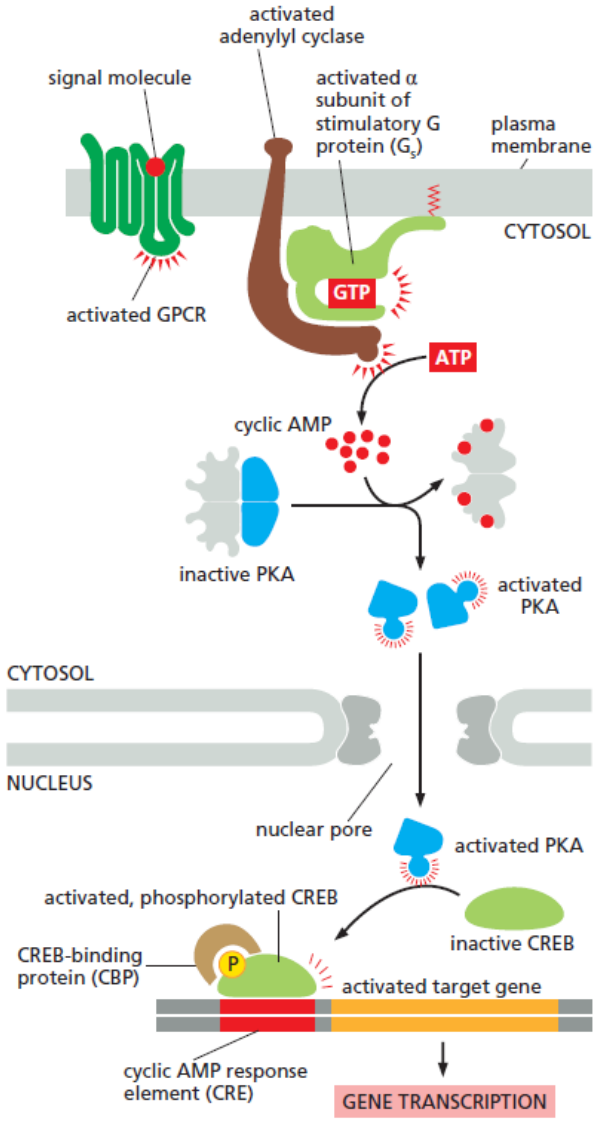
R: regulatory subunit

C: catalytic subunit activity kinase

There is a “pseudosubstrate” sequence in the R subunit that hides the active center where phosphorylable substrates enter in C. The binding of cAMP releases the R subunit. The C subunit with kinase activity is exposed and can accept substrates in order to phosphorylate them.

Chandar and Viselli, Cell and Molecular Biology, Lippincot, 2nd ed (2019)

EXAMPLE: GENOMIC EFFECTS OF GPCR PROTEIN SIGNALING



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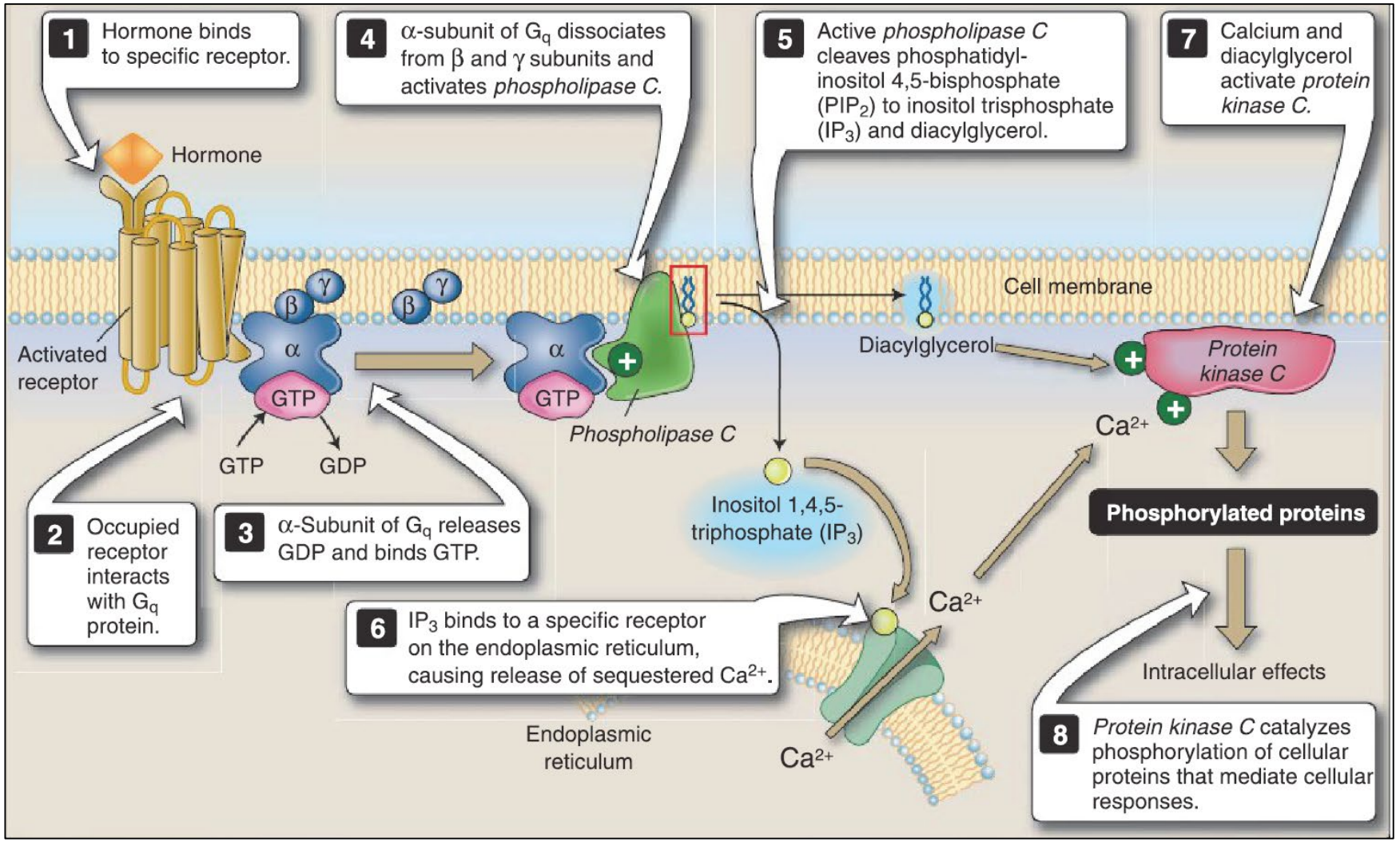
Binding to GPCR activates adenylate cyclase and increases the concentration of cAMP in the cytosol.

PKA is activated and the **PKA enters the nucleus** and phosphorylates the **transcription regulatory protein** CREB. CREB recruits a coactivator, which stimulates gene transcription.

G-protein-coupled receptors (GPCR): SECOND MESSENGER EXAMPLES

Phospholipase C and I3P, DAG (α-adrenergic receptors)
Activated by G-GTP releases IP3 and DAG. Both DAG and CA2+ activate PKC



Chandar and Viselli, Cell and Molecular Biology, Lippincot, 2nd ed (2019)

2. RECEPTORS WITH CATALYTIC ACTIVITY: RECEPTOR WITH INTRINSIC TYR-KINASE, RECEPTOR ASSOCIATED WITH TYR-KINASE

RECEPTORS WITH INTRINSIC TYROSINE KINASE ACTIVITY: INSULIN

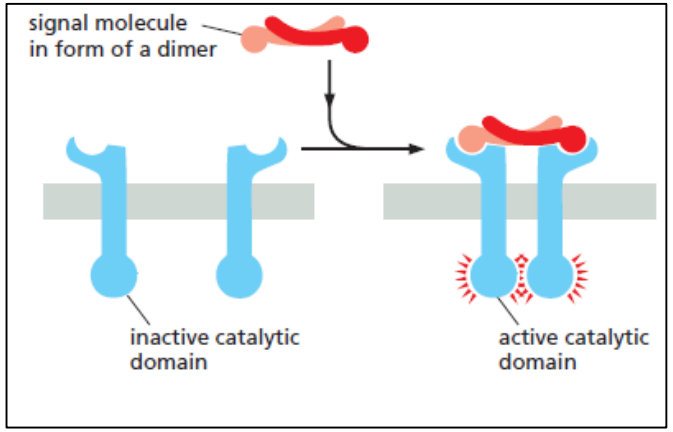
Growth factor, hormone and antigen receptors.

-In **some cases, dimerization of the receptor** and stimulation of intrinsic tyrosine kinase activity (**AUTOPHOSPHORYLATION**).

-**Phosphorylation of adjacent proteins and/or generation of binding sites** for **adapters and functional proteins** (Grb2, PI3K, phospholipase C, etc.). **Second messengers:** PIP3 and DAG (Ca2+ mobilization) which activate kinases that:

1. phosphorylate and activate enzymes of metabolic pathways.
2. phosphorylate proteins that are translocated to the nucleus and act as transcription factors.

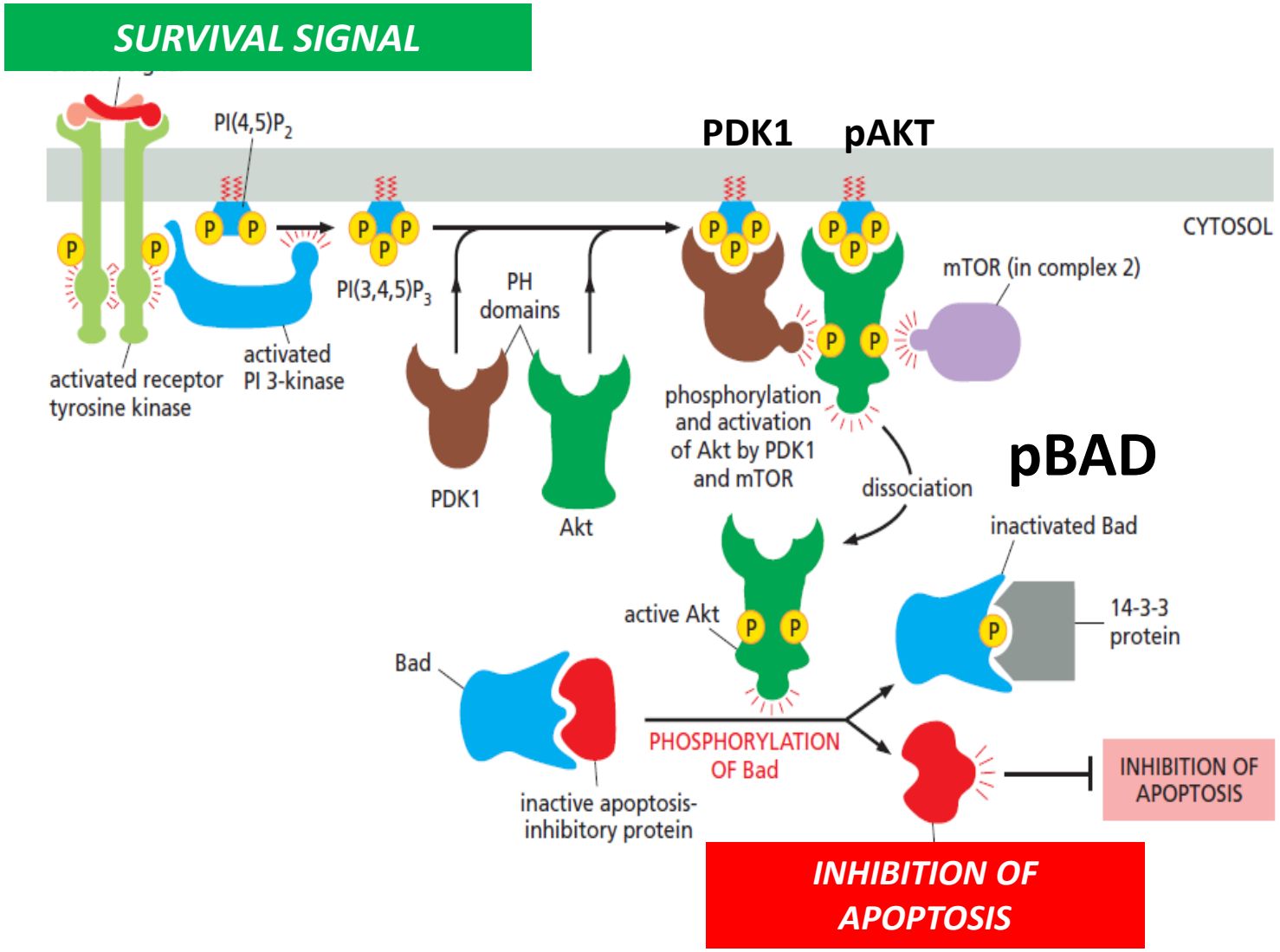
DIMERIZATION AND AUTOPHOSPHORYLATION



Alberts, 6th edition, Molecular Biology of the Cell

Survival and Growth: Critical in Cancer

EXAMPLE OF INTRINSIC ACTIVITY TYR-KINASE: SIGNALING MEDIATED BY PI3 KINASE



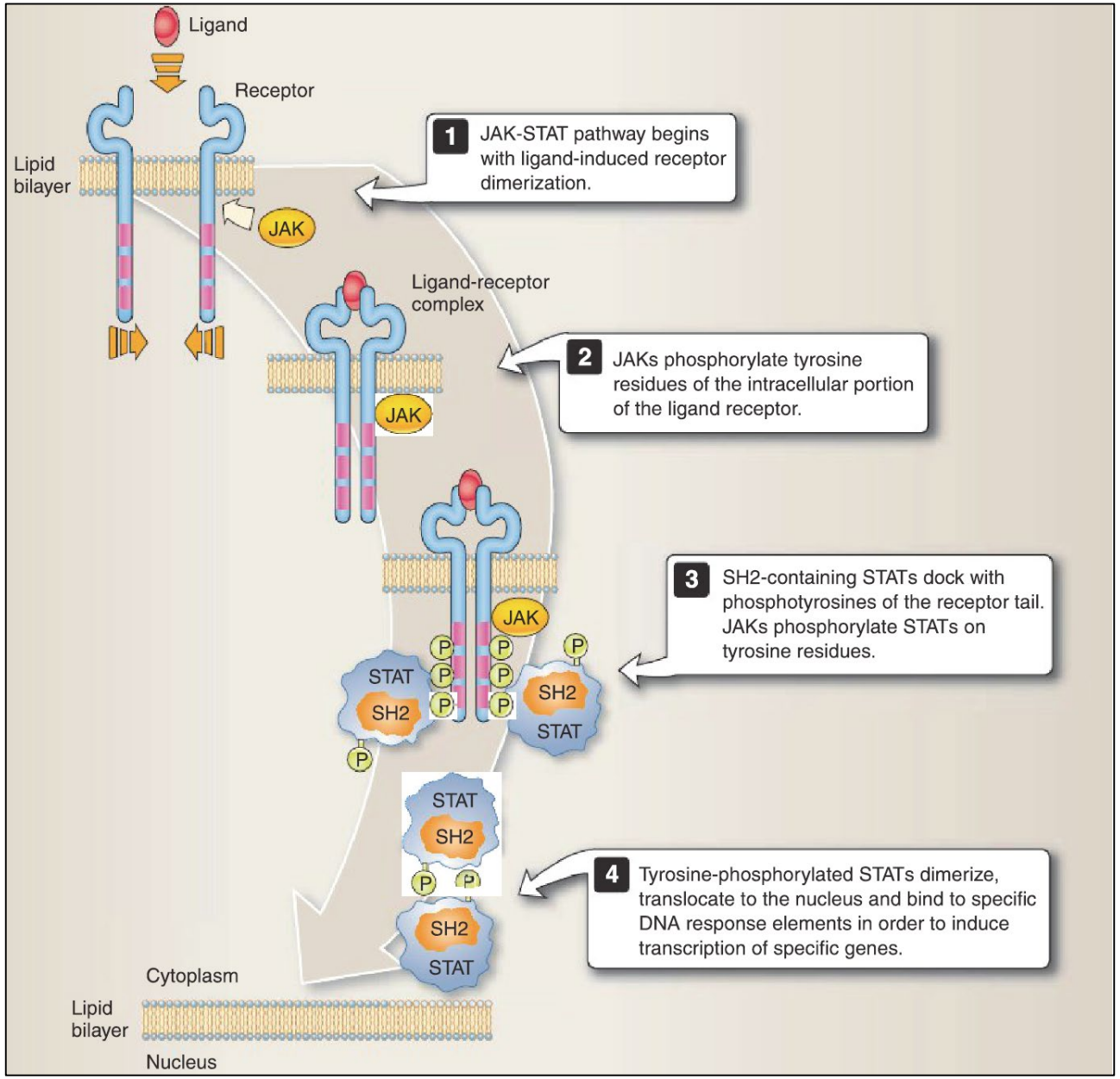
Mechanism

PI3K binds to the phosphorylated receptor and phosphorylates inositol phospholipids: **GENERATION OF PHOSPHATIDYLINOSITOL TRIPHOSPHATE (PIP3).**

PIP3 recruits PDK1 and AKT phosphorylates and activates them. AKT phosphorylates and inactivates BAD, thus blocking APOPTOSIS. Cell survival is promoted.

Alberts, 6th edition, Molecular Biology of the Cell

RECEPTORS WITH ASSOCIATED PROTEIN WITH TYROSINE KINASE ACTIVITY: JAK CYTOKINE RECEPTOR



Chandar and Viselli, Cell and Molecular Biology, Lippincot, 2nd ed (2019)

-**Cytokine and hormone** receptors

-No activity but **recruit and non-covalently bind to Tyr-protein kinases**, which phosphorylate the receptor and activate it.
-One of the best-known families is the JANUS KINASE FAMILY (JAK)

Mechanism

RECEPTOR is phosphorylated by JAK
JAK-RECEPTOR-P binds the transcriptional factors STAT that are phosphorylated by JAK.

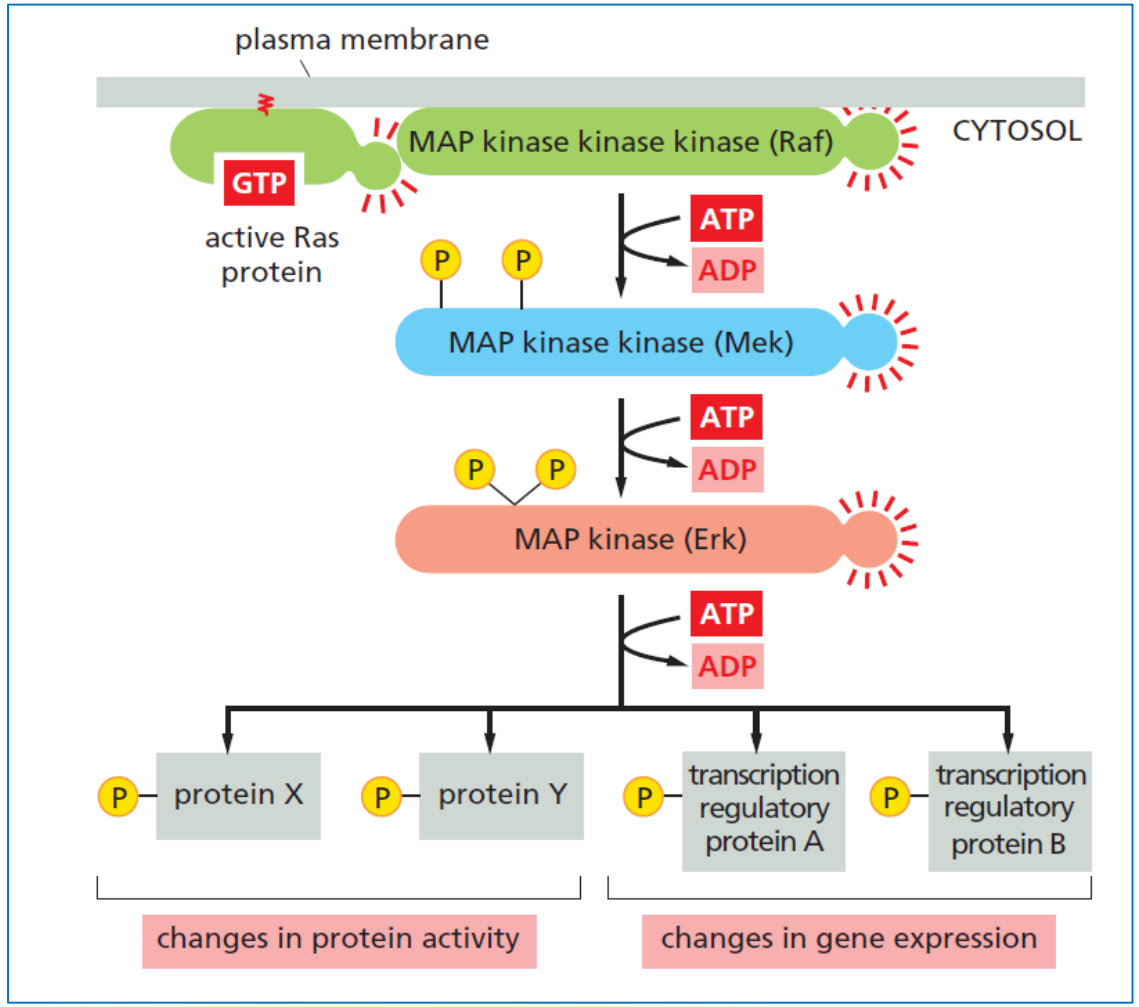
STAT-Pi translocates to the nuclei and activates the transcription of genes.

EXAMPLE: activation of differentiation genes in immune cells such as the transcription factor STAT5, which activates FOXP3.

OTHER EXAMPLES OF MEMBRANE RECEPTOR TRANSDUCTION

PHOSPHORYLATION CASCADES OF METABOLIC PATHWAYS COUPLED TO GCPR: ADRENALINE OR GLUCAGON, MITOGENS

MAPK: MITOGEN-ACTIVATED PROTEIN KINASES



Alberts, 6th edition, Molecular Biology of the Cell

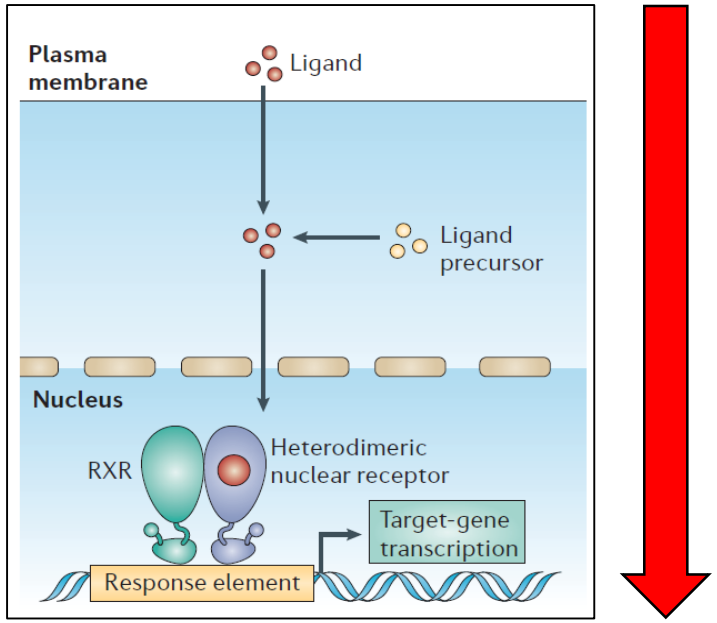
NUCLEAR RECEPTOR-MEDIATED SIGNALING: CHARACTERISTICS

-Intracellular proteins that respond to SIGNALS THAT ARE FAT-SOLUBLE MOLECULES AND CAN CROSS MEMBRANE.

-NUCLEAR RECEPTORS are intracellular proteins that act as **TRANSCRIPTION FACTORS** and produce a regulation of gene expression. They are in the nucleus or translocate to the nuclei after binding to the ligand.

-EFFECTS IN GENE EXPRESSION: control of the development, homeostasis and metabolism of the organism.

-DNA BINDING: The receptor is a transcriptional factor and therefore has DNA-binding elements.



Glass and Ogawa, ***Nat Rev Immunol,*** 2006

SIGNALS ARE HYDROPHOBIC AND CAN CROSS THE MEMBRANE

GENE-EXPRESSION ACTIVATION

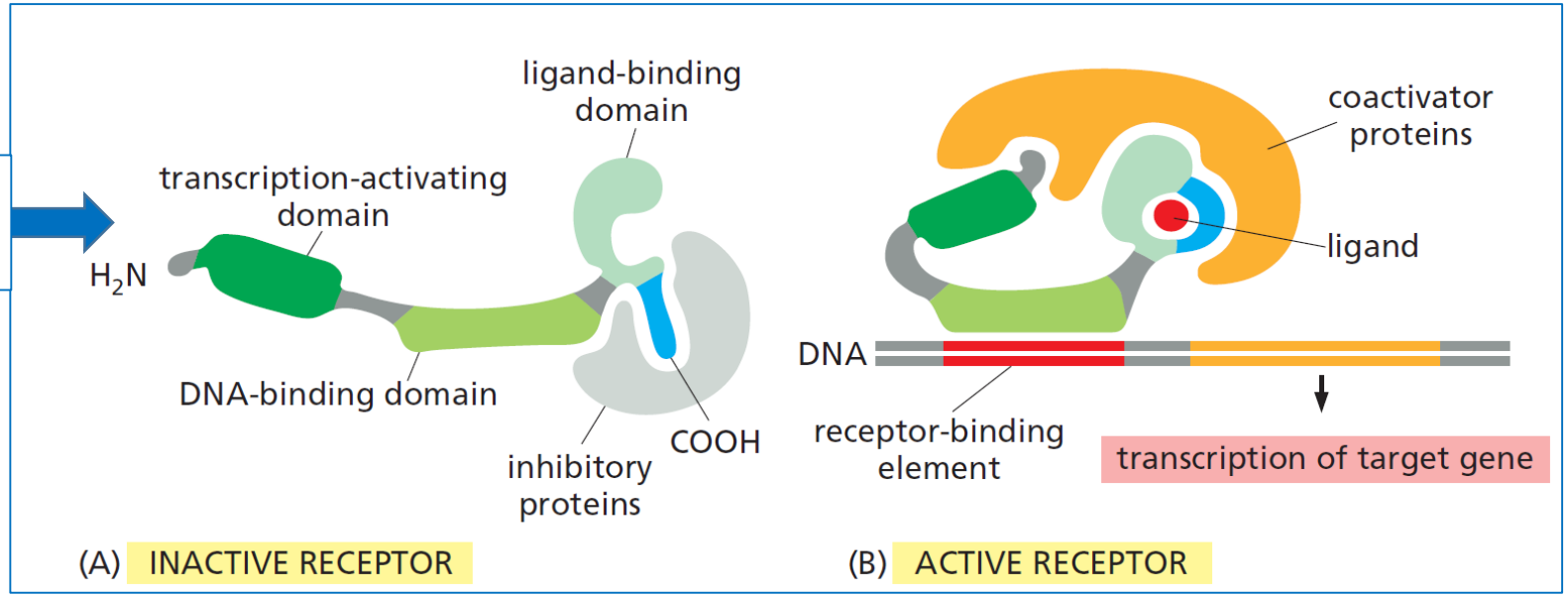
NUCLEAR RECEPTOR-MEDIATED SIGNALING: CHARACTERISTICS

MECHANISM:

The ligand induces a **CONFORMATIONAL CHANGE** in the receptor that activates it and enables it to stimulate **GENE EXPRESSION.**

Union of CO-REPRESSORS OR CO-ACTIVATORS

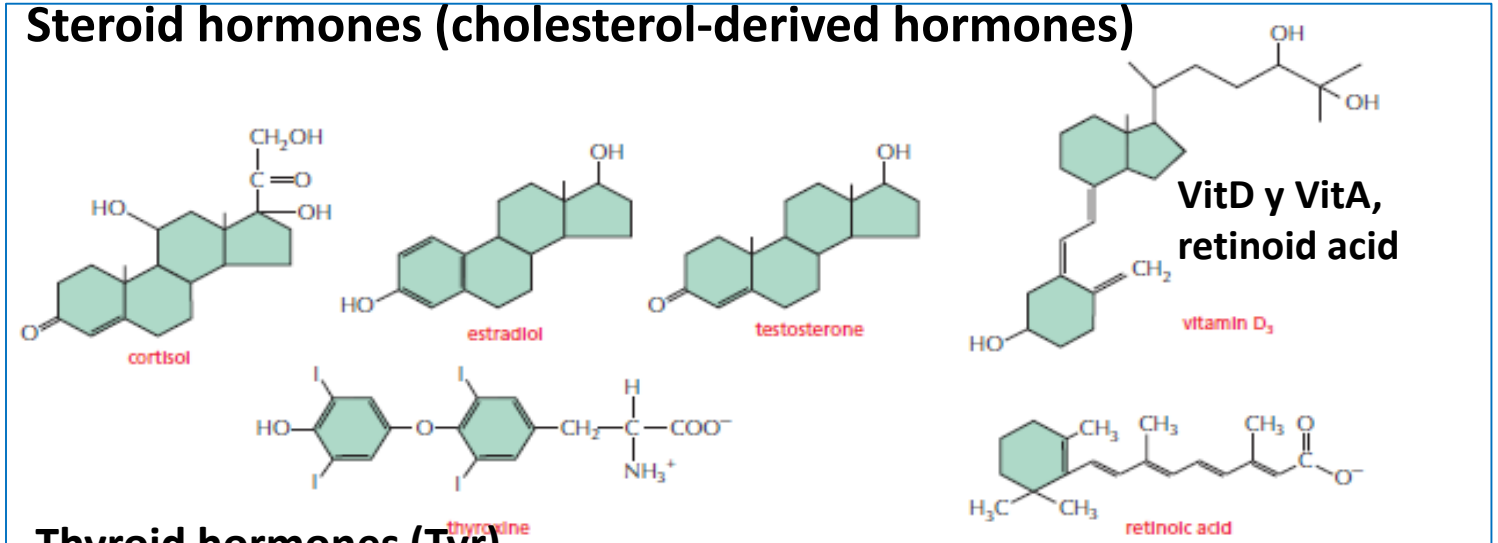
STRUCTURE AND CONFORMATIONAL CHANGE WHEN THE LIGAND BINDS



Alberts, 6th edition, Molecular Biology of the Cell

NUCLEAR RECEPTORS: LIPOPHILIC OR HYDROPHOBIC LIGANDS

Steroid hormones (cholesterol-derived hormones)

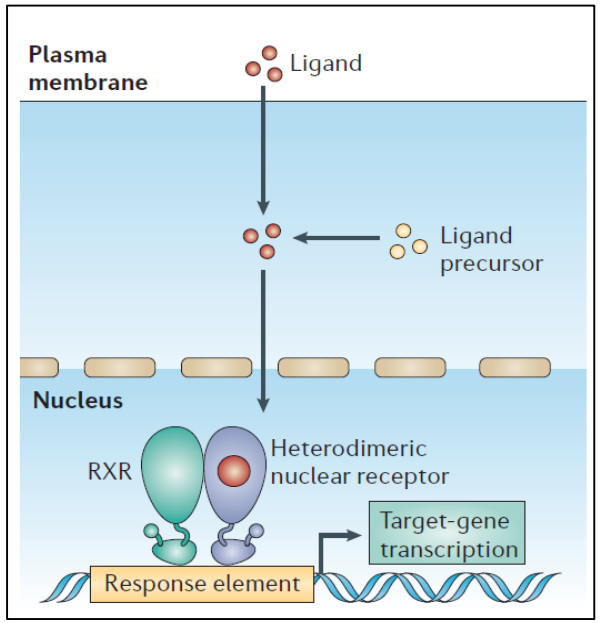


VitD y VitA, retinoid acid

Thyroid hormones (Tyr)

Alberts, 6th edition, Molecular Biology of the Cell

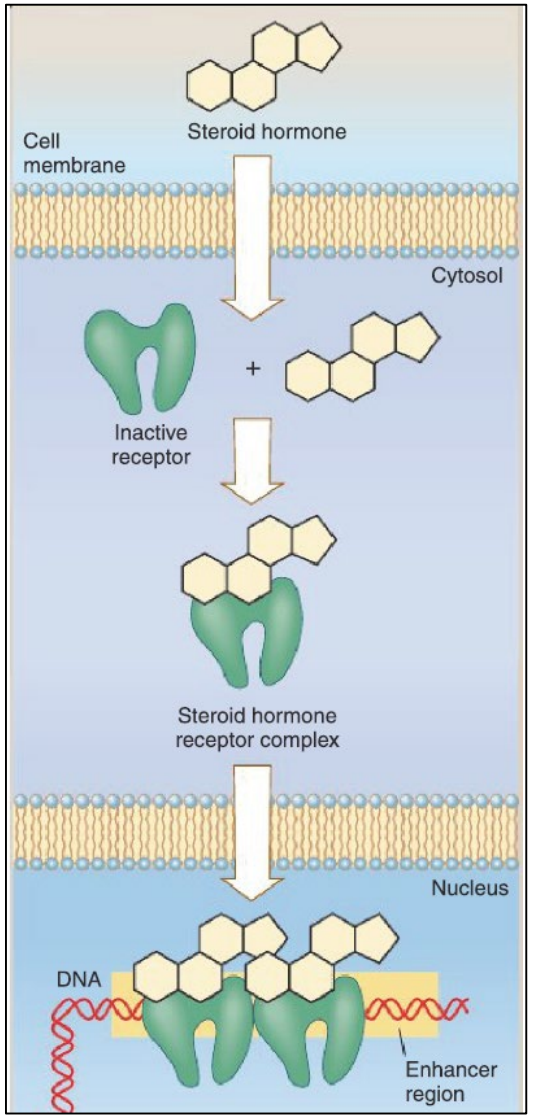
EXAMPLE



Glass and Ogawa, ***Nat Rev Immunol,*** 2006

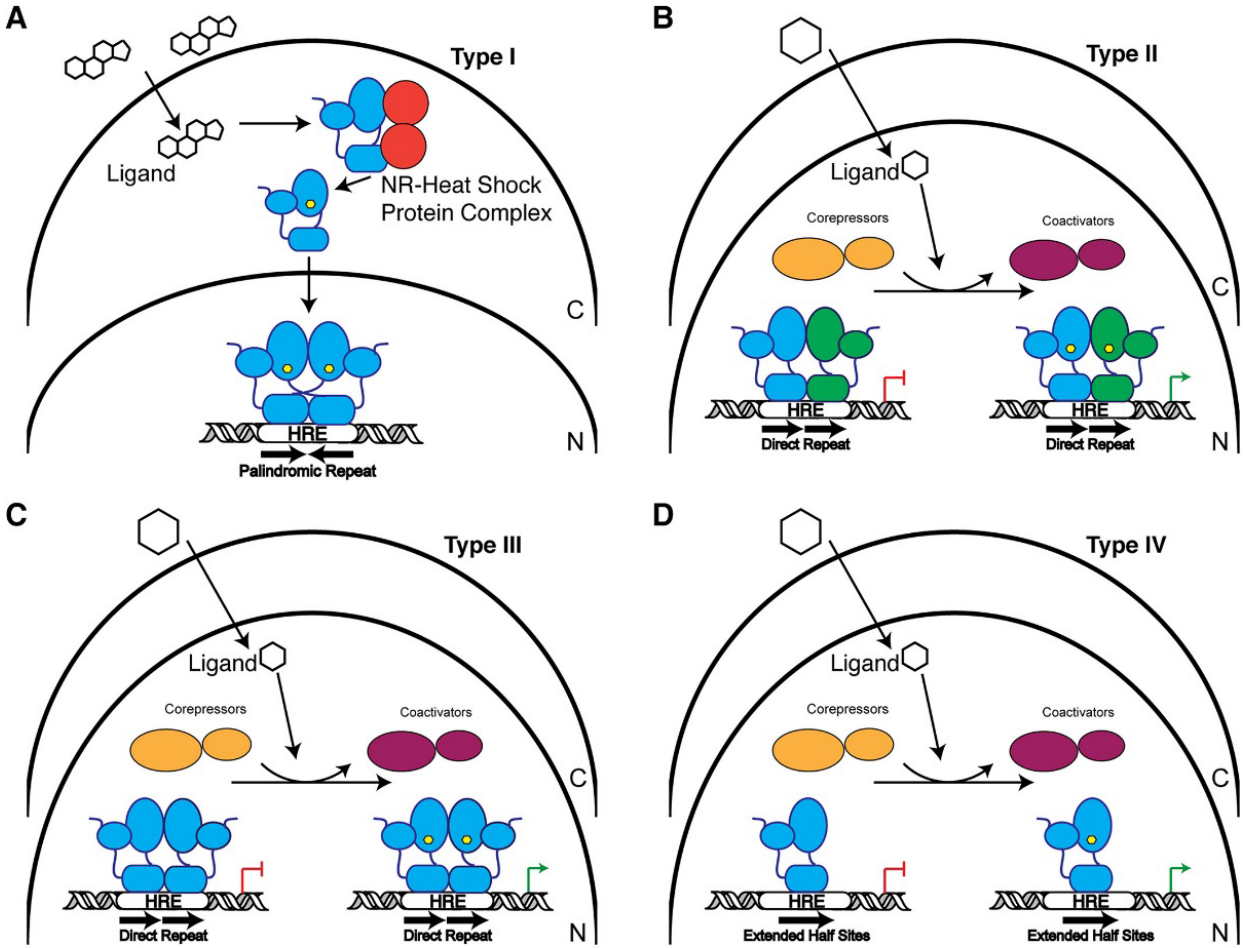
ACTIVATION OF GENE EXPRESSION

EXAMPLE



Chandar and Viselli, Cell and Molecular Biology, Lippincot, 2nd ed (2019)

TYPES OF NUCLEAR RECEPTORS ACCORDING TO THE MECHANISM OF ACTION



Protein Science, Volume 27, Issue 11, Pages 1876-1892; First published: 15 August 2018, DOI: (10.1002/pro.3496)

TYPE I: receptors for cholesterol-derived steroid hormones. Examples include androgens, estrogens and glucocorticoids**.**

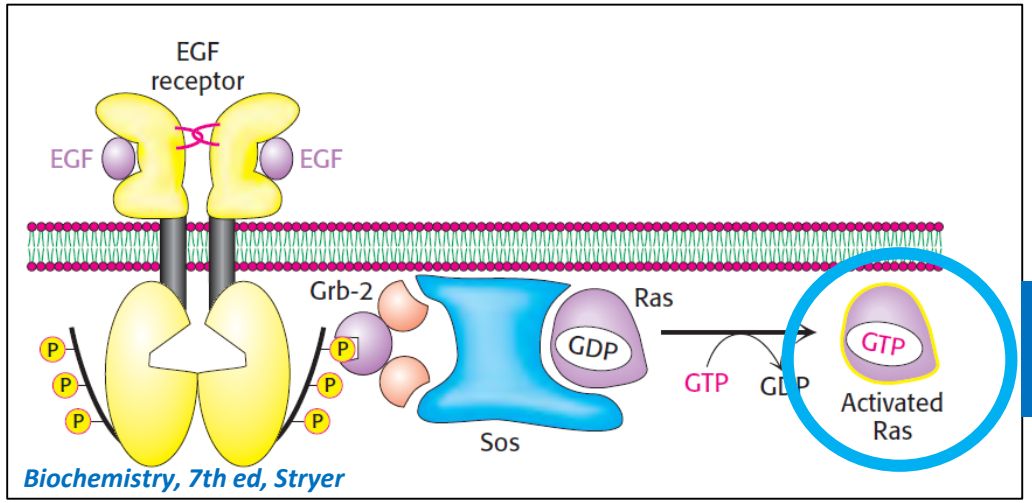
After ligand-binding, the receptor is released from chaperones and is translocated to the nucleus, where they form homodimers.

TYPE II: **RAR and LXR or PPAR heterodimerize with RXR.** After ligand-binding, they are released from a repressor.

TYPE III: vitamin D receptor.

TYPE IV: binding to DNA as monomers (these are called orphan receptors).

MUTATIONS IN SIGNAL TRANSDUCTION PROTEINS OF THE GPCR SIGNALING: MUTATIONS IN RAS AND CANCER



Up to 90% of pancreatic tumors carry mutations in the K-Ras gene. N-Ras protein mutations are more common in hematopoietic cancers.

Ras permanently activated

Mutations in the RAS gene and cell proliferation

RAS is a monomeric G-protein. The RAS mutations lose GTPase activity; GTP is therefore permanently bound and signaling cascade is activated.

THERAPEUTIC TARGET OF MANY DISEASES

RAS PROTEIN: PROTO-ONCOGENE

RAS PROTEIN

↓

MUTATIONS IN RAS, monomeric G-protein, does not hydrolyze GTP. The route is permanently activated.

↓

OVERGROWTH AND CANCER

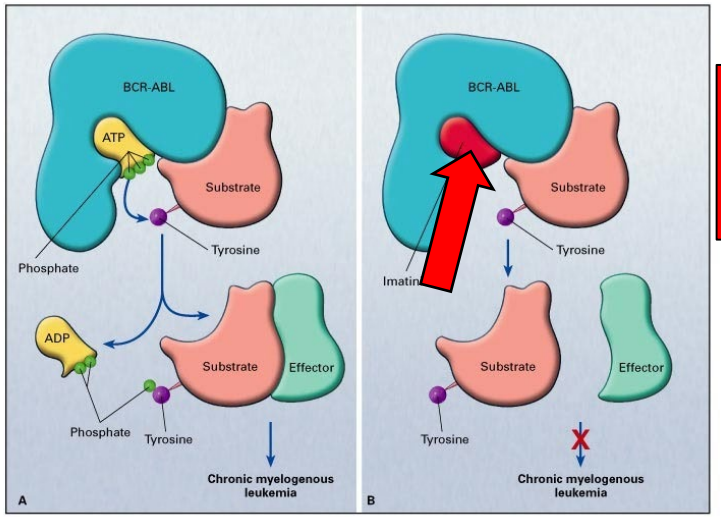
Cancer Res; 72(10); 2457–67. ©2012 AACR.

MUTATIONS IN RECEPTORS WITH TYROSINE KINASE ACTIVITY

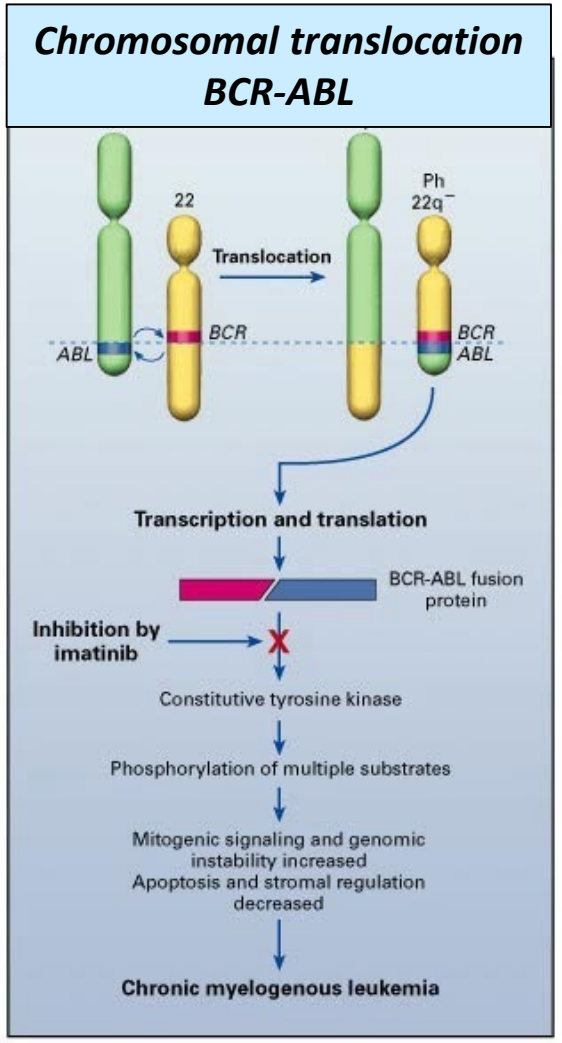
Over 90% of patients with chronic myeloma show an alteration in the kinase c-Abl (c-kit) that involves fusion with another gene (Bcr).

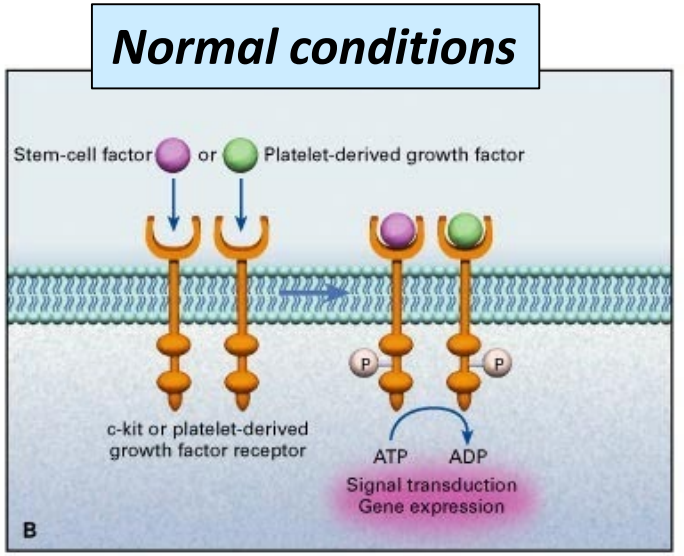
BCR-ABL FUSION PROTEIN → **INCREASED TYROSINE KINASE** → **Growth stimulation**

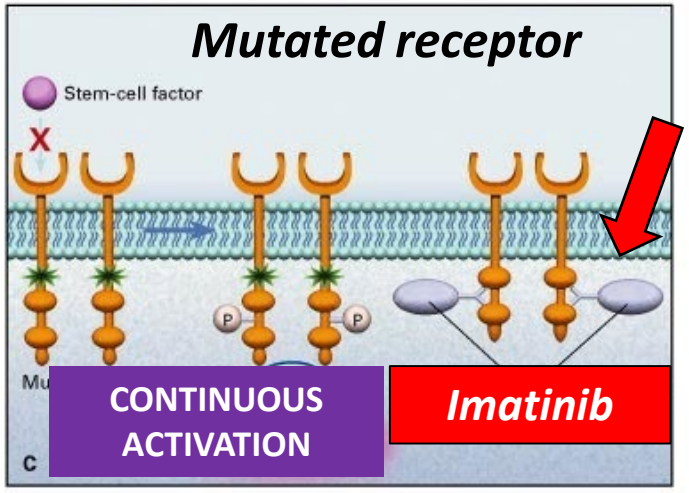
CANCERS: chronic myeloma
TREATMENT: specific inhibitor of Bcr-Abl
Gleevec (STI-571, **IMATINIB mesylate**)



Imatinib prevents phosphorylation and signal transduction

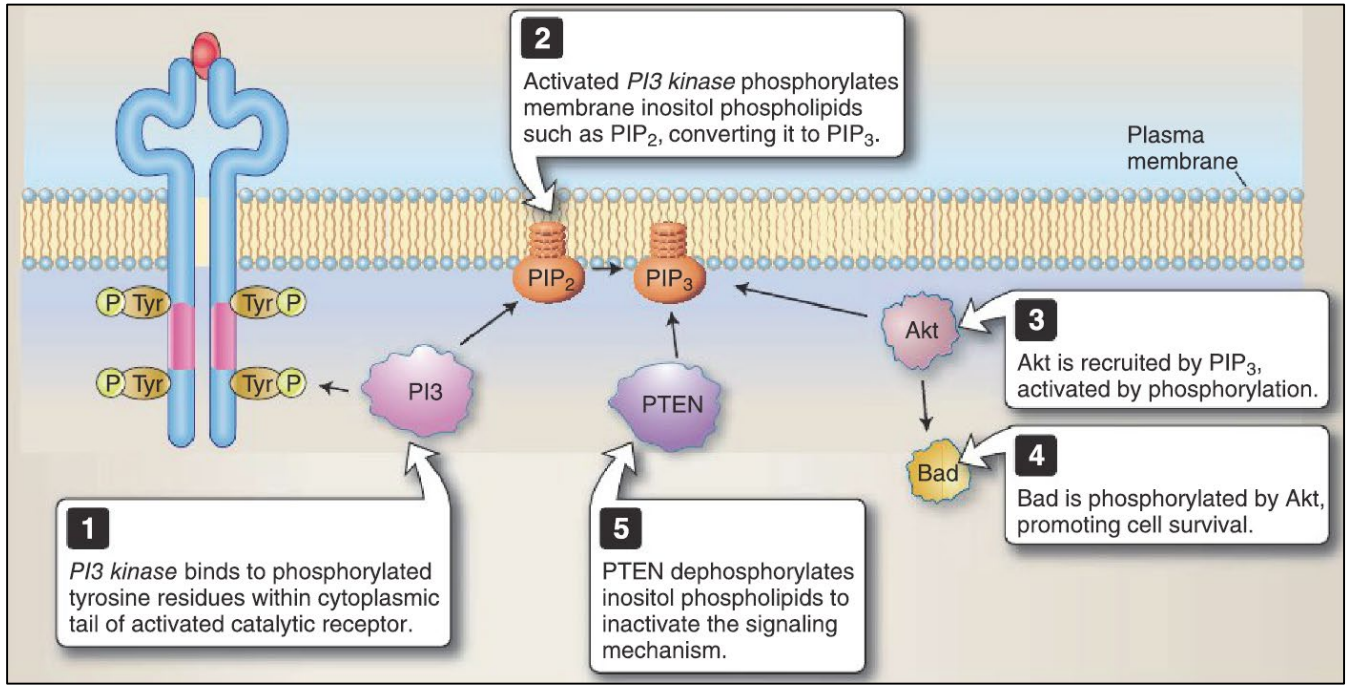






February 28, 2002 N Engl J Med 2002; 346:683-693 DOI: 10.1056/NEJMra013339

MUTATIONS IN SIGNAL TRANSDUCTION PROTEINS: MUTATIONS IN PTEN PHOSPHATASE



Chandar and Viselli, Cell and Molecular Biology, Lippincott, 2nd ed (2019)

Mechanism

Pi3K binds to the phosphorylated receptor and phosphorylates inositol phospholipids: phosphatidylinositol 3 phosphate generation.

PIP3 recruits AKT, and this is activated by phosphorylation. AKT phosphorylates and inactivates BAD, which plays a role in survival.

PTEN is a phosphatase that terminates the signal by dephosphorylating PIP3.

***PTEN MUTATIONS INDUCE CANCER due to a poor dephoshorylation of* PIP3.**

Mutations in PTEN in which **phosphatase activity is lost**: these are common in **brain tumors** (glioblastomas and astrocytomas) and an aggressive form of melanoma skin cancer.

PTEN: TUMOR SUPPRESSOR

https://medlineplus.gov/genetics/gene/pten/

LESSON 16. CELL SIGNALING (II): INTRODUCTION TO HORMONE SIGNALING.

E-mail: herminia.gonzalez@uv.es

Herminia González Navarro 2022

INDEX

CHARACTERISTICS OF HORMONES

Hormones are molecules (chemical primary messengers) that, AFTER BINDING TO A RECEPTOR, PROMOTE CELL SIGNALING in order to produce changes.

Endocrine hormones are produced in specialized organs and released into circulation for signaling in various target organs. **Paracrine hormones** act at a shorter distance in bneraby cell. **Autocrine hormones they are produced and act** on the same cell.

SYNTHESIS: homones are produced in specialized organs such as the pancreatic islets adrenal cortex or medulla or other cell-types such as epithelial cells or in other types of different tissues example of L, K cells of the intestine (like the incretins GLP1 and GIP).

TRANSPORT: hormones are transported in the bloodstream or via interstitial circulation. They can be transported free or bound to proteins to increase their stability.

BLOOD CONCENTRATION is highly regulated, pg a ng/mL; fast and efficient disposal mechanisms (minutes).

Hormones belong to the ENDOCRINE SYSTEM:

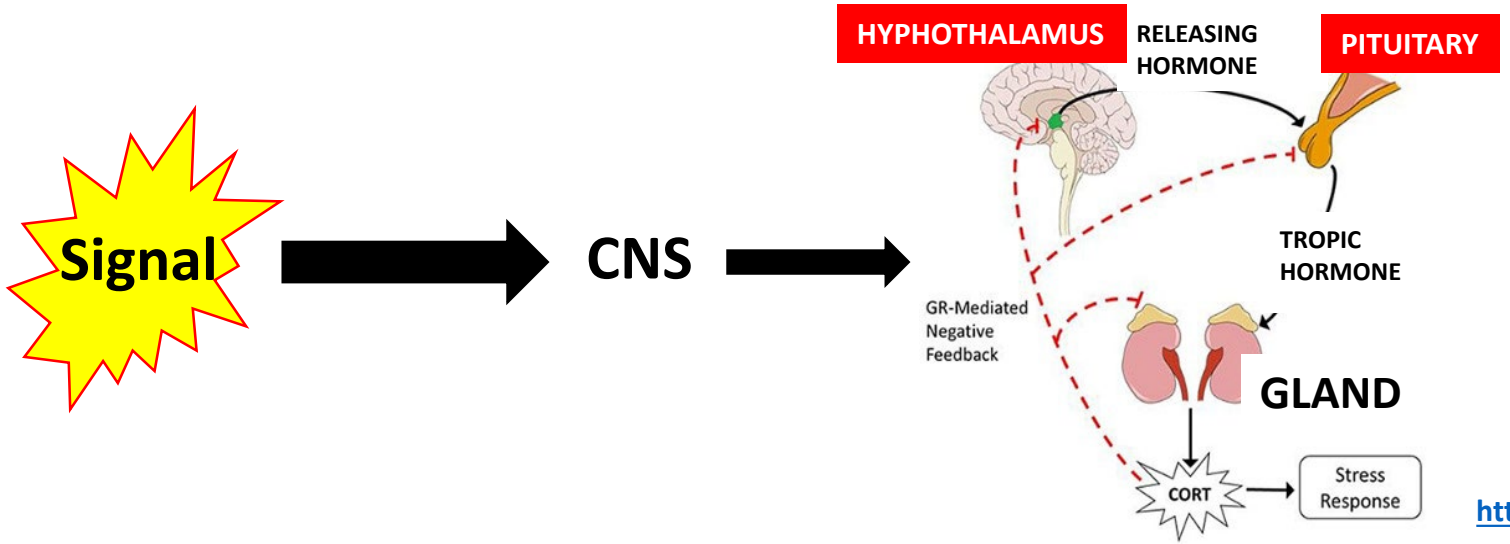
-THEY MAY BE REGULATED BY THE NERVOUS SYSTEM, which inhibits or stimulates the secretion of hormones. Nervous and endocrine systems coordinate to maintain the functions of the organism.

-THEY MAY NOT BE REGULATED BY THE NERVOUS SYSTEM (INSULIN, GLUCAGON, INCRETINS).

CHARACTERISTICS OF HORMONES

ENVIRONMENT OR INTERNAL SIGNAL

Temperature, noise or stress; reduced hormone levels (internal sensor).

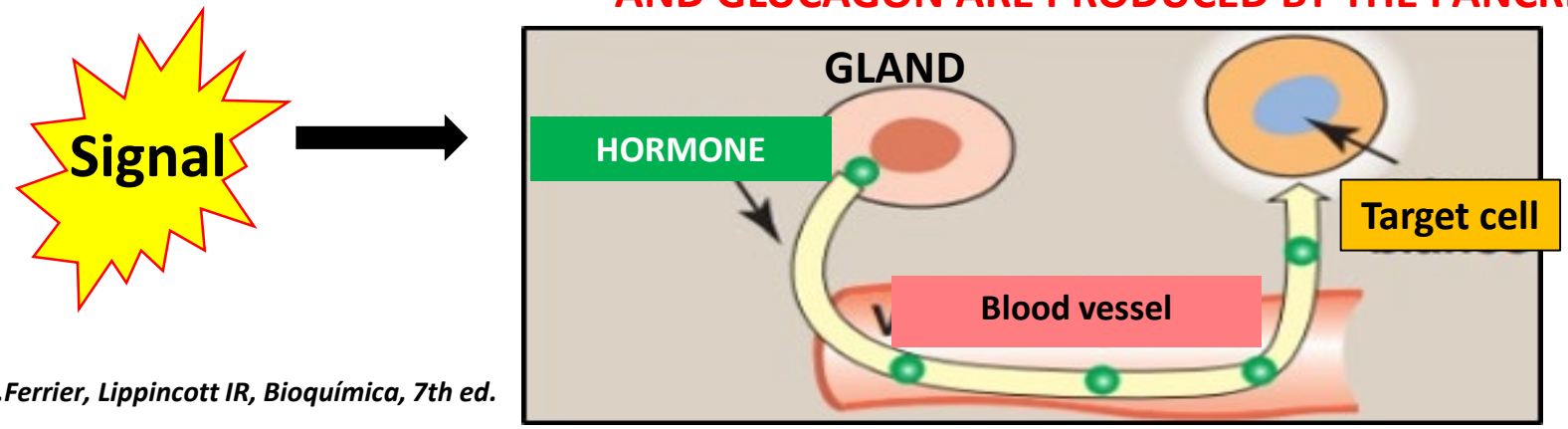


PARTICIPATION HYPOTHALAMIC-PITUITARY AXIS IN THEIR SECRETION

EXAMPLES: ADRENALIN, CORTISOL

https://doi.org/10.3389/fneur.2019.00345

METABOLIC HORMONES: INCRETINS, GLP1 AND GIP ARE PRODUCED IN THE INTESTINE; INSULIN AND GLUCAGON ARE PRODUCED BY THE PANCREAS.



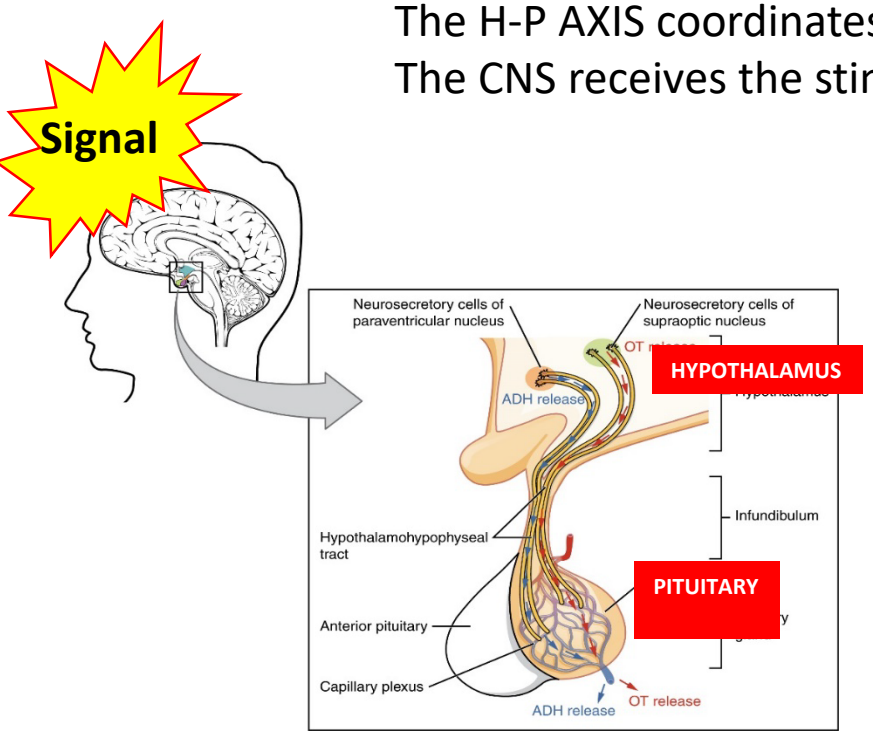
THEY DO NOT PARTICIPATE IN THE HYPOTHALAMIC-PITUITARY AXIS

THEY ARE REGULATED BY THE AVAILABILITY OF NUTRIENTS AND RESPOND TO A FASTING-FEEDING CYCLE.

D.Ferrier, Lippincott IR, Bioquímica, 7th ed.

HYPOTHALAMIC-PITUITARY COMPLEX STRUCTURE: STIMULATION OF HORMONAL SECRETION

The H-P AXIS coordinates messages between the endocrine and the nervous systems.
The CNS receives the stimulus communicated to this complex, thus increasing hormone production.



HYPOTHALAMUS-PITUITARY
Endocrine System Control Center

1. Secretion of response hormones.
2. Stimulation of glands to produce hormones. **EFFECTOR HORMONE (mg)**

The hormonal cascade amplifies the signal

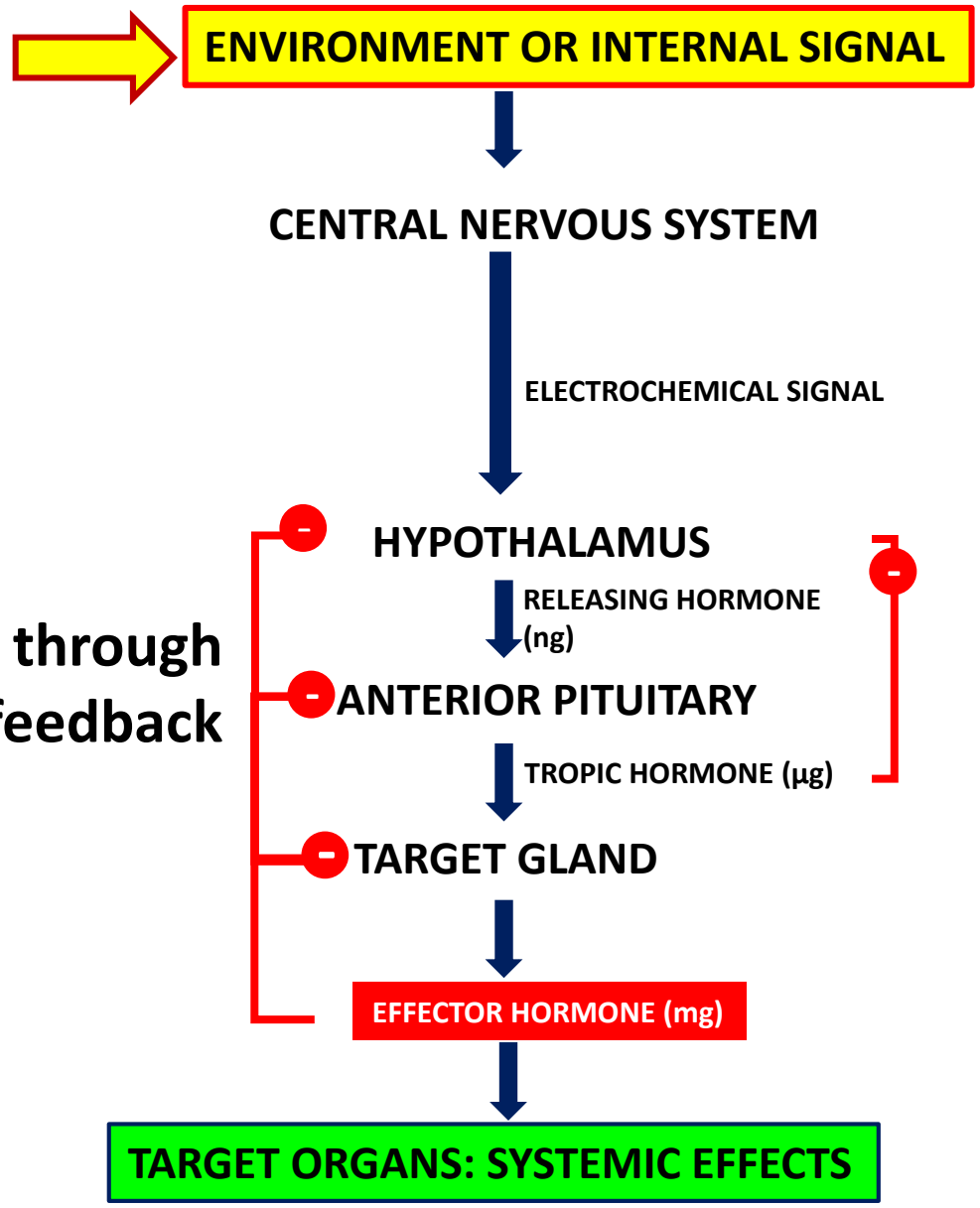
TARGET ORGANS: SYSTEMIC EFFECTS

THE HYPOTHALAMIC-PITUITARY AXIS DOES NOT INTERVENE IN THE PANCREAS, GASTROINTESTINAL HORMONES, PARATHYROID

https://openstax.org/books/anatomy-and-physiology/pages/17-3-the-pituitary-gland-and-hypothalamus

HORMONAL CASCADE: SIGNAL → CNS → HYPOTHALAMUS-PITUITARY → TARGET GLAND

Temperature, noise or stress; reduced hormone levels (internal sensor).



Regulation through negative feedback

The SIGNALING CASCADE starts with a signal on the CNS:

Stimulation of the HYP-PIT AXIS.

Activation of the axis leads to hormonal secretion, which activates the GLAND THAT PRODUCES THE EFFECTOR HORMONE.

THE EFFECTOR HORMONE systemically signals AND INHIBITS, THROUGH NEGATIVE FEEDBACK, ITS PRODUCTION at various levels.

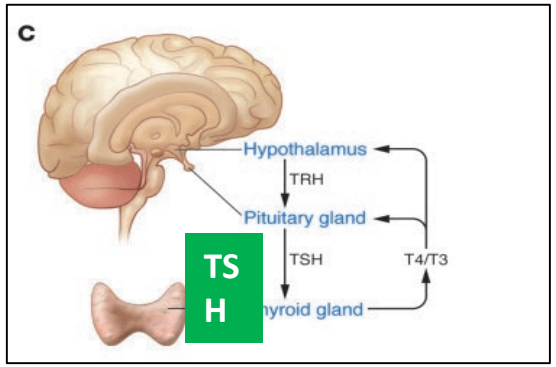
Scheme based on Textbook of Biochemistry with Clinical Correlations, Devlin

SIGNALING OF IMPORTANT HORMONES IN METABOLISM

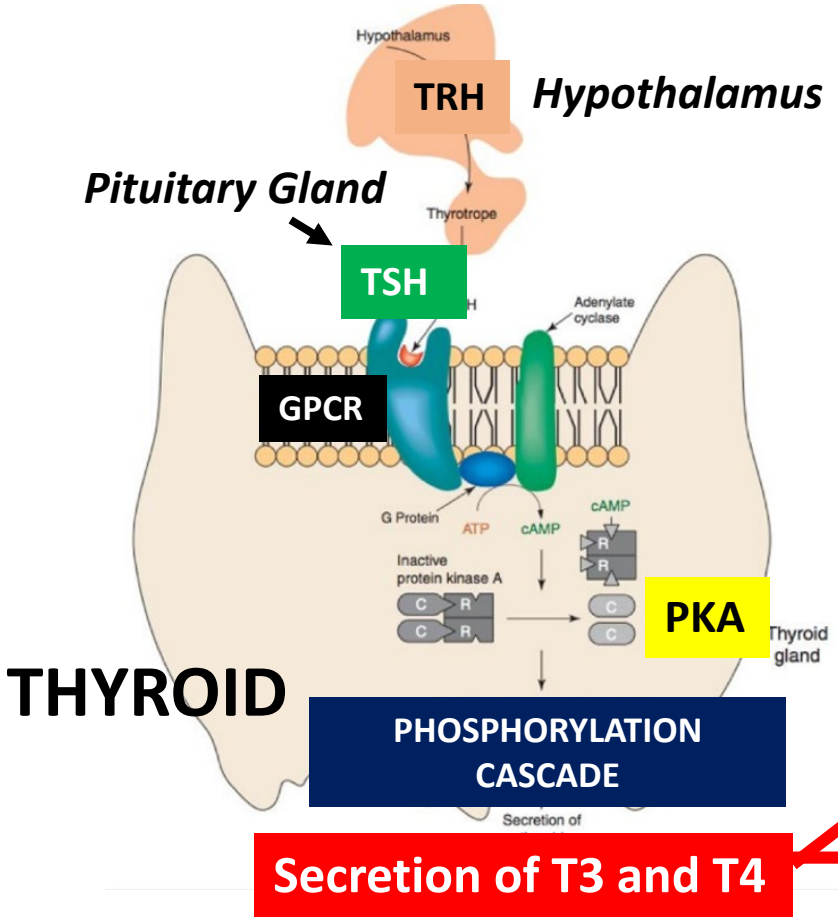
HORMONE	GLAND	RECEPTOR	ADAPTER	SECOND MESSENGER AND SECOND MESSENGER GENERATOR	PROTEIN KINASE	CELLULAR EFFECT
THYROID HORMONES T3 (TRIIODOTHYRONINE) and T4 (TIROXINE)	THYROID GLAND	Nuclear thyroid receptor	-	-	-	PERIPHERAL TISSUES Increased metabolic rate
ADRENALINE	ADRENAL (MARROW/MEDULLA)	Surface: GPCR α,β adrenergic receptors	G Protein	α: phospholipase C, Ca2+, IP3, DAG β: Adenylate cyclase cAMP	α: PKC β: PKA	Glycogenolysis activation and glycogenesis inhibition lipolysis in adipocytes
CORTISOL	ADRENAL (CORTEX)	Nuclear glucocorticoid receptor	-	-	-	Decreased inflammation Increased blood glucose
INSULIN	PANCREAS β cells	Tyrosine kinase surface receptor	Irs, Grb2	PI3K, cAMP	PKA, AKT, PKC, MAPK	Anabolism (Glycogenesis, amino acid synthesis, lypogenesis) Decreased blood glucose
GLUCAGON	PANCREAS A cells	Surface: GPCR	G Protein	Adenylate cyclase cAMP	PKA, MAPK	Increased blood glucose Catabolism

Thyroid hormones: hormonal cascade and signaling mechanism

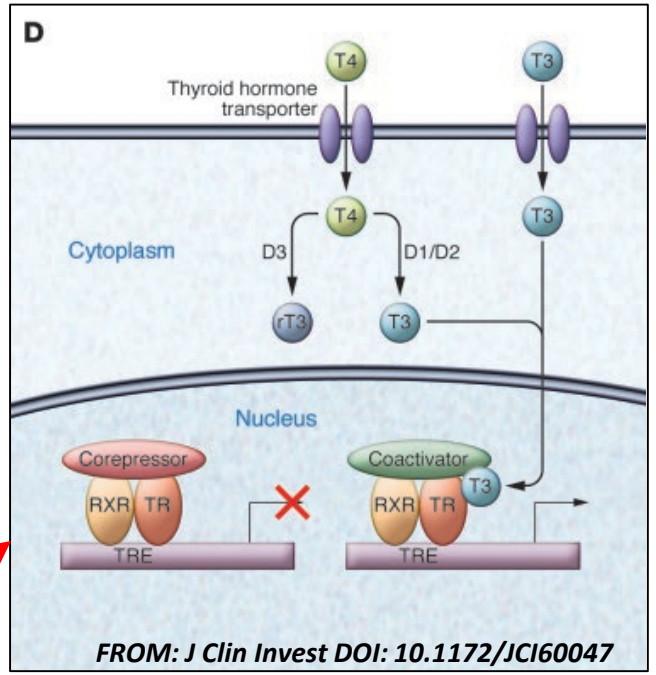
INTERNAL SIGNAL: LOW CIRCULATING LEVELS OF THYROID HORMONE



J Clin Invest DOI: 10.1172/JCI60047



T3 and T4 target cells



REGULATION IS BY NEGATIVE FEEDBACK

T3 (TRIIODOTHYRONINE) and T4 (TIROXINE)

The thyrotropin-releasing hormone (TRH), which is produced in the hypothalamus, stimulates production of the **thyroid-stimulating hormone (TSH**) in the pituitary gland. **The regulation, done by T3 and T4 by negative feedback, is fundamental for maintaining thyroid hormone levels.**

Devlin, Textbook of Biochemistry with Clinical Correlations, 7th ed.

THYROID HORMONES T3 AND T4: SYNTHESIS AND SECRETION

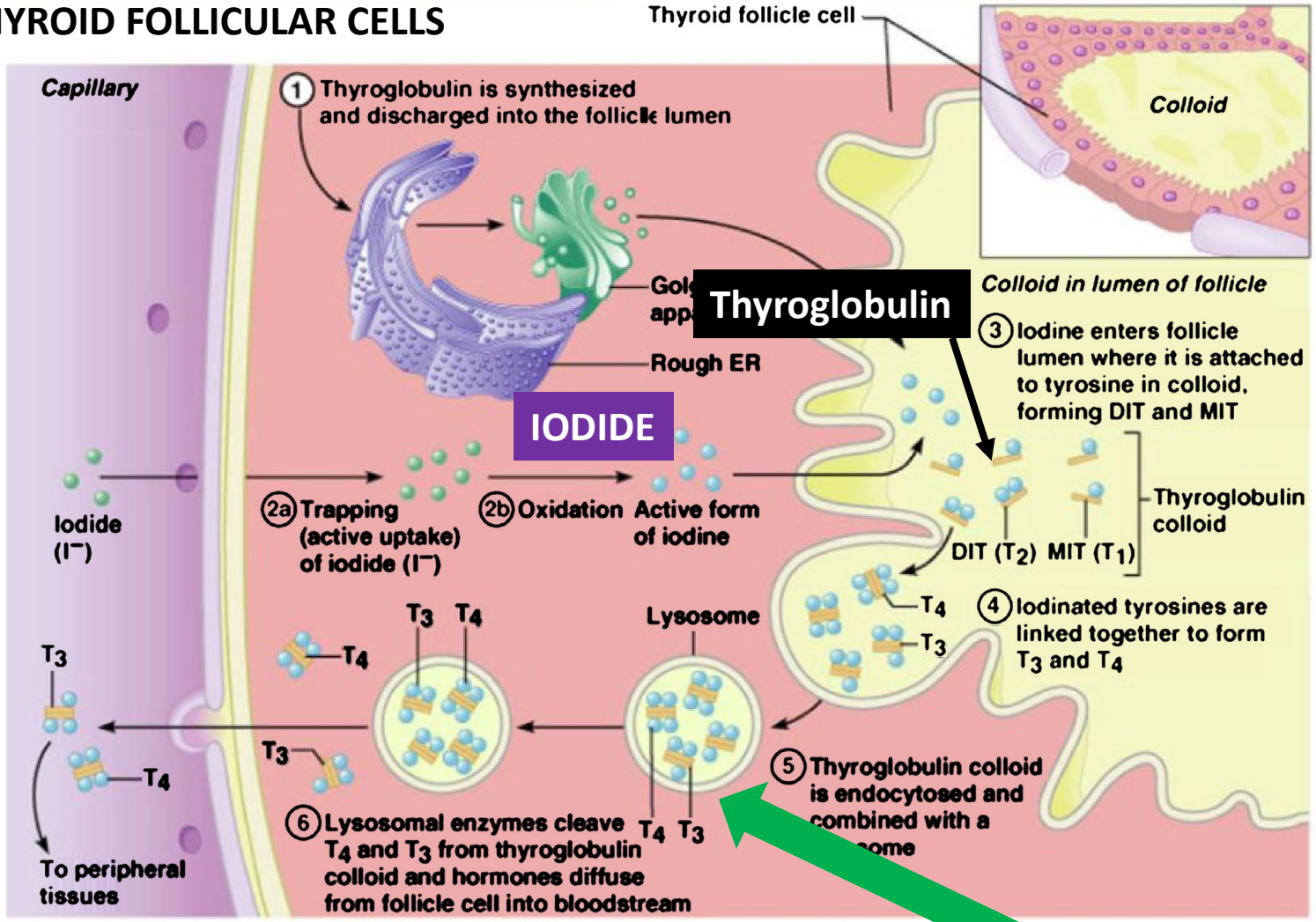


Figure 11. Molecular structure of T4 and T3 and thyroid hormone synthesis.

The production of T3 and T4 comes from the iodynization of Tyr AAs of **thyroglobulin** (glycoprotein).

T3 and T4 form colloids that are incorporated into vesicles.

Activation of PKA by cAMP, generated by AC stimulated by TSH-GPCR-G protein signaling, activates the release of T3 and T4.

PKA ACTIVATION INDUCES THE RELEASE OF T3 AND T4 FROM VESICLES

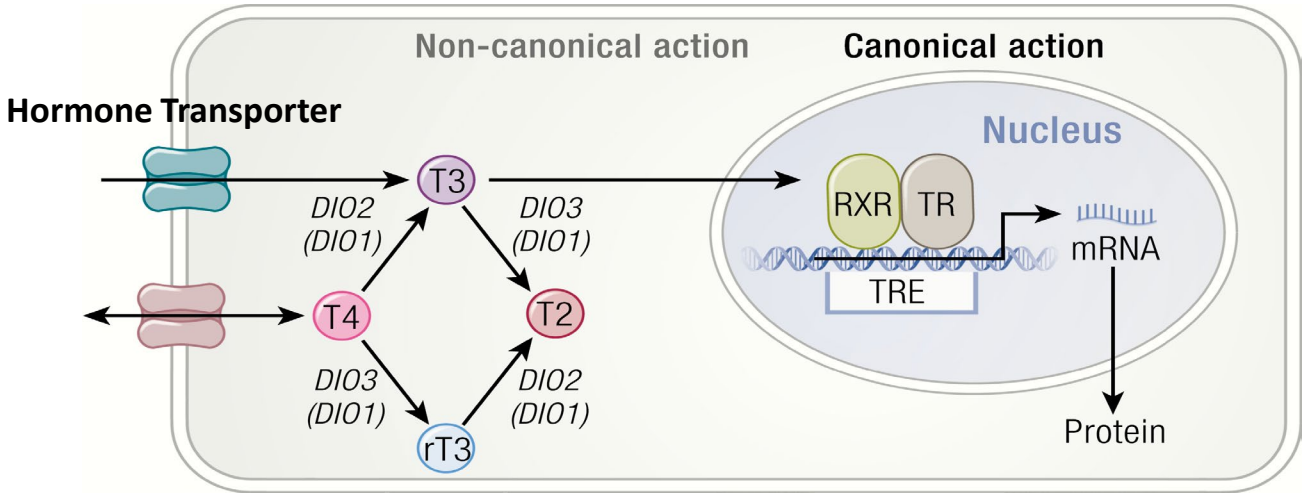
Int. J. Otolaryngology and Head & Neck Surgery
DOI: 10.4236/ijohns.2018.74019

THYROID HORMONES T3 AND T4 HAVE NUCLEAR RECEPTORS: CELLULAR EFFECTS

1. T3 (TRIIODOTHYRONINE) and T4 (TIROXINE) are transported into the cell with the thyroid hormone transporter.

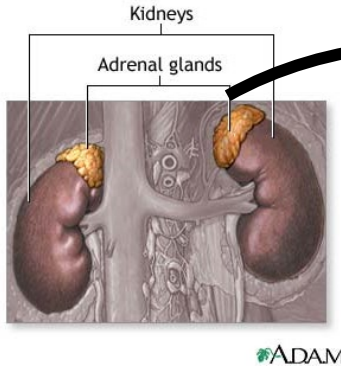
2. Effects on mitochondrial receptors: T3 and T4 increase the basal metabolic rate by promoting catabolism and the use of O2 to generate ATP. **This process is inefficient and increases body temperature.**

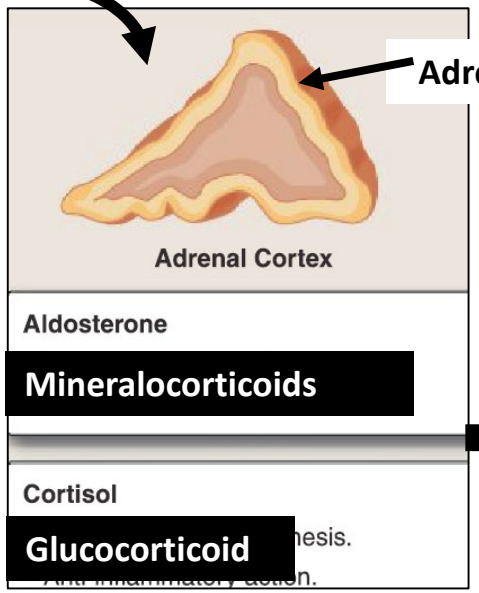
3. Nuclear effects: In the nucleus, T3 binds to the TR, which dimerizes with nuclear receptors to activate metabolism genes. **Lipid and carbohydrate metabolic genes.**



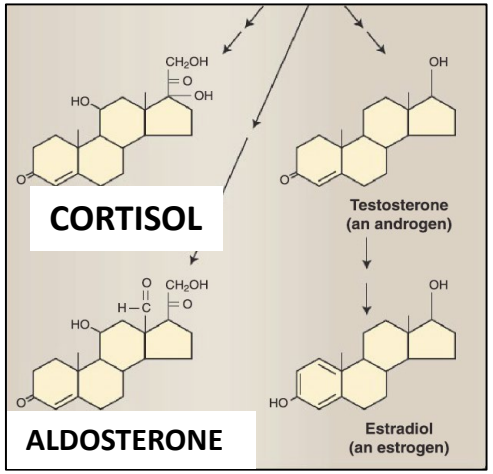
***Endocr Rev*, Volume 41, April 2020, Pages 146–201,**
https://doi.org/10.1210/endrev/bnz008

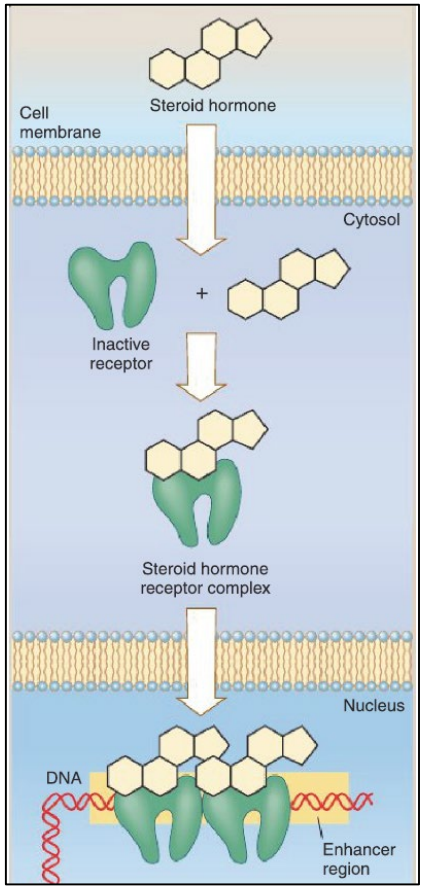
ADRENAL GLAND CORTEX HORMONES: MINERALOCORTICOIDS AND GLUCOCORTICOIDS (DERIVED FROM CHOLESTEROL) HAVE NUCLEAR RECEPTORS





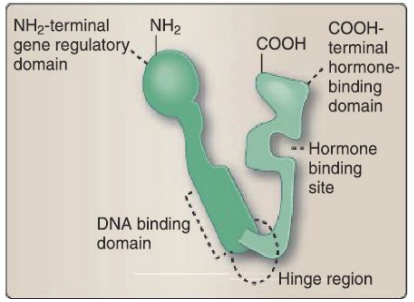
Hormones derived from CHOLESTEROL





Adrenal gland cortex hormones:
-They are steroid hormones
-They signal through nuclear receptors
-They are released stimulated by **severe or intense stress (infection)**

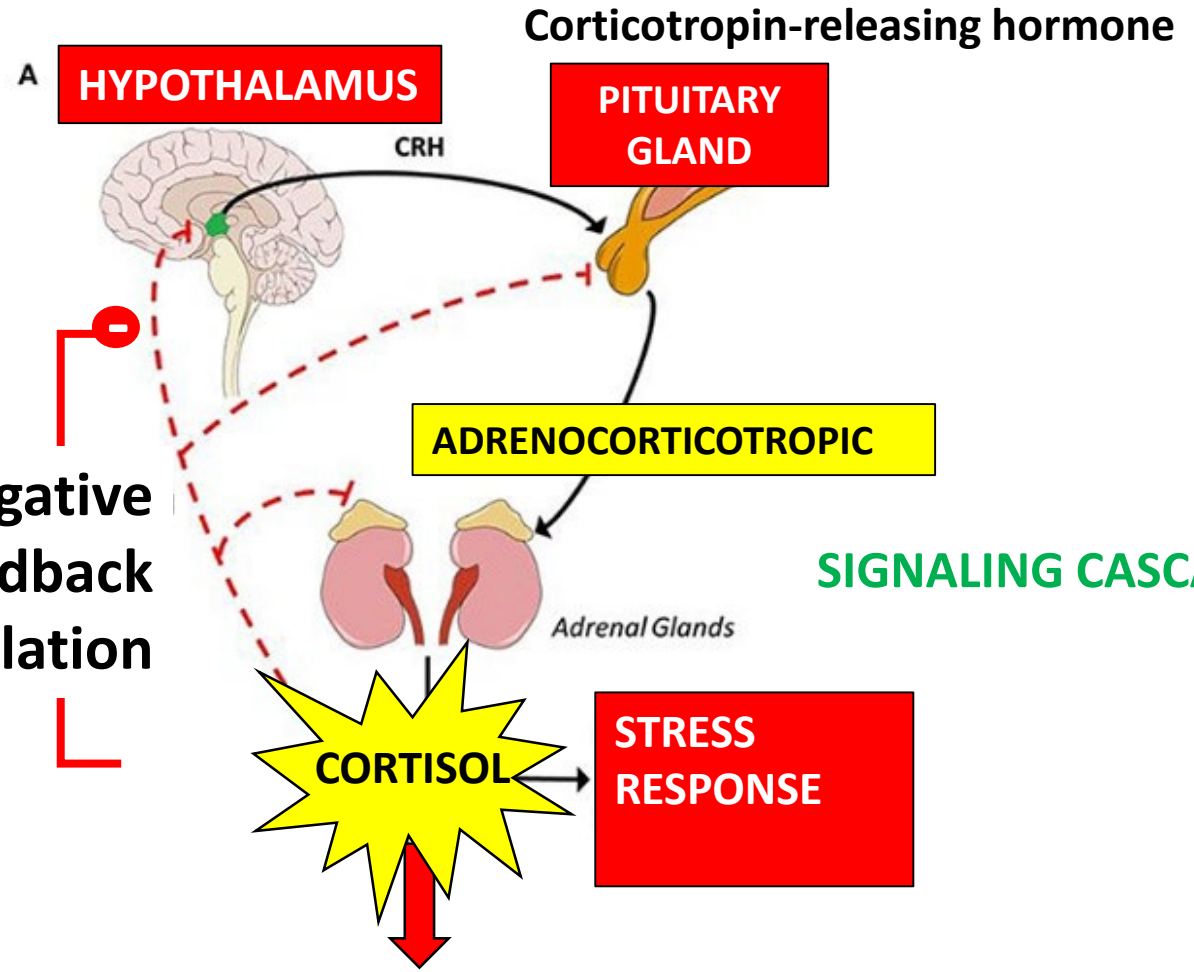
Structure of the nuclear hormone receptor



Hormone-binding domain
DNA-binding domain (zinc fingers)
Regulatory domain

Chandar and Viselli, Cell and Molecular Biology, Lippincott 2nd ed. (2019)

HYPOTHALAMIC-PITUITARY AXIS → ADRENAL GLAND



Negative feedback regulation

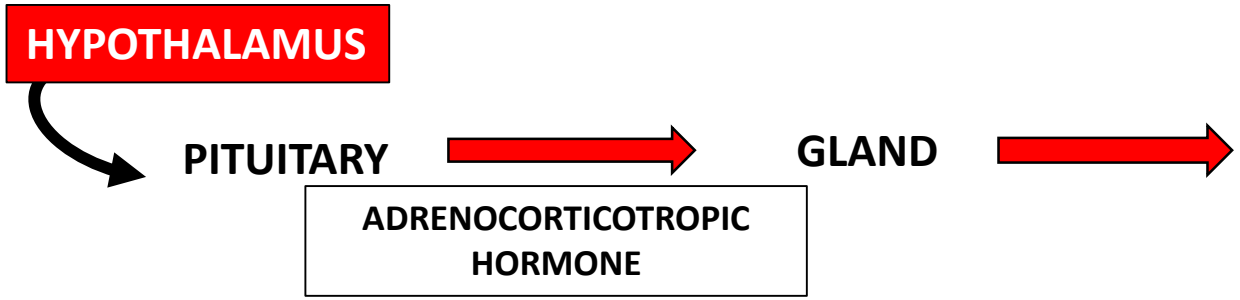
SIGNALING CASCADE FOR CORTISOL SECRETION

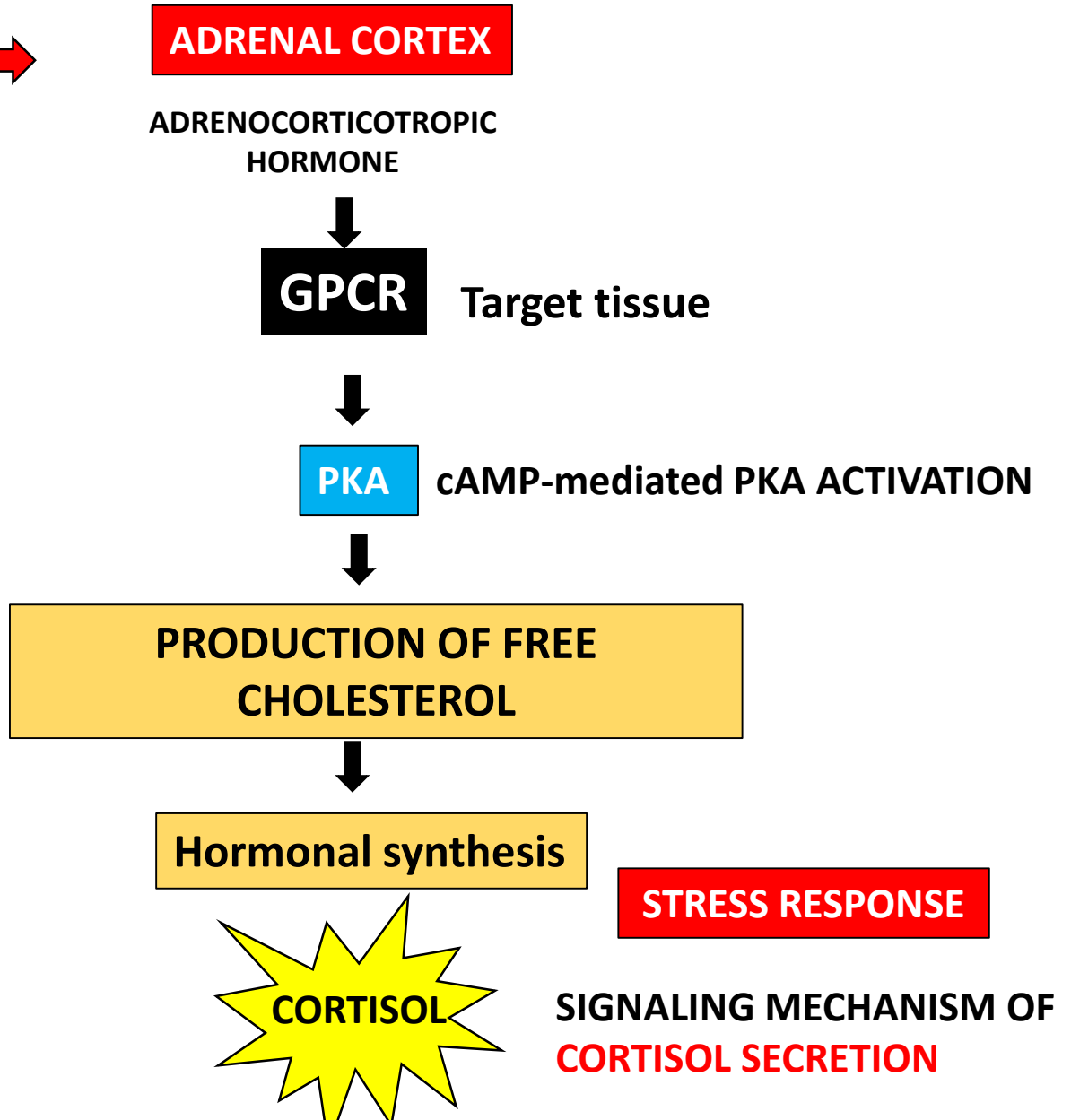
Elevated cortisol inhibits THE HYPOTHALAMUS AND THE PITUITARY GLAND

The production is regulated by negative feedback.

https://doi.org/10.3389/fneur.2019.00345

HORMONES OF THE CORTEX ADRENAL GLAND: ADRENOCORTICOTROPIC HORMONE





SIGNALING MECHANISM:

-Through a surface receptor with 7 transmembrane domains and a receptor associated with G protein (**GPCR**).

-By generating a second Messenger **cAMP**

-By activation of **PKA**, which generates free cholesterol for the synthesis of **CORTISOL.**

COMMON MECHANISM FOR VARIOUS HORMONES

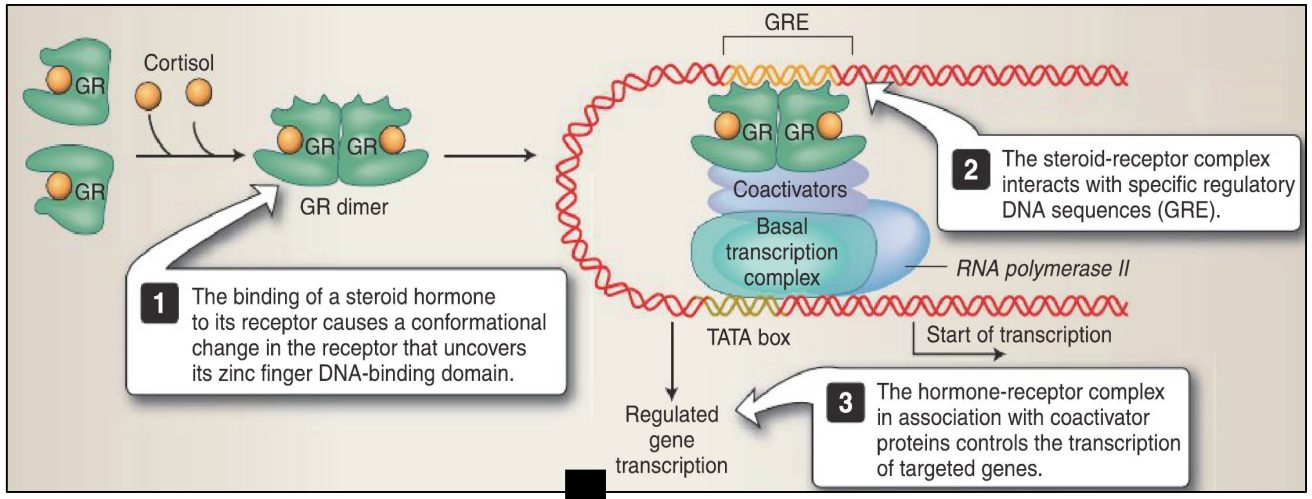
CORTISOL (HYDROPHOBIC) HAS A NUCLEAR RECEPTOR ON THE TARGET CELL

Circulation

Entrance to the cell

CORTISOL

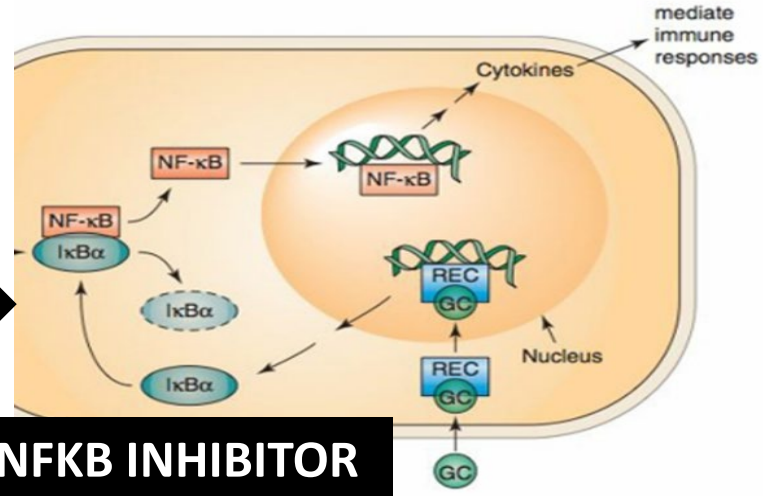
Cell membrane



NUCLEAR RECEPTOR

INCREASED GLUCONEOGENESIS AND INCREASED BLOOD GLUCOSE

DECREASES THE IMMUNE RESPONSE. INHIBITS THE TRANSCRIPTIONAL FACTOR, NFKB, OF INFLAMMATORY MOLECULES.



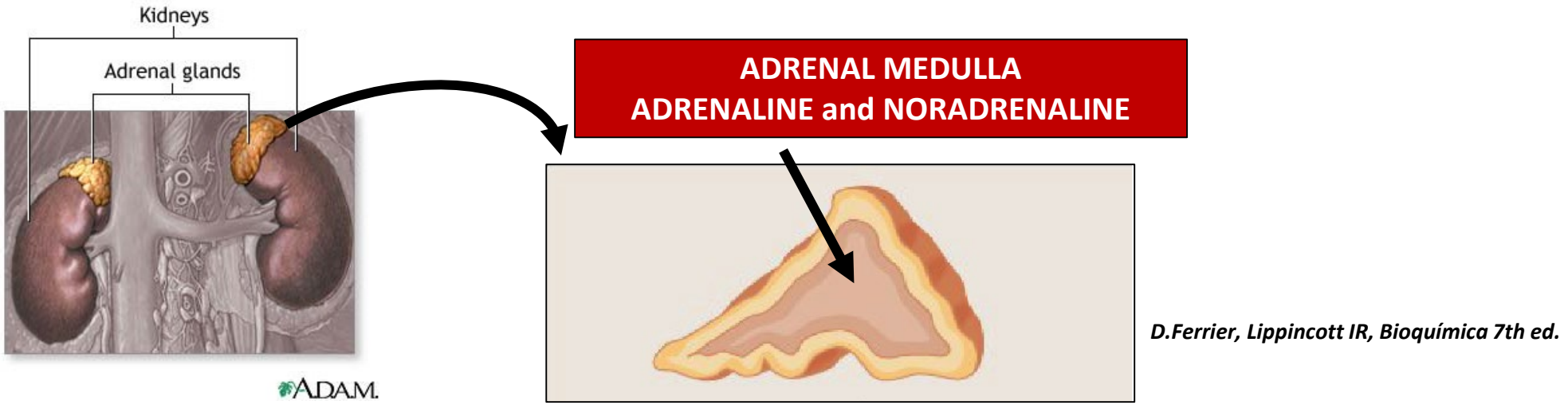
NFKB INHIBITOR

CORTISOL

NFKB IS A TRANSCRIPTION FACTOR THAT ACTIVATES THE TRANSCRIPTION OF INFLAMMATORY GENES (PROTEINS).

Chandar and Viselli, Cell and Molecular Biology, Lippincott 2nd ed. (2019)

ADRENAL GLAND MEDULLA HORMONES: CATECHOLAMINES ADRENALINE AND NORADRENALINE



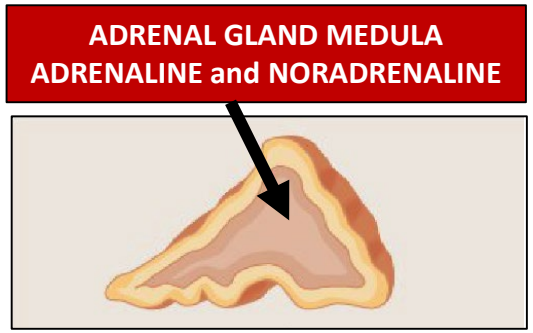
D.Ferrier, Lippincott IR, Bioquímica 7th ed.

-They are amines in nature and called **BIOGENIC AMINES.** They are synthesized from tyrosine.
-They participate in the integration of energy metabolism as a response to short-term stress (**infection, hypoxia, and vigorous exercise).**

-**ADRENALINE FUNCTION**: **rapid fuel mobilization**

ACTIVATION OF:
GLYCOGENOLYSIS (liver, muscle)**, GLUCONEOGENESIS** (liver)
LIPOLYSIS (adipose tissue).
Increased heartbeat VASODILATION (increased O2).
-HAVE MEMBRANE SURFACE RECEPTORS: α AND β ADRENERGIC RECEPTORS

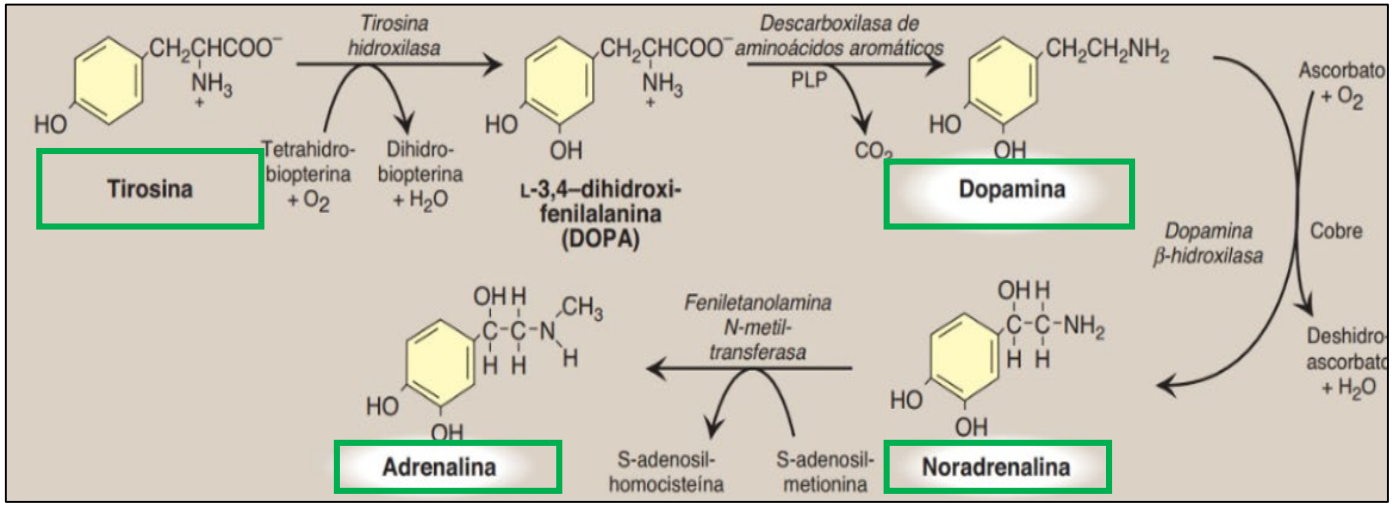
ADRENAL GLAND MEDULLA HORMONES: CATECHOLAMINES ADRENALINE AND NORADRENALINE



The **biosynthesis of catecholamines** takes place in the central nervous system (**CNS**) and in the **adrenal gland**. In the CNS, the pathway produces dopamine and noradrenaline. The **adrenal gland medulla mostly produces noradrenaline and adrenaline.** These are synthesized **from the amino acid Tyr**.

BIOSYNTHESIS OF CATECHOLAMINES

BIOGENIC AMINES



CENTRAL NERVOUS SYSTEM

ADRENAL MEDULLA

PLP: pyridoxal phosphate
This is a cofactor required by the enzymes of the biosynthesis pathway.

D.Ferrier, Lippincott IR, Bioquímica, 7th ed.

ADRENALINE-MEDIATED SIGNALING: β-ADRENERGIC RECEPTOR

β-ADRENERGIC RECEPTOR: MUSCLE, LIVER, AND ADIPOSE TISSUE

GPCR → G PROTEIN → AC → AMPc → PKA

OBJECTIVE: TO INCREASE THE AVAILABLE ENERGY SOURCE

cAMP binding to PKA AND ACTIVATION

LIVER AND MUSCLE: active/inactive by Pi glycogenolysis and glyconeogenesis enzymes
The signaling **INCREASES BLOOD GLUCOSE**

MUSCLE, LIVER

GLYCOGEN PHOSPHORYLASE IS ACTIVATED – WITH GROUP Pi: GLYCOGEN DEGRADATION

GLYCOGEN SYNTHASE IS INHIBITED – WITH Pi GLYCOGEN SYNTHESIS INHIBITION

In ADIPOSE TISSUE the signaling activates ENZYMES THAT PRODUCE FATTY ACIDS AND GLYCEROL from TG to generate energy.

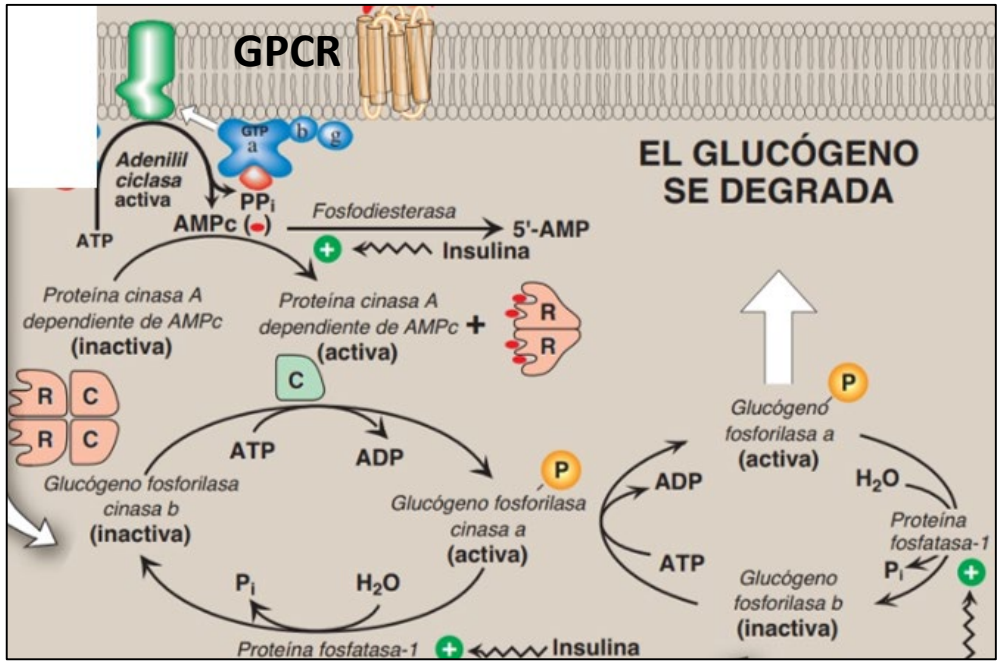
ADIPOSE TISSUE

ACTIVATION OF HORMONE-SENSITIVE LIPASE.

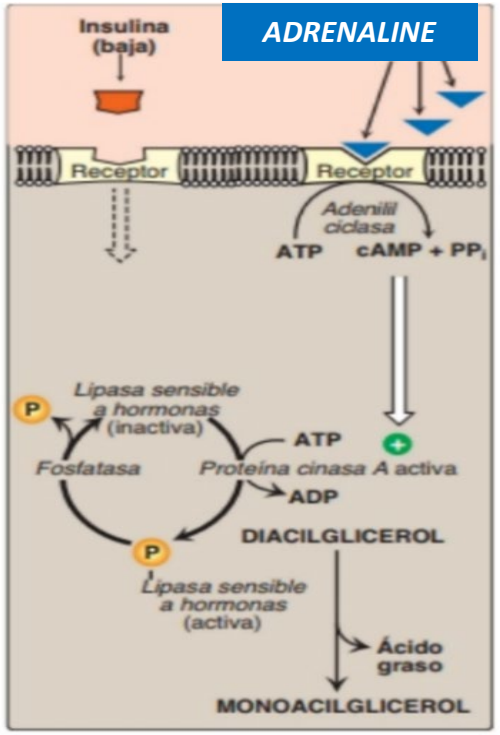
ADRENALINE-MEDIATED SIGNALING: β-ADRENERGIC RECEPTOR

OBJECTIVE: TO INCREASE THE AVAILABLE ENERGY SOURCE

MUSCLE, LIVER



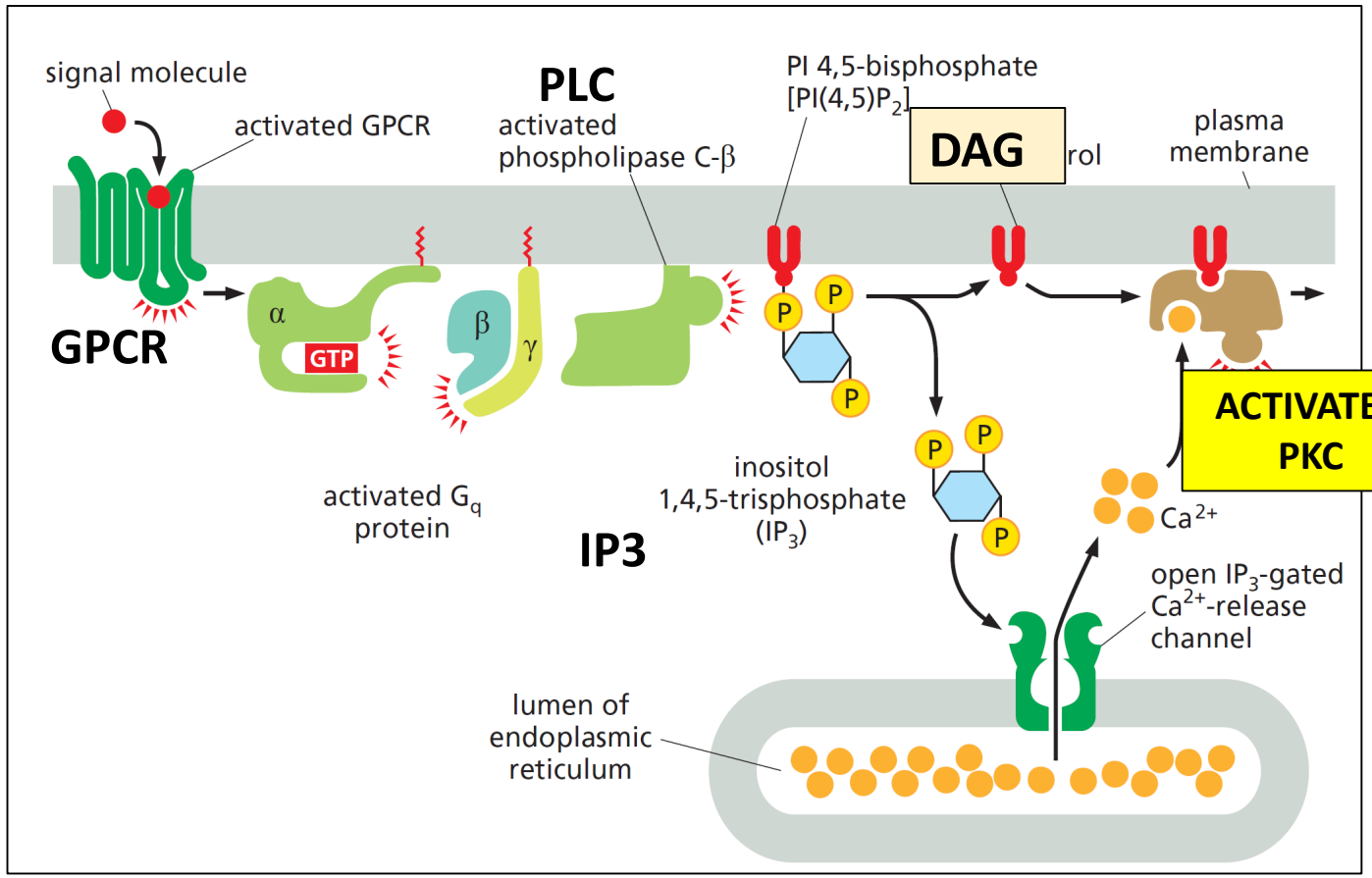
ADIPOSE TISSUE



D. Ferrier, Lippincott IR, Bioquímica 7th ed.

ADRENALINE-MEDIATED SIGNALING: α-ADRENERGIC RECEPTOR

ADRENALINE BINDING TO α1-ADRENERGIC RECEPTOR: LIVER



GPCR → G prot. →ACTIVATION OF PHOSPHOLIPASE C.

EFFECTS:

PRODUCTION OF IP3

Calcium release

DAG generation

PKC ACTIVATION

ACTIVATED PKC →

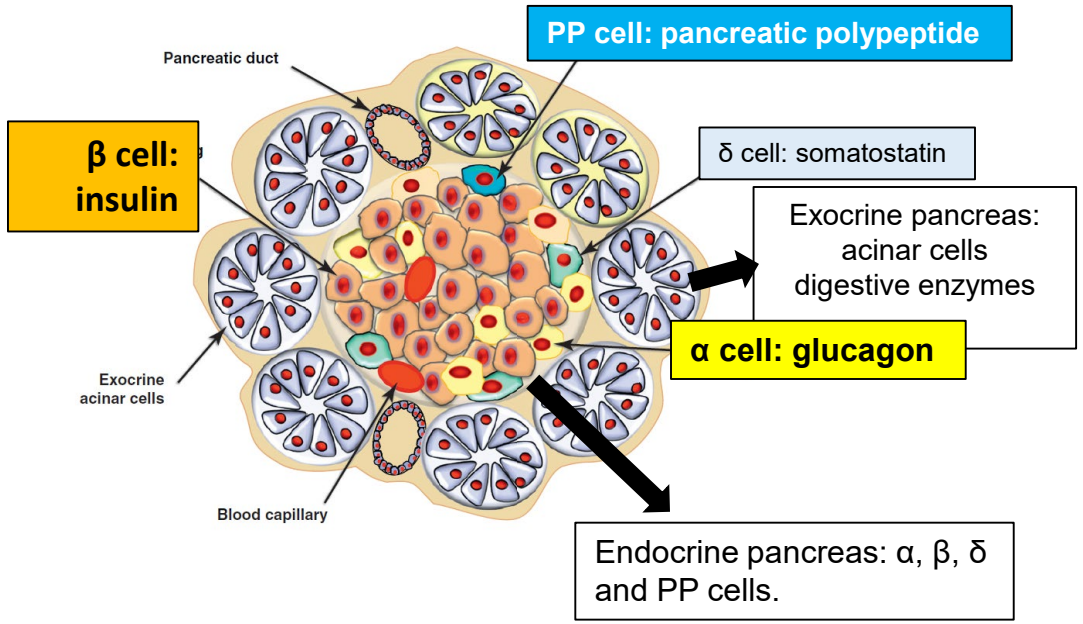
LIVER: active/inactive by Pi glycogenolysis/gluconeogenesis enzymes.

Adrenaline increases blood glucose.

GPCR → G Protein → PHOSPHOLIPASE C (PLC) → IP3 Ca2+ DAG → PKC

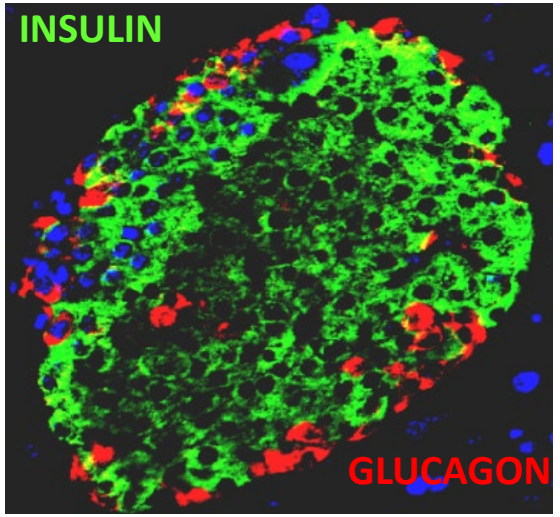
Alberts, 6th edition, Molecular Biology of the Cell

SIGNALING OF HORMONES PRODUCED IN ENDOCRINE ORGANS: PANCREAS



Efrat, S and Russ, HA 2012, *Trends in Endocrinology & Metabolism* 23, 278

Pancreatic Islet/Langerhans Islet



-THE HYPOTHALAMIC-PITUITARY AXIS DOES NOT INTERVENE
-REGULATION BY NUTRIENT AVAILABILITY

HORMONES THAT RESPOND TO FASTING-FEEDING CYCLE

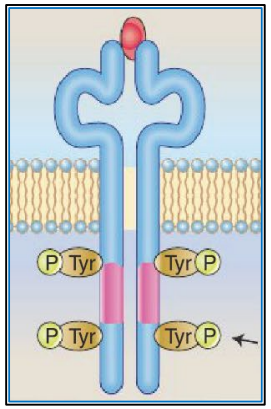
SIGNALING OF HORMONES PRODUCED IN ENDOCRINE ORGANS: PANCREAS

Insulin: nutrient availability

Anabolic effects

-Feeding state (postprandial state)

-Objective: to decrease blood glucose, by activating the uptake by sensitive tissues.



-Stimulation of lipid synthesis (lipogenesis), glycogenogenesis, and protein synthesis.

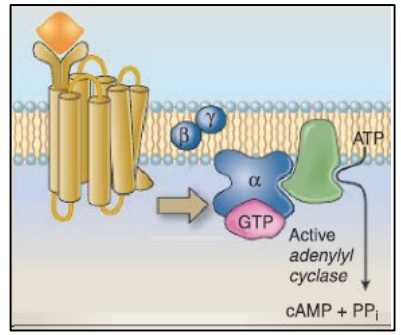
Receptor signaling: TYROSINE KINASE type. Cascade of phosphorylations.

Glucagon: **catabolic effects**

-Increased blood glucose from the liver

-Glycogenolysis, gluconeogenesis and lipolysis.

Receptor signaling: GPCR type, cAMP and PKA



D.Ferrier Lippincott IR, Bioquímica 7th ed.

GLUCAGON SIGNALING: ADENYLATE CYCLASE-COUPLED GPCR MEMBRANE RECEPTOR

THE GLUCAGON EFFECT:

1. maintains **blood glucose** levels by activating hepatic **glycogenolysis and gluconeogenesis**.

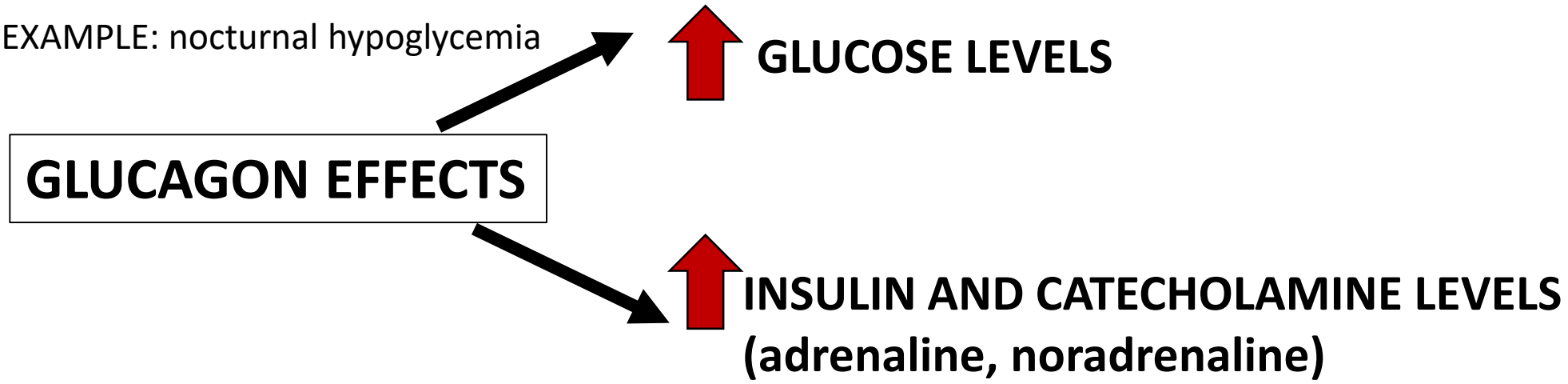
2. activates **lipolysis:** mobilization of fatty acids.

GLUCAGON SECRETION increases in fasting situations. Fasting status stimulates glucagon production by the α CELLS.

GLUCAGON:

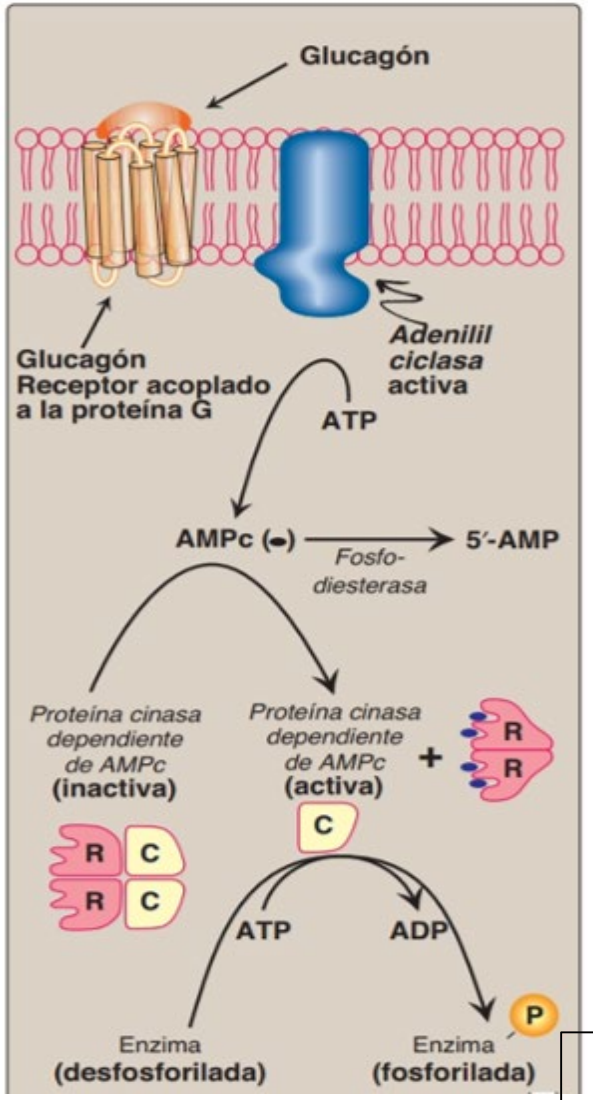
1. Increases BLOOD GLUCOSE LEVELS.
2. IN ANTICIPATION of HIGH glucose levels, it increases insulin levels and catecholamines (massive glucose use).
3. IN ADIPOSE TISSUE, it increases the availability of **FREE FA (LIPOLYSIS)** as an alternative energy source.

EXAMPLE: nocturnal hypoglycemia



GLUCAGON SIGNALING: ADENYLATE CYCLASE-COUPLED GPCR MEMBRANE RECEPTOR

https://www.nature.com/scitable/topicpage/gpcr-14047471/



D. Ferrier, Lippincott IR, Bioquímica 7th ed

GPCR

↓

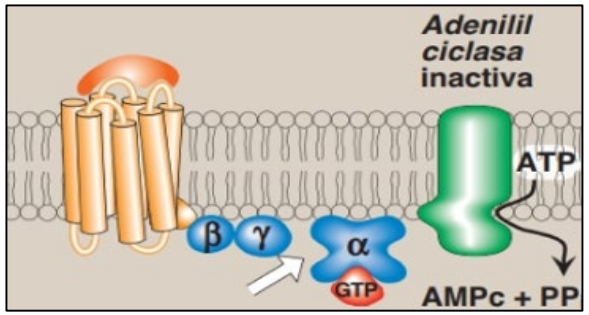
G Protein

↓

Adenylyl cyclase

↓

cAMPc



LIVER AND MUSCLE

PKA activated by cAMP

↓

Activated glycogen phosphorylase/inactivated glycogen synthase

↓

ACTIVATED GLYCOGENOLYSIS
INHIBITED GLYCOGENGENESIS

ADIPOSE TISSUE

PKA activated by cAMP

↓

ACTIVATED HORMONE-SENSITIVE LIPASE (HSL)

↓

LIPOLYSIS: FA, ALTERNATIVE ENERGY SOURCE

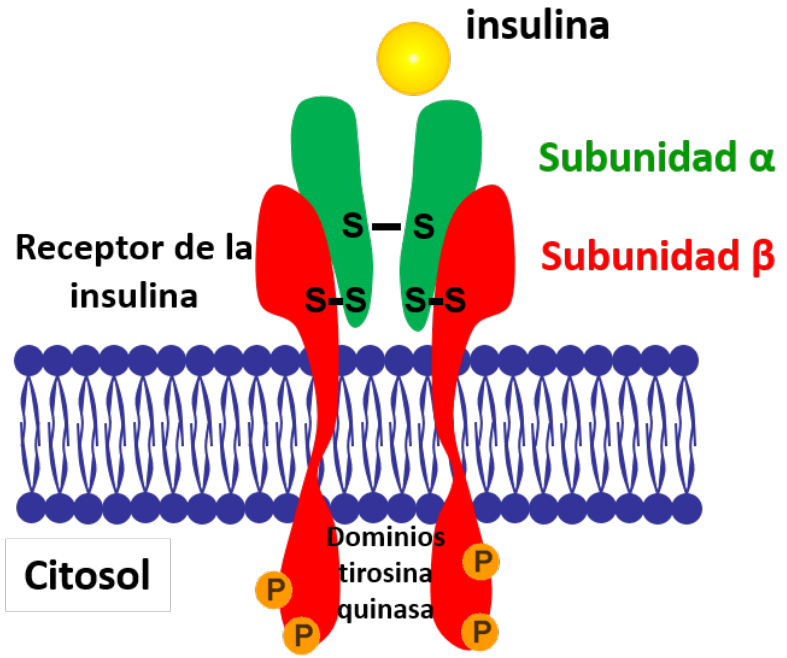
TERMINATION OF SIGNALING:

G PROTEINS NEED GTP TO BE ACTIVATED. AS THEY ARE, GTPases self-inactivate and lead to the termination of signaling.
DEPHOSPHORYLATION OF EFFECTOR enzymes.

INSULIN SIGNALING: MEMBRANE RECEPTOR WITH TYROSINE KINASE ACTIVITY

The **INSULIN RECEPTOR** is a membrane receptor tyrosine kinase with two subunits, α and β, linked by disulfide bridges.

Autocatalytic activity with multiple phosphorylation sites in Tyr.



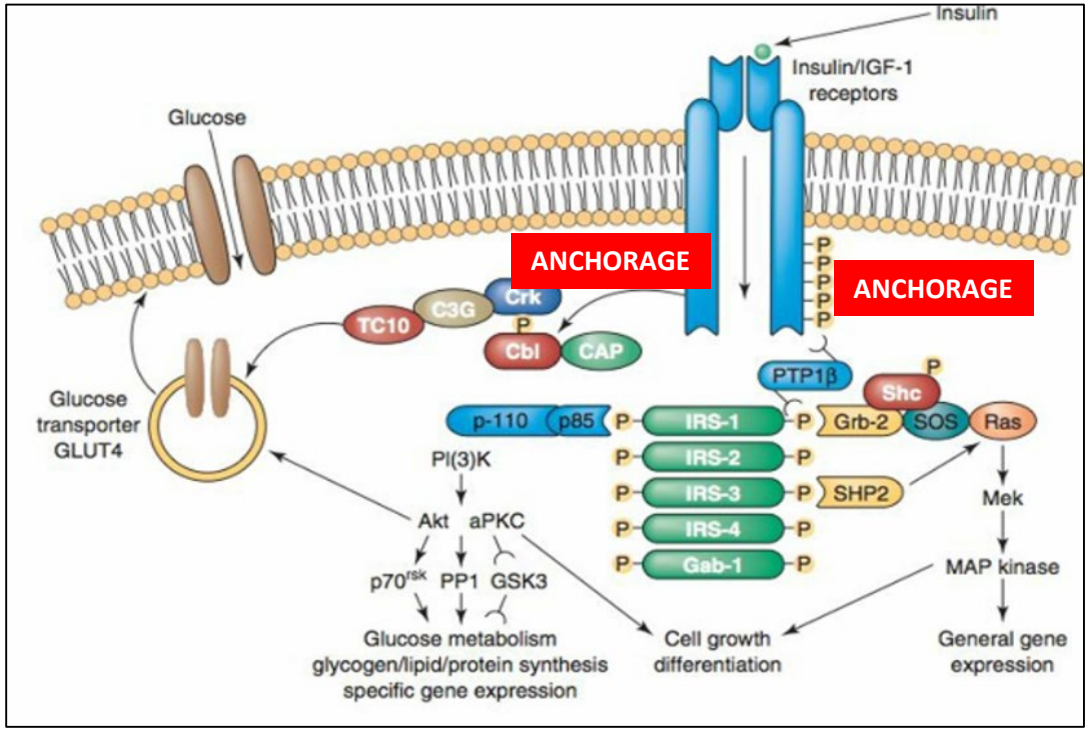
INSULIN SECRETION

β CELLS: GLUT2 in cell β acts as a glucose sensor that promotes insulin secretion through changes in Ca2+ channels that favor the mobilization of vesicles with insulin.

Similar mechanisms exist for detecting the **presence of Aas and fatty acids.**

Gastrointestinal hormones (incretins, GLP1, GIP) also promote insulin secretion.

INSULIN RECEPTOR SIGNALING MECHANISM: MEMBRANE RECEPTOR TYROSINE KINASE



1. IR phosphorylates: polypeptide/subunit β IRS, Grb2/SHC, CBL.

2. Phosphorylated proteins serve as anchors for other proteins that activate short- and long-term signaling pathways.

3. CELLULAR EFFECTS:

-**ANABOLIC:** protein synthesis, glycogenesis and lipid synthesis.

-**GLUT4 TRANSLOCATION** and decreased blood glucose.

IRS interacts with p85, a regulatory subunit of PI3 kinase, thereby activating it.
IRS forms a complex with proteins such as Grb2 through the SHC adaptor protein. This interaction activates SOS, RAS and MAP kinases.

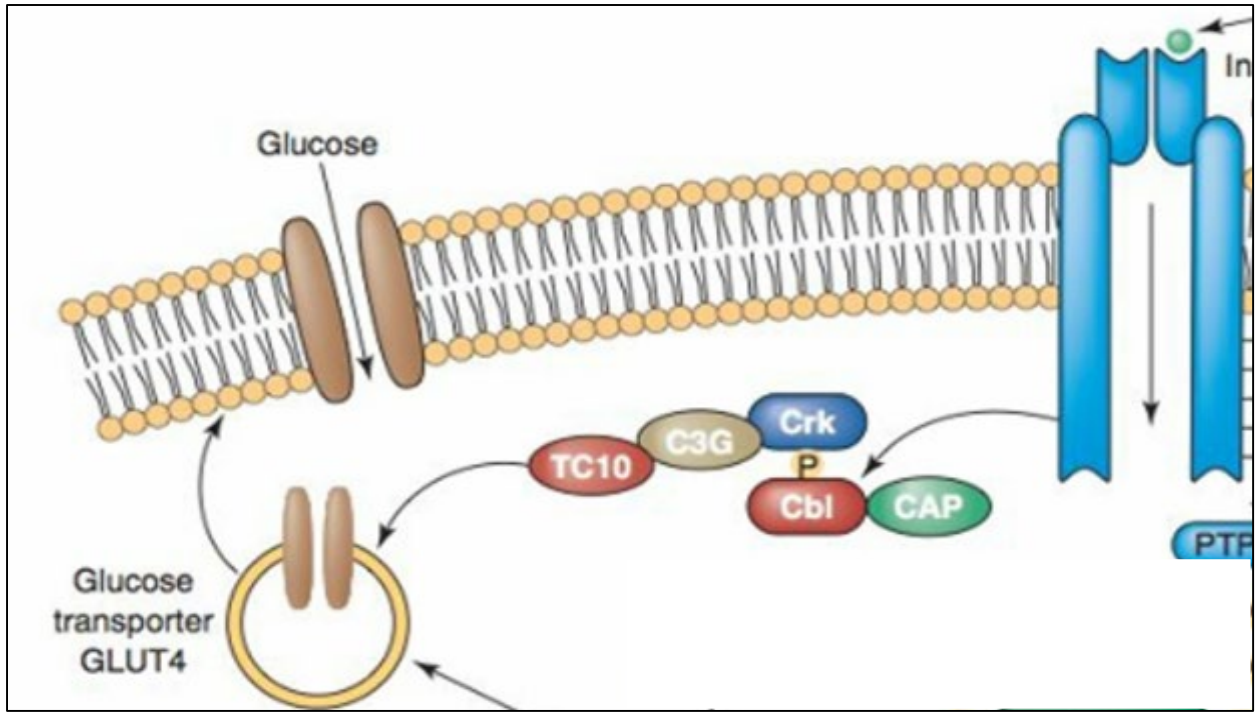
Devlin, *Textbok of Biochemistry with Clinical Correlations* (adapted from Saltiel and Kahn, *Nature* 2001)

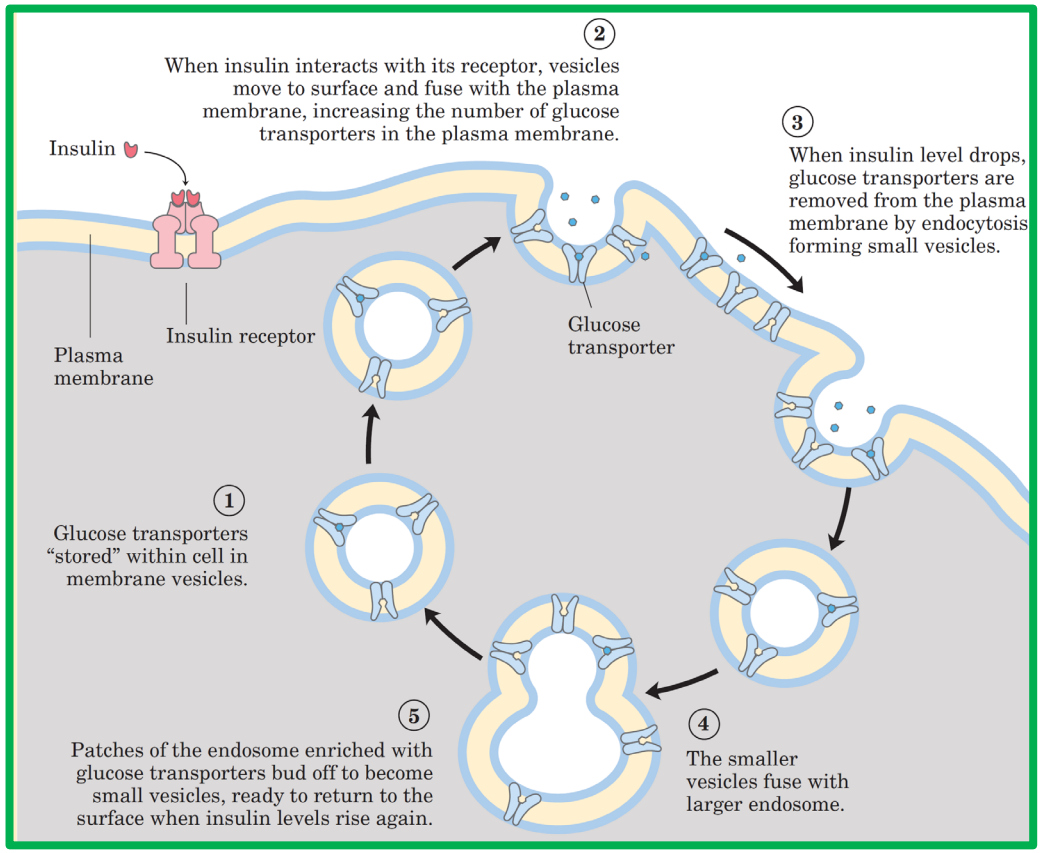
INSULIN RECEPTOR SIGNALING MECHANISM: MEMBRANE RECEPTOR TYROSINE KINASE

SHORT-TERM EFFECT:

Translocation of Glut4 in insulin-sensitive tissues such as **muscle and adipose tissue for glucose uptake.**

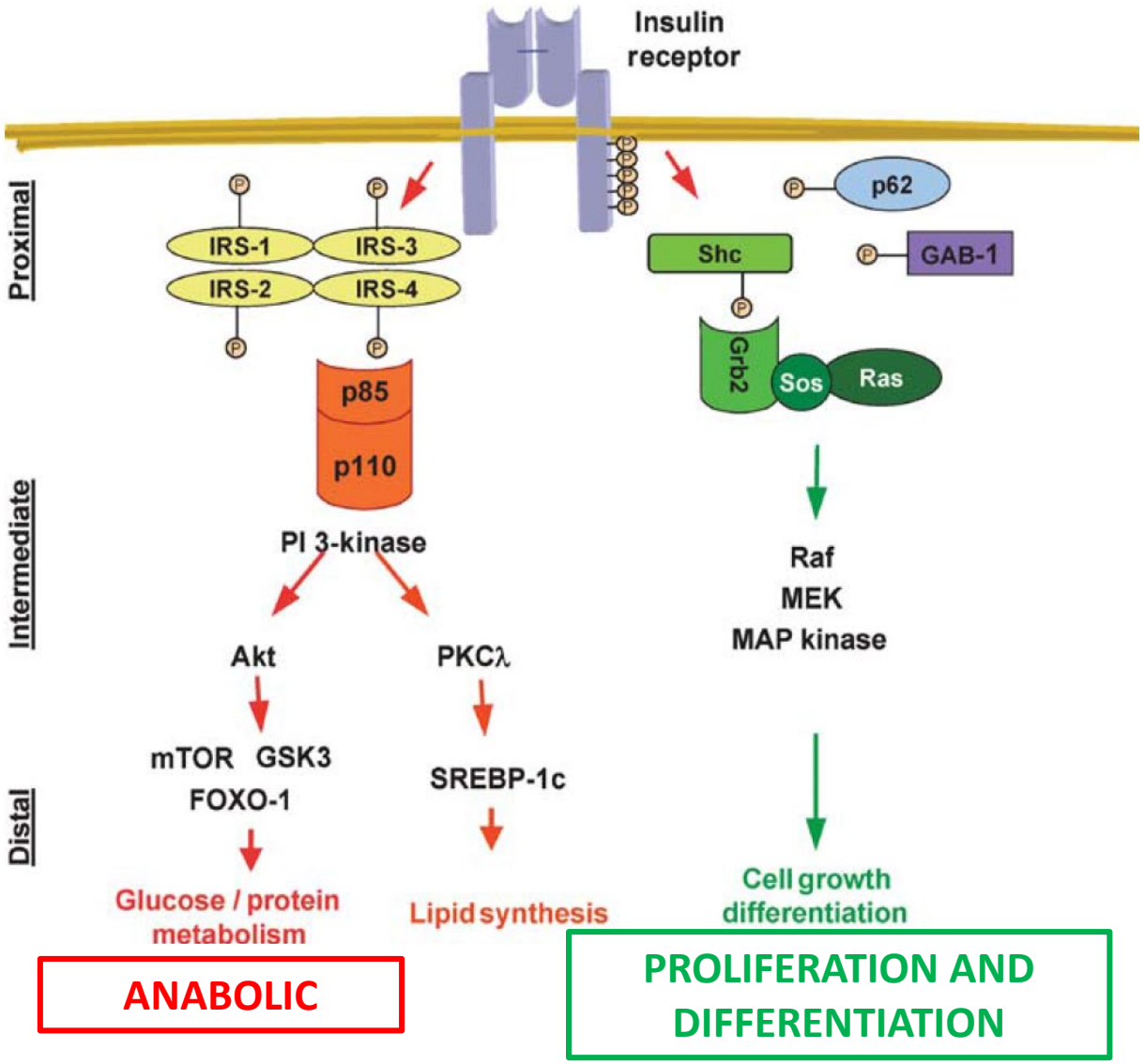
The **EFFECT IS MEDIATED BY TC10** , a GTP-binding protein that promotes the translocation of Glut4 to the membrane.





Devlin, *Textbok of Biochemistry with Clinical Correlations* (adapted from Saltiel and Kahn, *Nature* 2001)

INSULIN RECEPTOR SIGNALING MECHANISM: MEMBRANE RECEPTOR TYROSINE KINASE



Sudha B. Biddinger and C. Ronald Kahn Annu. Rev. Physiol. 2006. 68:123–58
doi: 10.1146/annurev.physiol.68.040104.124723

MEDIUM-TERM EFFECTS

SIGNALING VIA IRS PROTEINS:

1. IRS-Pi binds to p85 and activates PI3K p110.

2. PI3K generates the second messenger PIP3, which activates PKC and PDK1.

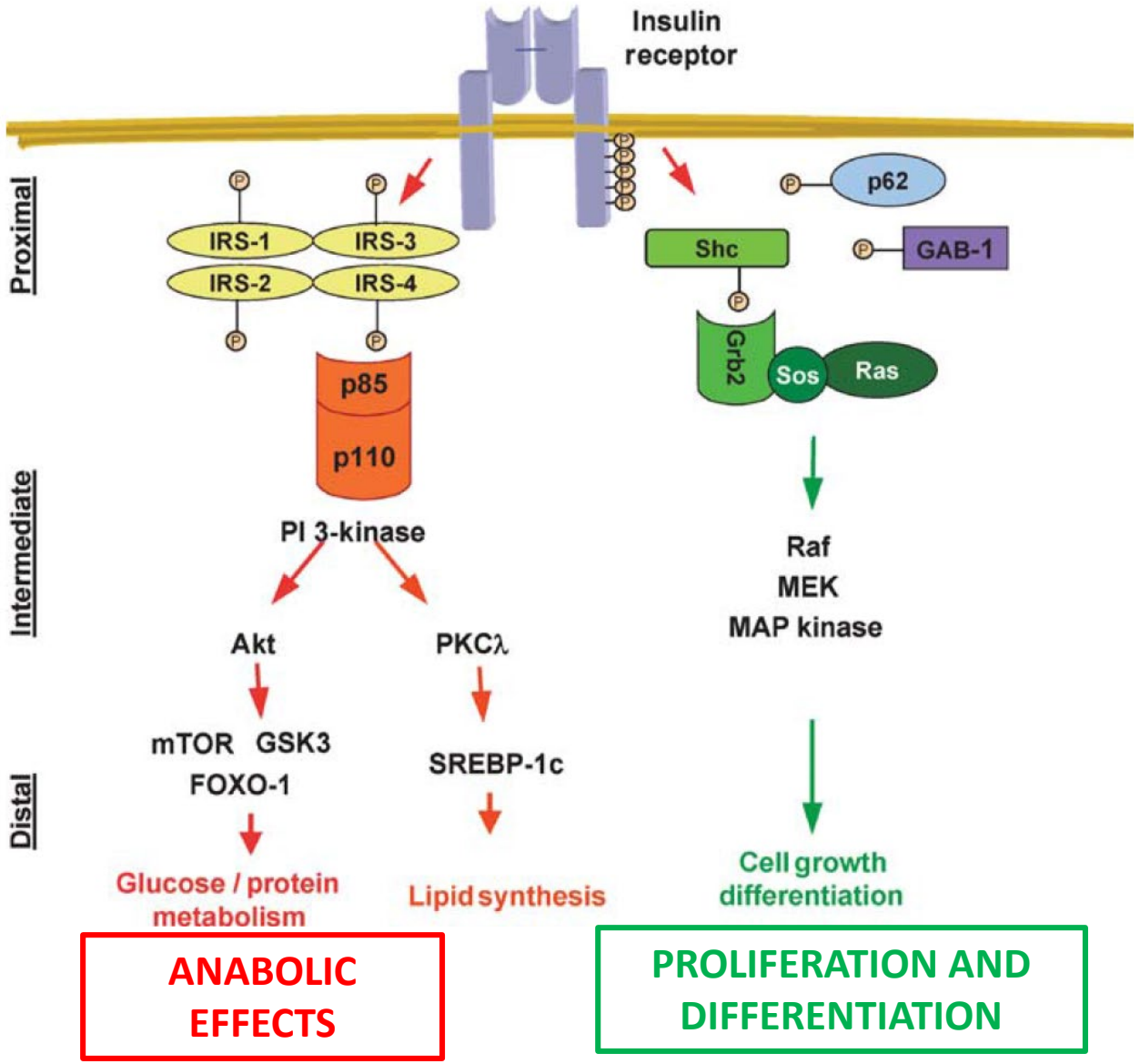
3. GLYCOGENESIS AND PROTEIN SYNTHESIS:

PDK1 phosphorylates and activates AKT and a cascade of phosphorylations that lead to the activation of mTOR and the inhibition of GSK3 (glycogen synthase kinase, which phosphorylates and inactivates glycogen synthase).

4. LIPID SYNTHESIS:

PKC leads to the activation of SREBP1c, which activates cholesterol synthesis.

INSULIN RECEPTOR SIGNALING MECHANISM: MEMBRANE RECEPTOR TYROSINE KINASE



LONG-TERM EFFECTS: Genomic

Signaling via Shc proteins:

1. Shc-Pi binds to Grb.
2. Grb recruits Ras (G protein) through Sos.
3. Ras activates, by phosphorylation cascades, the MAP kinase pathways (Raf, MEK, ERK).

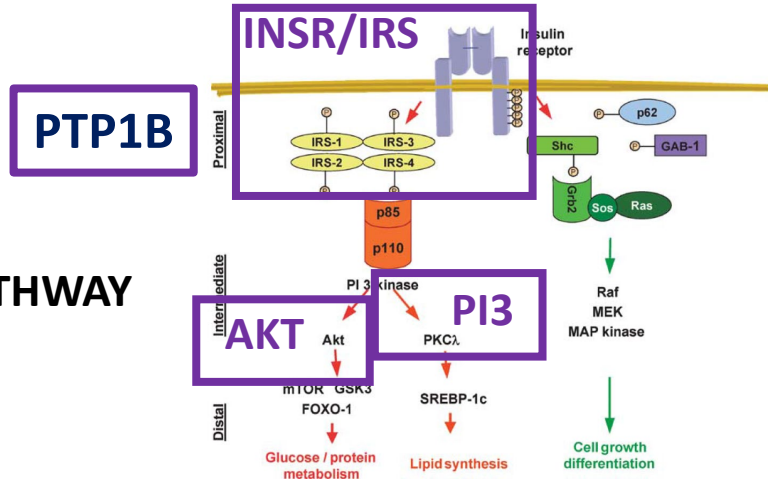
INSULIN HALF-LIFE:
After signaling, the insulin is internalized with the receptor, thus resulting in a short half-life.

Sudha B. Biddinger and C. Ronald Kahn Annu. Rev. Physiol. 2006. 68:123–58
doi: 10.1146/annurev.physiol.68.040104.124723

INSULIN RECEPTOR SIGNALING: TERMINATION MECHANISMS

Phosphorylated proteins in serine, threonine or tyrosine residues are very stable.
PROTEIN **PHOSPHATASES ARE REQUIRED**: enzymes that remove Pi groups to terminate signaling.
ORIGIN OF TERMINATION PHOSPHATASES: phosphatases are activated or recruited **as part of the insulin response.**

THE SIGNALING ROUTE ITSELF PREPARES FOR COMPLETION.



WHAT PHOSPHATASES ARE THEY?

THREE CLASSES OF ENZYMES CLOSE THE SIGNALING PATHWAY

PROTEIN TYROSINE PHOSPHATASES: RECEIVER AND IRS
Example: PTP1B

LIPID PHOSPHATASES: HYDROLYZE PIP3 TO PIP2 and hence PDK1 gets inactivated.

PROTEIN PHOSPHATASES: THESE ACT ON ACTIVATED KINASES SUCH AS AKT.

Sudha B. Biddinger and C. Ronald Kahn Annu. Rev. Physiol. 2006. 68:123–58
doi: 10.1146/annurev.physiol.68.040104.124723

LESSON 17. INTERMEDIARY METABOLISM AND BIOENERGETICS (I)

E-mail: herminia.gonzalez@uv.es

Herminia González Navarro 2022

INDEX

INTERMEDIATE METABOLISM

Intermediate metabolism is defined as the set or **NETWORK OF INTERCONNECTED CHEMICAL REACTIONS** that transform some molecules into others.

PURPOSE:

1. The extraction of energy and molecules with reducing potential (energy potential), NADH, FADH2.

2. The formation of the **structural elements** that are part of the **macromolecules**.

INTERMEDIATE METABOLISM IS CHARACTERIZED BY:

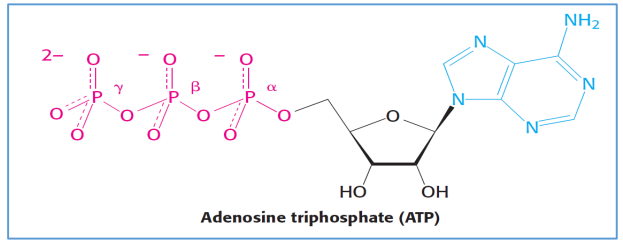
-**Coherent design of the chemical reactions** involved in the above processes.

-Existence of **an energy currency,** i.e. the molecule adenosine triphosphate (**ATP**).

-**Recurrent use of activated metabolic intermediates** and existence of **metabolic regulation** mechanisms.

-**Compartmentalized reactions** in cellular and tissue organelles.

ATP

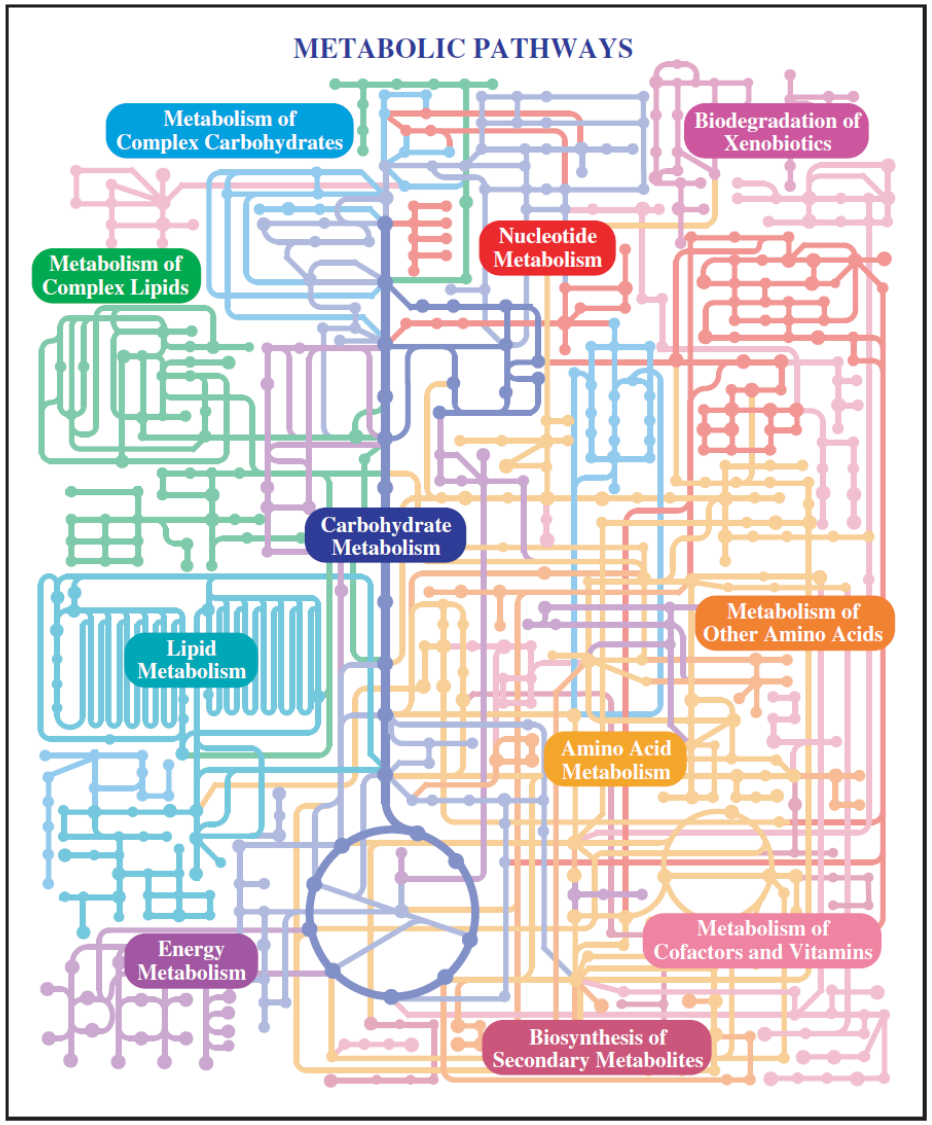


Adenosine triphosphate (ATP)

Stryer, 7th ed., Biochemistry

GENERAL PRINCIPLES OF INTERMEDIATE METABOLISM

Multiple metabolic pathways



FROM: Kyoto Encyclopedia of Genes and Genomes

1. THE "COMBUSTIBLE MOLECULES" degrade and the MACROMOLECULES are formed in a series of consecutive reactions in metabolic pathways.

2. Adenosine triphosphate **(ATP) CONNECTS** energy-producing pathways with energy-consuming pathways.

3. The oxidation of reduced carbon molecules enables the generation of ATP.

4. A limited number of specific reaction types and intermediates are common to many metabolic pathways. Recurring **MOTIFS and REACTIONS**.

5. Metabolic pathways are **highly regulated by recurrent mechanisms.**

METABOLIC PATHWAYS BY STEPS

A→B→C→D→E→F→G→… → M

GENERAL PRINCIPLES OF INTERMEDIATE METABOLISM

METABOLISM EXTRACTS ENERGY FROM THE ENVIRONMENT TO MAINTAIN SUPRAMOLECULAR STRUCTURES AND FUNCTIONS THAT ARE CHARACTERISTIC OF LIFE.

CATABOLISM IS THE DEGRADATION OF MACROMOLECULES: it involves metabolic pathways (catabolic reactions) that convert the energy contained in combustible molecules (glucose) into cellular energy (ATP).

ANABOLISM IS THE BIOSYNTHESIS OF MACROMOLECULES: it involves metabolic pathways (anabolic reactions) that require energy, e.g. the synthesis of glucose, fatty acids or DNA. These generate complex molecules from simple molecules.

DEGRADATION → **BIOSYNTHESIS OF COMPLEX MOLECULES**

Energetic molecules

Catabolism: **OXIDATION**

CH, Fats (fuel) →→CO2+ H2O+energy

Anabolism: **REDUCTION**

Simple molecules + energy→→ complex molecules

AMPHIBOLIC ROUTES

CAN FUNCTION AS DEGRADATIVE AND BIOSYNTHETIC in response to cellular energy status.

CHARACTERISTICS OF METABOLIC PATHWAYS

1. The biosynthetic and degradative metabolic pathways of a specific metabolite differ from each other. The goal is metabolic control. They may have some steps in common but not all of them.

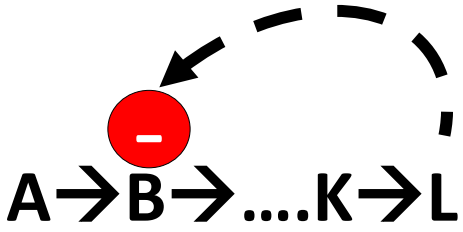
2. The metabolic pathways may be linear, branched, cyclical and spiral.

3. The metabolic pathways are highly regulated: endogenously, by the final product; changes in enzyme activity, by **COVALENT MODIFICATION** enzyme; enzyme production or degradation; by external molecules as **ALLOSTERIC MODULATORS**.

4. There is a **LIMITING STEP** on the route. This step is highly **REGULATED, EXERGONIC AND IRREVERSIBLE.**

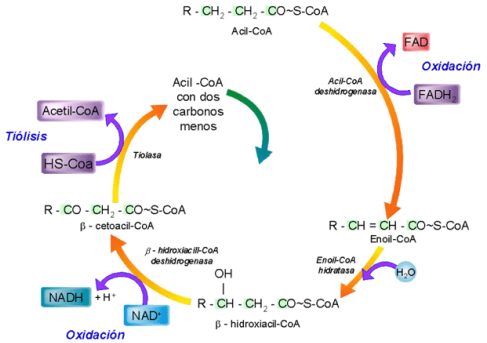
5. There are opposite metabolic pathways in different compartments: **COMPARTMENTALIZATION** segregates opposite routes. Tissue compartmentalization enables efficient global biochemistry.

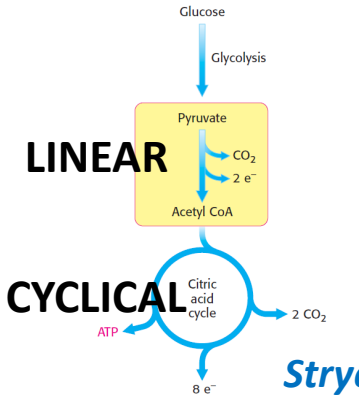
6. MULTIPLE STEPS: advantages in multiple regulation, optimization and energy efficiency.



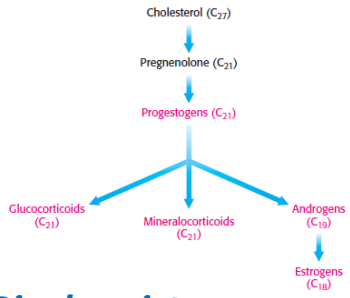
Feedback inhibition

SPIRAL:





BRANCHED



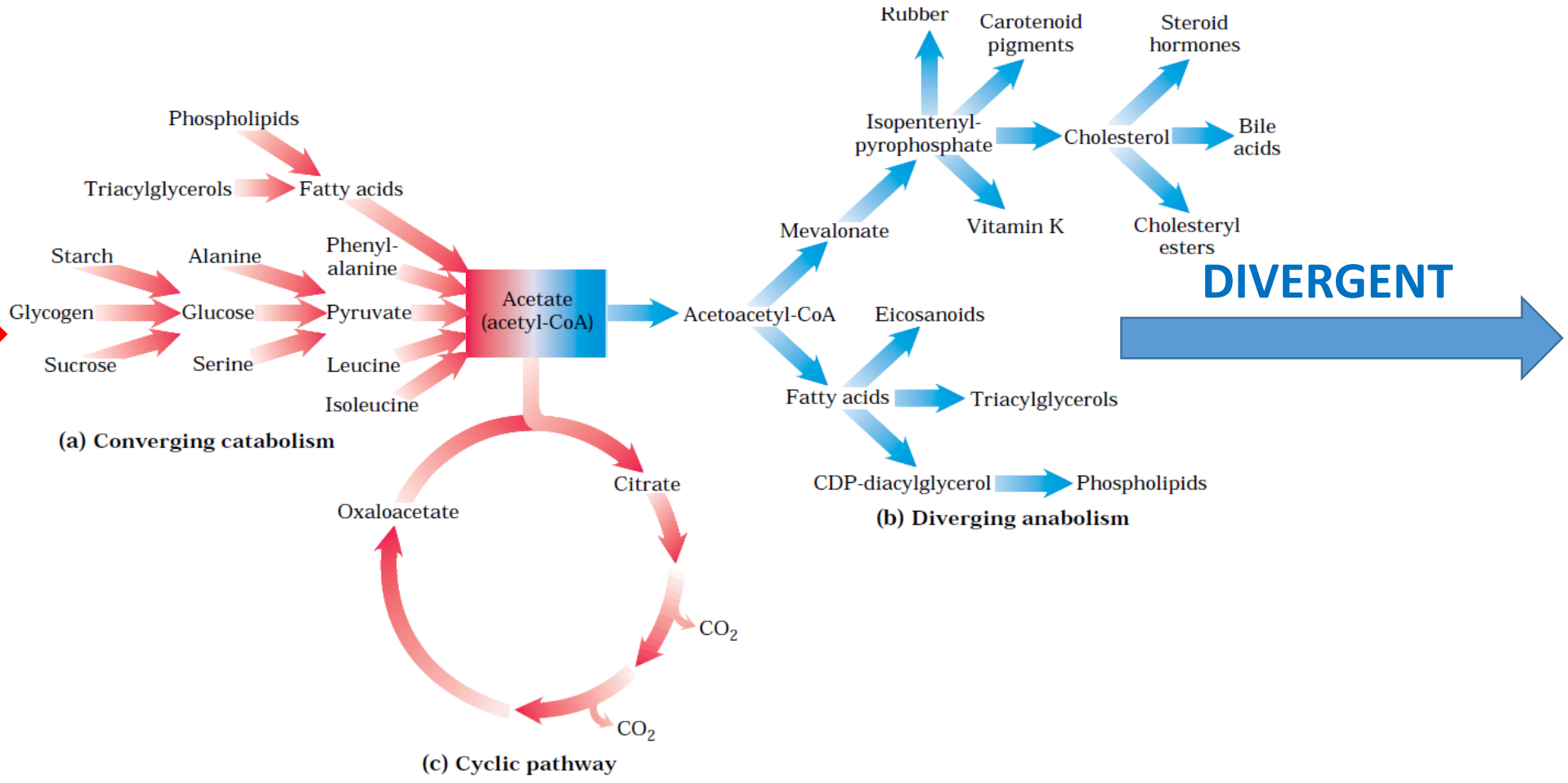
Stryer, 7th ed., Biochemistry

GENERAL OUTLINE OF METABOLIC PATHWAYS:

CATABOLISM, THE DEGRADATION OF MACROMOLECULES:

ANABOLISM, THE BIOSYNTHESIS OF MACROMOLECULES:

CONVERGENT



DIVERGENT

CYCLE

Lehninger, 7th Ed., Principles of Biochemistry

THE THIRD LAW OF THERMODYNAMICS APPLIES TO CLOSED SYSTEMS WHERE ENERGY IS EXCHANGED.

ΔG: CHANGE IN FREE ENERGY A ⟶ B

THIRD LAW

$\Delta G = \Delta H - T\Delta S$ ⟶ **This allows us to know in a closed system whether a reaction is spontaneous.**

ΔH: change in **ENTHALPY**, i.e. the change in heat content in the transformation from A to B; the heat released or absorbed in a chemical reaction.
ΔS: change in **ENTROPY** or disorder in the transformation from A to B.
T: constant temperature

$\Delta H < 0$ heat loss/exergonic
$\Delta S > 0$ increased disorder

BIOENERGETICS AND THERMODYNAMICS IN BIOCHEMISTRY

BIOENERGETICS is a branch of biology that studies and describes the generation, transformation, storage and use of energy in biological systems.

It **applies thermodynamics to the biological processes of living matter** to predict whether a biological process is possible.

ΔG<0 FAVOURABLE REACTIONS

ΔG: CHANGE IN FREE ENERGY

Metabolic pathways follow the thermodynamic principles of ENERGY TRANSFORMATION.

THE FIRST LAW OF THERMODYNAMICS: THE TOTAL AMOUNT OF ENERGY IS INVARIABLE.

The energy difference between A and B will be the work done and heat. ENERGY RELEASE TRANSLATES INTO WORK.

ΔU= W + Q

U= ENERGY
W= WORK
Q= HEAT

THE SECOND LAW OF THERMODYNAMICS: IN AN ISOLATED SYSTEM, **entropy (S) increases (ΔS>0)**. Spontaneous reactions are those that involve an increase in S.

AN ISOLATED SYSTEM DOES NOT EXCHANGE ENERGY OR MATTER.
A CLOSED SYSTEM EXCHANGES ENERGY BUT NOT MATTER.
AN OPEN SYSTEM EXCHANGES ENERGY AND MATTER.

THE THIRD LAW OF THERMODYNAMICS: THIS APPLIES TO CLOSED SYSTEMS WHERE ENERGY IS EXCHANGED.

In a closed system, the energy available to perform work in a chemical reaction is **the Gibbs free energy (G)**. The **change in Gibbs free energy predicts** whether a chemical process or reaction is possible.

ΔG is the energy available to perform work/carry out a chemical reaction spontaneously**.**
Example: the transformation from A to B.

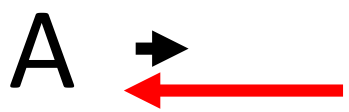
ΔG: CHANGE IN FREE ENERGY A ⟶ B

ΔG: CHANGE IN THE FREE ENERGY DURING A CHEMICAL REACTION/BIOCHEMICAL PROCESS IN A CLOSED SYSTEM

ΔG<0 FAVOURABLE
An exergonic reaction increases disorder and is spontaneous.

ΔG>0 UNFAVORABLE
An endergonic reaction increases order and is not spontaneous.

ΔG=0 EQUILIBRIUM



Living organisms are highly ordered systems

?

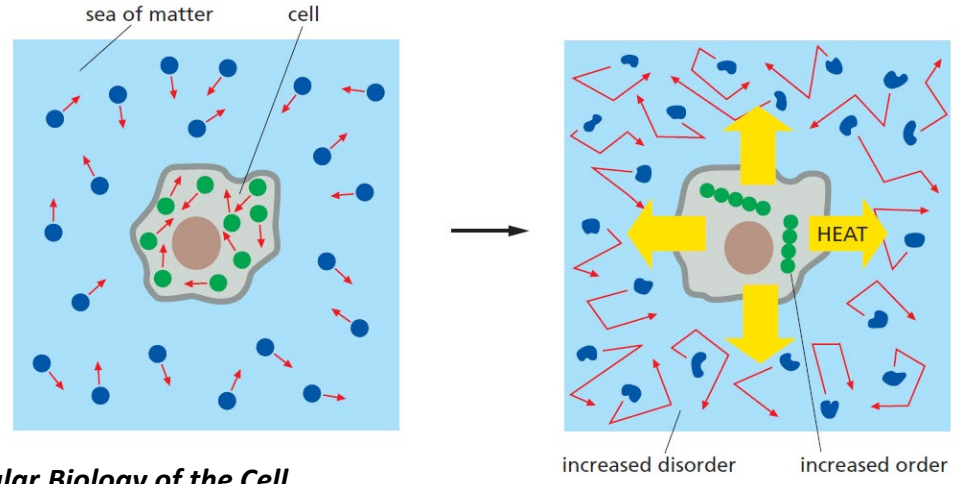
THE SECOND LAW OF THERMODYNAMICS: ENTROPY INCREASES IN ISOLATED SYSTEMS

$\Delta G = \Delta H - T\Delta S$

-Organisms are **OPEN SYSTEMS** (the Second Law, which refers to entropy S, applies to isolated systems): there is an exchange of matter and energy with the environment.

-Organisms are **NOT IN EQUILIBRIUM**: they are dissipation systems and maintain their complexity, which leads to increased entropy in their environment.

*Organisms maintain their complexity, thus causing increases in the **entropy of their environment***



Alberts, 6th edition, Molecular Biology of the Cell

THERMODYNAMICS APPLIED TO BIOENERGETICS

1. **Metabolism enables CELLS TO CAPTURE ENERGY/MATTER** from the environment or to generate it from exergonic chemical reactions. **OPEN SYSTEMS.**

2. Metabolism produces **endergonic reactions by COUPLING them to exergonic reactions**.

IT ENABLES ENDERGONIC SYNTHESIS PATHWAYS**.**

3. The internal transfer of metabolic energy is done primarily **through the ATP molecule.**

4. The **GLOBAL PROCESS IS EXERGONIC** and the energy difference is dissipated in the form of heat and/or increased system disorder (ENTROPY).

The energy produced in the oxidation of molecules is conserved in molecules with highly energetic bonds or released as heat.

ΔG: CHANGE IN FREE ENERGY DURING A CHEMICAL REACTION/BIOCHEMICAL PROCESS IN A CLOSED SYSTEM

ΔG<0 FAVORABLE

ΔG>0 UNFAVORABLE

ΔG=0 EQUILIBRIUM

ΔG>0 a thermodynamically unfavorable reaction can occur if there is an input of energy. This energy can be produced by ATP hydrolysis, by the consumption of reducing power (NADPH) or by the coupling of molecules that release energy (AcetylCoA).

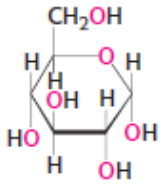
The ΔG of a specific metabolic pathway: THE SUM OF ΔG of the individual reactions WILL BE NEGATIVE.

A→B→C→D→E→F→G→… → M **GLOBAL ΔG = INDIVIDUAL SUM of the steps <0**

THERE IS AN ENERGETIC COUPLING BETWEEN METABOLIC PATHWAYS: CATABOLISM AND ANABOLISM

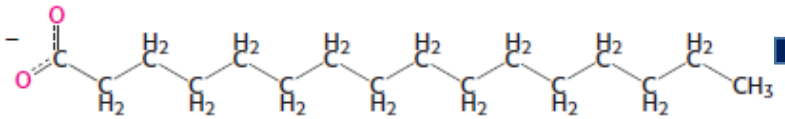
-In metabolism there is a **coupling between** spontaneous processes (**catabolism**) and non-spontaneous processes (**anabolism**).

GLUCOSE



Glucose

FATTY ACID



Fatty acid

OXIDATION

CO_2 + ENERGY (Energy molecules: NADH, FADH2+AcetylCoA+ATP)

High-energy compounds or energy carriers make coupling possible.

HIGH-ENERGY COMPOUNDS ARE MOLECULES WHOSE BONDS, WHEN BROKEN, RELEASE A LARGE AMOUNT OF ENERGY.

Stryer, 7th ed., Biochemistry

THE OXIDATION OF CARBON FUELS IS AN IMPORTANT SOURCE OF CELLULAR ENERGY

REDUCED MOLECULE

High energy content

Most energy → Least energy

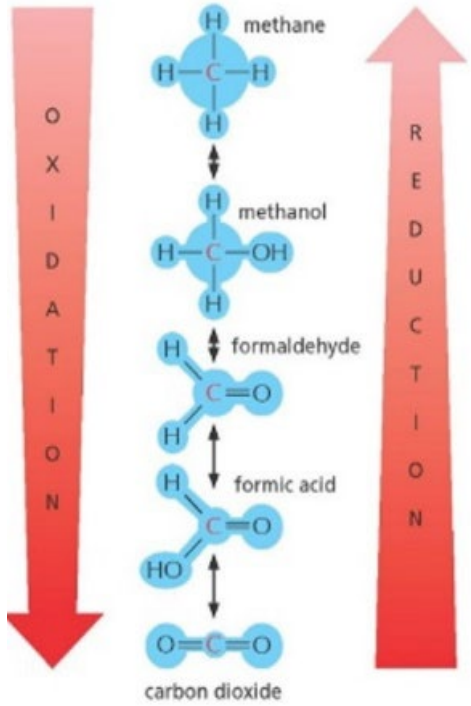
OXIDIZED MOLECULE

Low energy content

	Methane	Methanol	Formaldehyde	Formic acid	Carbon dioxide
$\Delta G^{\circ\prime}_{oxidation}$ (kJ mol^{-1})	−820	−703	−523	−285	0
$\Delta G^{\circ\prime}_{oxidation}$ (kcal mol^{-1})	−196	−168	−125	−68	0

Process of obtaining energy or ATP

EXTRACTION OF ELECTRONS THAT ARE CAPTURED IN ELECTRON-CARRYING MOLECULES



Alberts, 6th edition, Molecular Biology of the Cell

ATP serves as the main immediate donor of energy. It is not stored but used for movement, contraction, and biosynthesis.

STORAGE: MOLECULES WITH REDUCING POWER THAT ULTIMATELY GENERATE ATP.

THE MORE REDUCED IS THE FIRST MOLECULE IN ELECTRON-EXTRACTION REACTIONS, THE MORE MOLECULES WITH ENERGY CONTENT THE REACTIONS WILL PRODUCE.

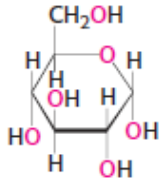
Stryer, 7th ed., Biochemistry

CATABOLISM:

BREAKING COVALENT BONDS

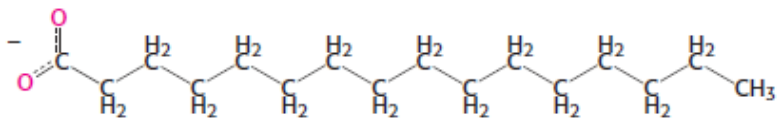
C-C = 347 kjul/mol

GLUCOSE



Glucose

FATTY ACID



Fatty acid

OXIDATION

CO2 + ENERGY

First Law of Thermodynamics

ΔU=W+Q

THESE ARE MOLECULES WHOSE BONDS, WHEN BROKEN, RELEASE A LARGE AMOUNT OF ENERGY.

ENERGY → **NADH/FADH2** **ATP**

IN THE FORM OF REDUCING POWER

Biosynthesis of macromolecules

ANABOLISM:

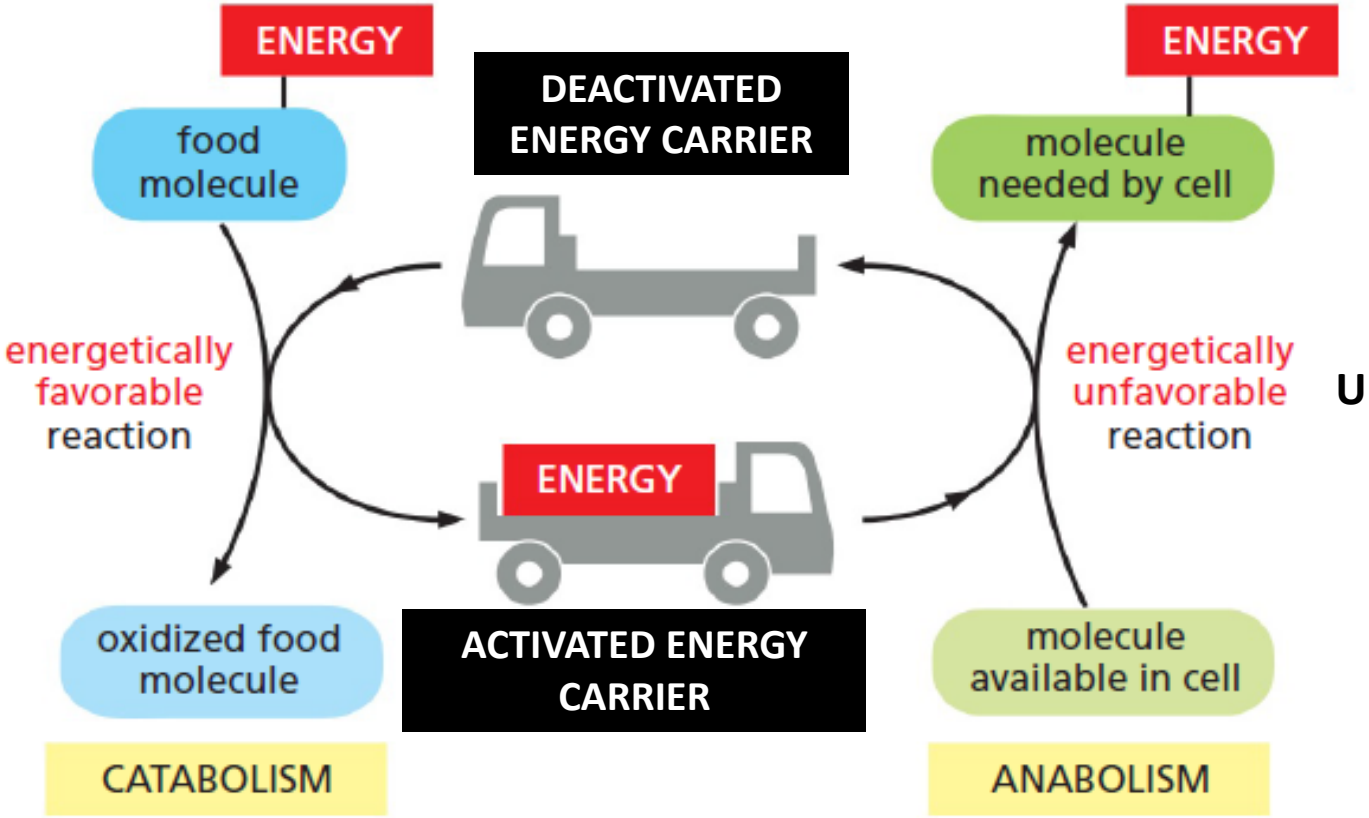
Simple biomolecules + **ENERGY** → **REDUCTION** → **FORMATION OF COMPLEX STRUCTURES BY COVALENT AND NON-COVALENT BONDS**

This process goes against the Second Law of Thermodynamics:
IT REQUIRES ENERGY TO FORM COVALENT BONDS.

MOLECULES OF THE COUPLING BETWEEN CATABOLISM AND ANABOLISM

Activated energy-carrier molecules act as energy shuttles.

FAVORABLE REACTION

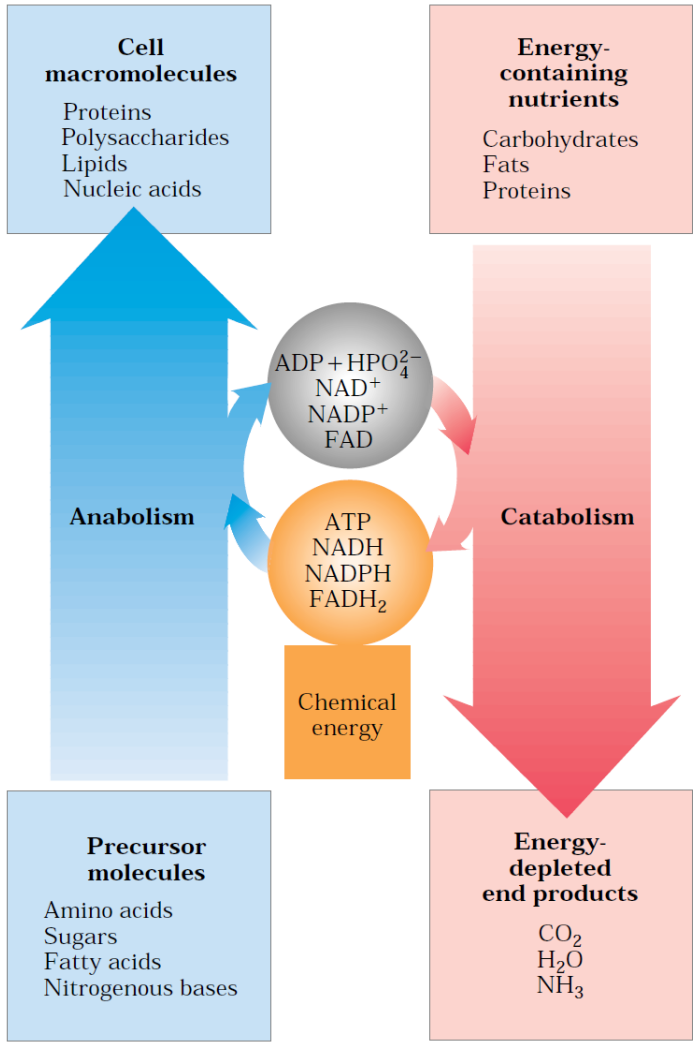


UNFAVORABLE REACTION

High-energy compounds or energy carriers make coupling possible.

Alberts, 6th edition, Molecular Biology of the Cell

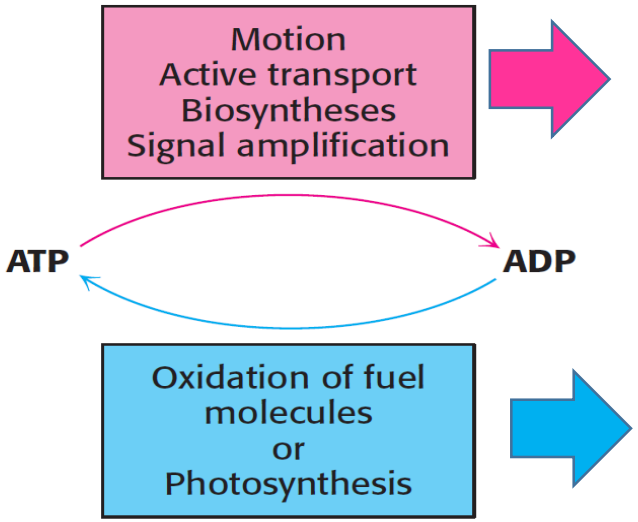
COUPLING BETWEEN CATABOLISM AND ANABOLISM



Lehninger, 7th Ed., Principles of Biochemistry

ATP IS A MOLECULE THAT CONTAINS ENERGY BUT IS NOT STORED.
IT IS CONSUMED WITHIN MINUTES OF BEING PRODUCED.

ATP WILL ALSO BE USED FOR OTHER PROCESSES



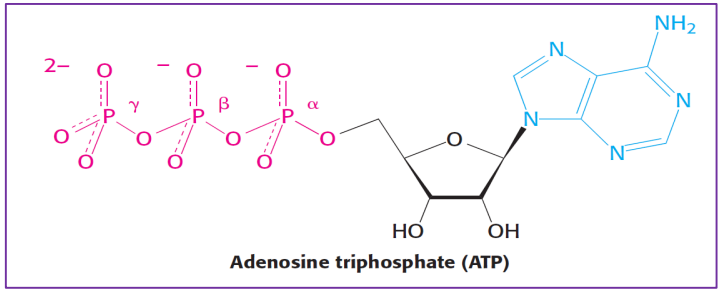
MOVEMENT, ACTIVE TRANSPORT, SIGNALING AND BIOSYNTHESIS CAN ONLY TAKE PLACE IF ATP IS CONTINUOUSLY REGENERATED FROM ADP.

ELECTRONS ARE CAPTURED TO PRODUCE REGENERATED ATP FROM ADP+Pi.

Stryer, 7th ed., Biochemistry

THE ATP, ENERGY CURRENCY FOR CONTAINING A HIGH ENERGY POTENTIAL

ATP (ADENOSINE TRIPHOSPHATE) HAS A VERY HIGH TRANSFER POTENTIAL OF THE P group due to its structure. HYDROLYSIS is favorable (ΔG<0) due to the products containing less energy.



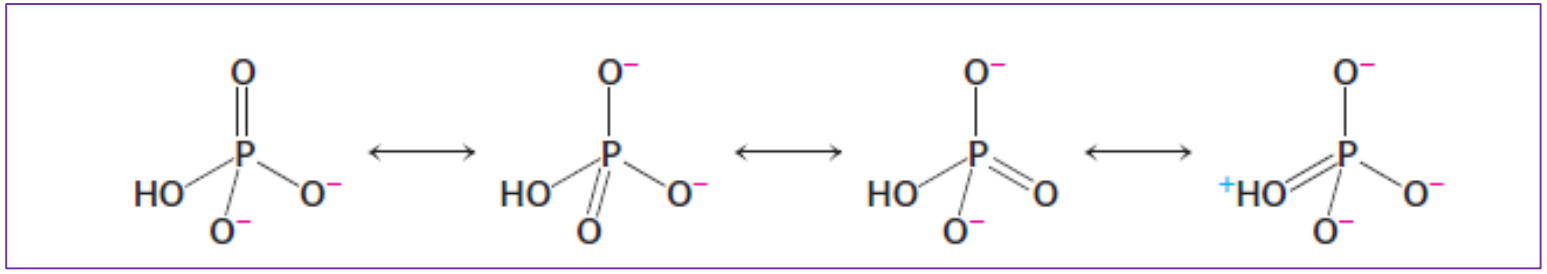
HIGH-ENERGY PHOSPHATE BONDS

THREE FACTORS ARE INVOLVED: RESONANCE STABILIZATION, ELECTROSTATIC REPULSION, AND HYDRATION STABILIZATION.

1. RESONANCE STABILIZATION OF THE PRODUCTS: ADP, AND ESPECIALLY Pi (orthophosphate), have several similar energy resonance forms. In the ATP, the group P has a smaller number.

ATP →→ ADP+ Pi ΔG<0

RESONANT FORMS OF THE Pi WHEN THEY ARE FREE



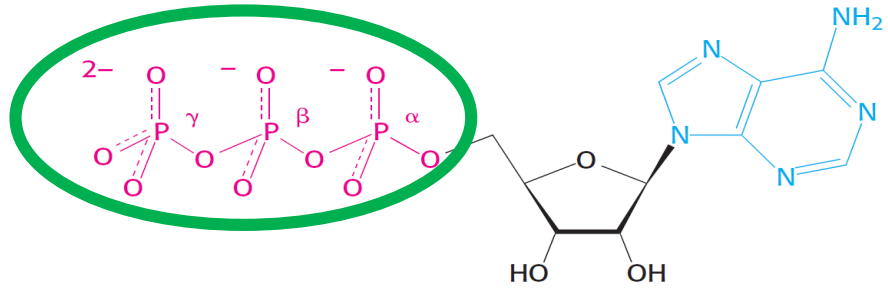
Stryer, 7th ed., Biochemistry

CELLULAR ENERGY CHARGING: ATP, ENERGY CURRENCY

2. ELECTROSTATIC REPULSION. At pH 7, in the ATP the triphosphate unit carries roughly four negative charges.

3. HYDRATION STABILIZATION. Water binds more effectively to ADP and Pi, which can bind to the phosphoanhydride component of ATP.

HYDRATION STABILIZES THE STRUCTURES RESULTING FROM HYDROLYSIS.

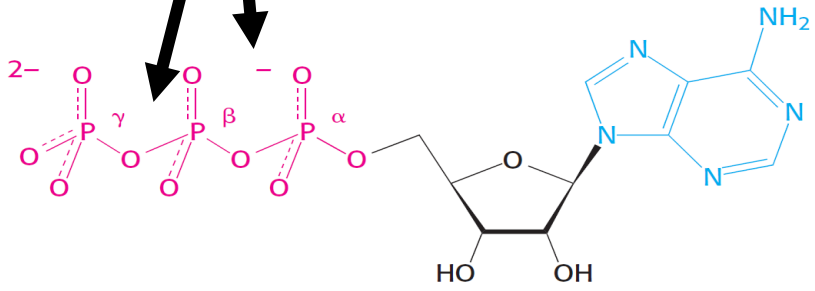


Adenosine triphosphate (ATP)

REPULSION OF NEGATIVE CHARGES THAT DO NOT EXIST IN THE HYDROLYSIS PRODUCT

ATP IS A HIGH-ENERGY PHOSPHATE COMPOUND. ITS PHOSPHOANHYDRIDE BONDS ARE KNOWN AS HIGH-ENERGY BONDS.

THESE TYPE OF MOLECULES ARE HIGH-ENERGYCONTENT MOLECULES WITH BONDS THAT RELEASE A LOT OF FREE ENERGY WHEN THE MOLECULES ARE HYDROLYZED.



Adenosine triphosphate (ATP)

Stryer, 7th ed., Biochemistry

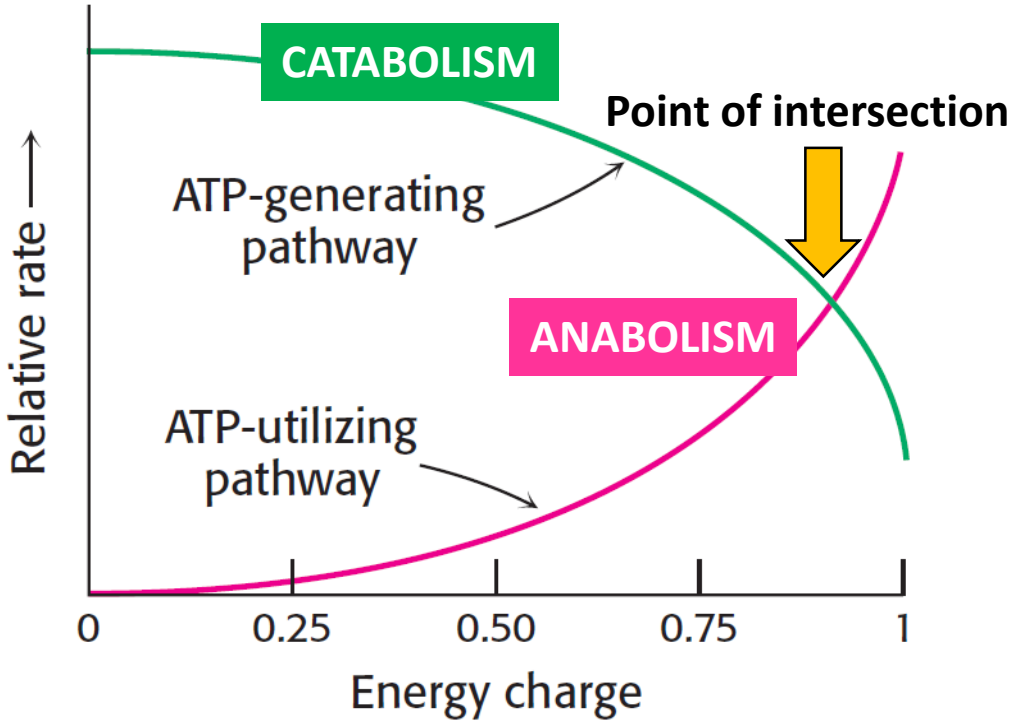
CELLULAR ENERGY CHARGE. ATP.

The energy charge (EC) determines the direction of biological processes in a cell.
If ATP levels are elevated, ATP-generating processes and catabolism are inhibited and processes using ATP and anabolism are increased.

EC = ([ATP] + [ADP]/2) / ([ATP] + [ADP] + [AMP])

- When EC=0, all nucleotides are in AMP form.
- When CE=1, all nucleotides are in ATP form.
- When EC > 0.85, the ATP-using pathways are activated.
- When EC < 0.85, the ATP-generating pathways are activated.

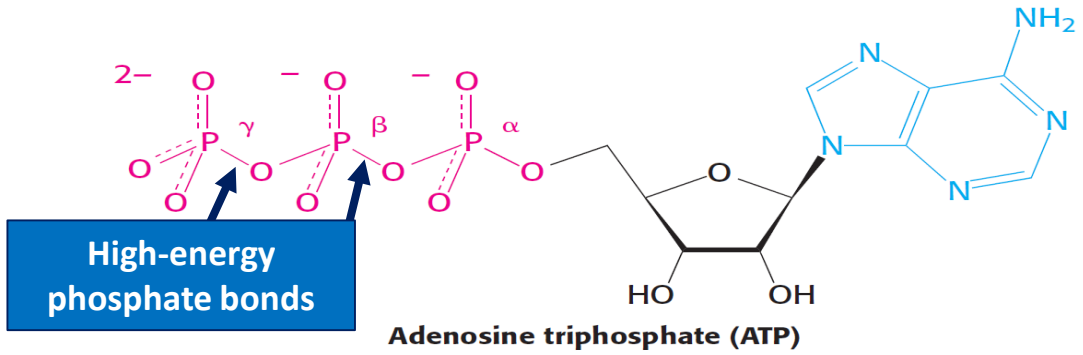
The EC in most cells ranges from 0.80 to 0.95.



$$\frac{([ATP] + [ADP]/2)}{([ATP] + [ADP] + [AMP])}$$

Stryer, 7th ed., Biochemistry

HIGH-ENERGY COMPOUNDS



ATP and GTP

ATP: Nucleotides (adenosine mono, di- and triphosphate)
GTP: Nucleotides (guanosine mono di and triphosphate)

NUCLEOSIDE DIPHOSPHATE KINASE

GTP + ADP → ATP + GDP

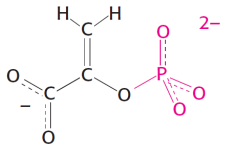
The transfer of Pi from ATP is used to perform endergonic reactions.

ATP is a carrier of Pi because the cleavage ATP → ADP + Pi is exergonic.

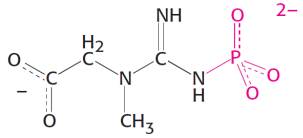
Stryer, 7th ed., Biochemistry

HIGH-ENERGY PHOSPHORYLATED COMPOUNDS

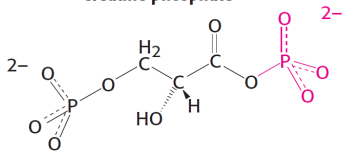
ENERGY-RICH INTERMEDIARIES **are highly energetic with phosphate transfer potential to ADP.**


Phosphoenolpyruvate (PEP)

PHOSPHOENOL PYRUVATE (Phase-2 glycolysis)


Creatine phosphate

CREATINE PHOSPHATE


1,3-Bisphosphoglycerate (1,3-BPG)

1,3-BISPHOSPHOGLYCERATE (Phase-2 glycolysis)

ATP SYNTHESIS AT SUBSTRATE LEVEL

X-P + ADP → X + ATP

HYDROLYSIS OF THESE COMPOUNDS HAS A FAVORABLE ΔG<0

IF THE ADP HAS A HIGH-ENERGY CONTENT, WHY IS IT POSSIBLE TO BE GIVEN A Pi?

THESE ENERGY-RICH MOLECULES HAVE A HIGHER PHOSPHORYL TRANSFER POTENTIAL THAN ATP.

CREATINE PHOSPHATE: the amount of ATP in the muscle is sufficient to maintain contractile activity for less than a second.

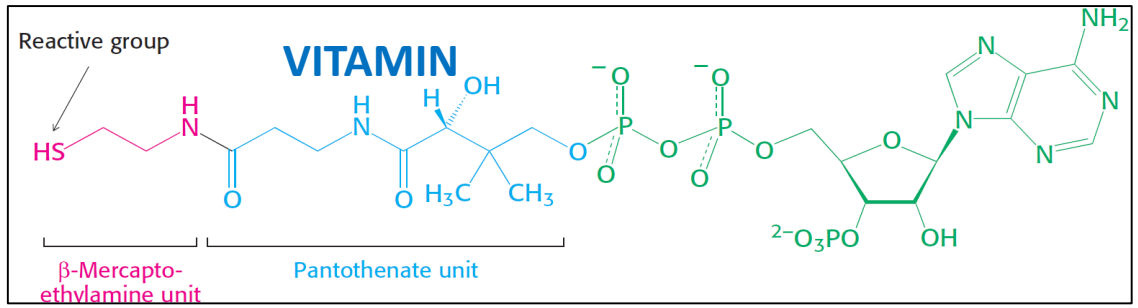
IN VERTEBRATES: creatine phosphate is a reservoir of high-potential phosphoryl groups that can be easily transferred to ADP.

Stryer, 7th ed., Biochemistry

HIGH-ENERGY COMPOUNDS: COENZYME A IS AN ENERGY AND ACYL GROUP TRANSPORTER

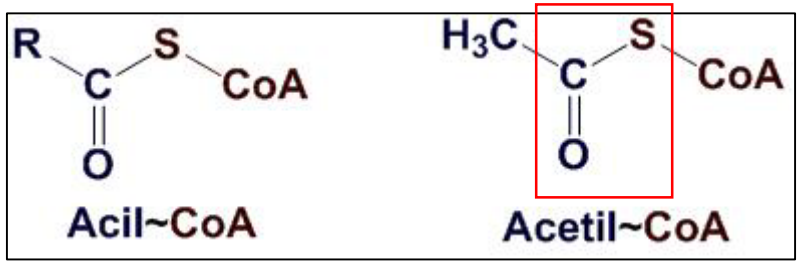
Acetyl~CoA transports acyl groups in a similar way to how ATP transports phosphate groups.

Coenzyme A



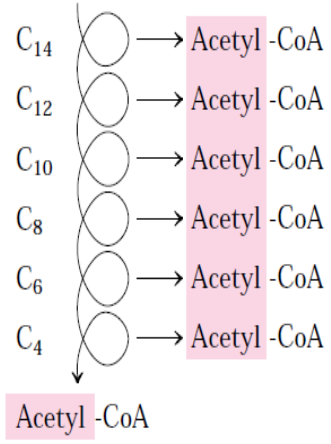
Stryer, 7th ed., Biochemistry

ACYL GROUPS BY THIOESTER BOND ARE CARRIED BY CoA

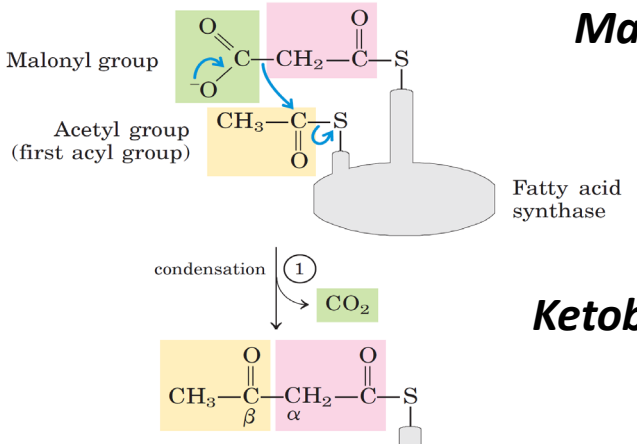


ACYL-CoA is IMPORTANT IN FATTY ACID OXIDATION AND LIPID SYNTHESIS.
Hydrolysis of the thioester bond is favorable because the C=O bonds allow for more stable resonant forms.

β FATTY ACID OXIDATION



FATTY ACID SYNTHESIS



Highly unstable molecule

Malonyl-ACP + ACETYL

UNFAVORABLE CONDENSATION

Ketobutyryl intermediate+ CO2

Lehninger, 7th Ed., Principles of Biochemistry

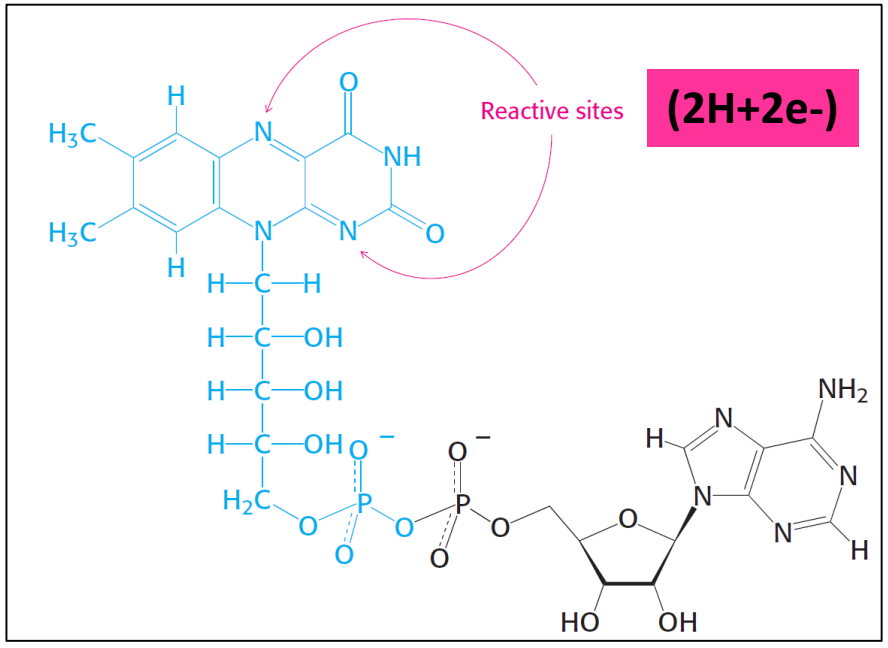
HIGH-ENERGY COMPOUNDS: ELECTRON CARRIERS FOR REDOX REACTIONS

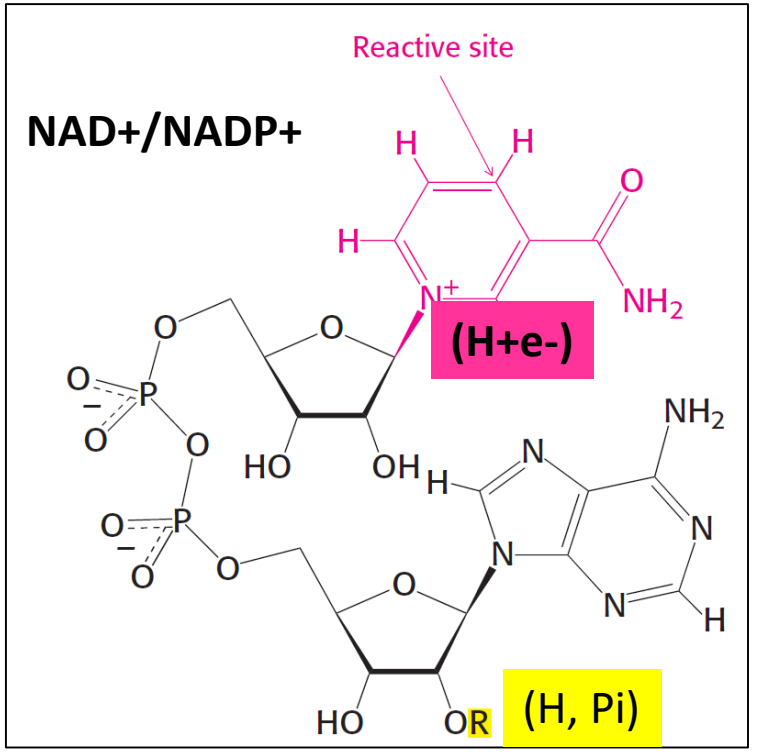
Other energy carriers are coenzymes:
FAD+: flavin adenine dinucleotide
NAD+: nicotinamide adenine dinucleotide
NADP+: nicotinamide adenine dinucleotide phosphate

NADH and NADPH act with dehydrogenase enzymes as soluble electron carriers.

NADH is generated in catabolism (glycolysis, FA oxidation)
NAPH is used in anabolism (the synthesis of FA and cholesterol)

FAD+





Stryer, 7th ed., Biochemistry

CHEMICAL REACTIONS IN METABOLISM: 6 types of recurrent reactions in metabolism

1. Oxidation-reduction reaction: electron transfer. $FAD^+ + 2e^- + 2H^+ \rightarrow FADH_2$

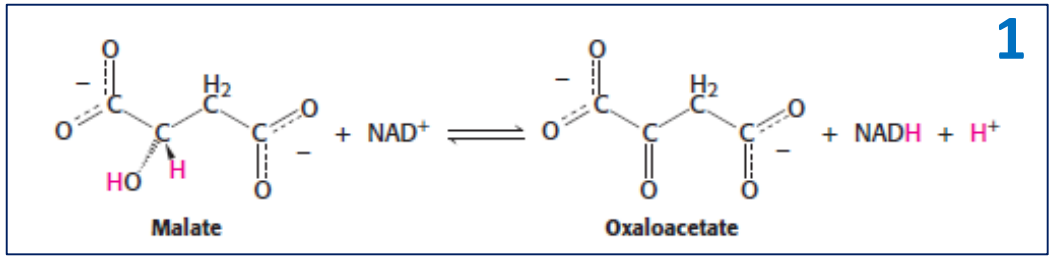
2. Ligation reaction coupled to an **ATP hydrolysis**: formation of covalent bonds (carbon–carbon).

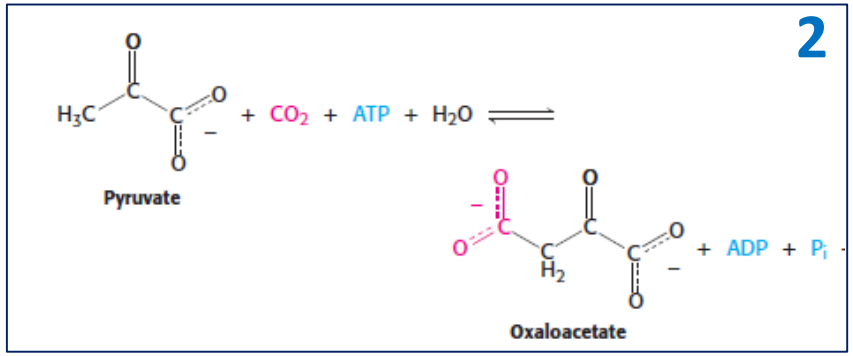
3. Isomerization reaction: rearrangement of atoms, generation of isomers.

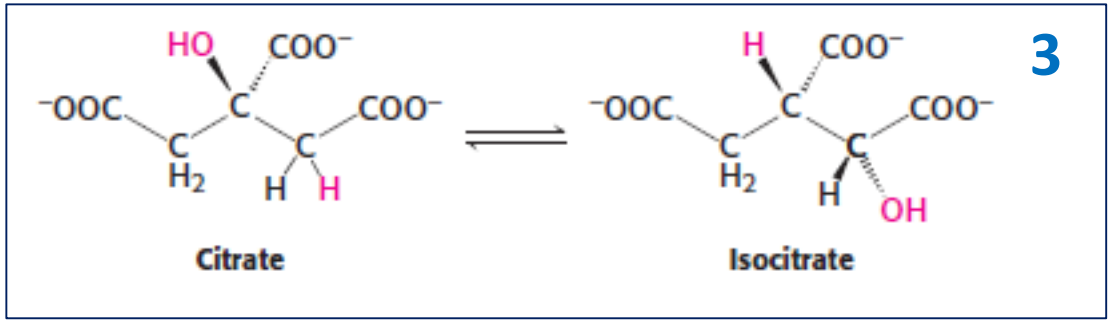
4. Group transfer reaction: from one molecule to another → GLUCOSE + ATP → GLUCOSE-6-P.

5. Excision reaction: hydrolysis, bond breakage by addition of H2O and **thiolysis,** breakage by addition of SH-CoA.

6. Addition or removal of functional groups: decarboxylation (CO2 removal), addition of Pi.







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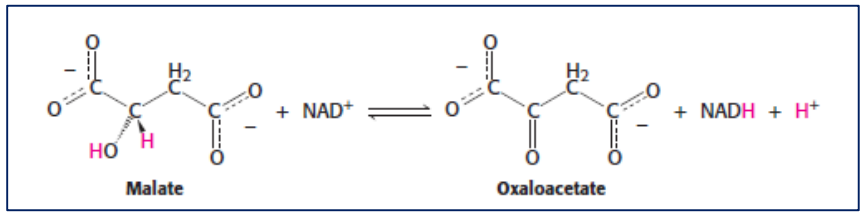
TYPES OF CHEMICAL REACTIONS OF METABOLISM

OXIDOREDUCTION REACTIONS

Electron transfer



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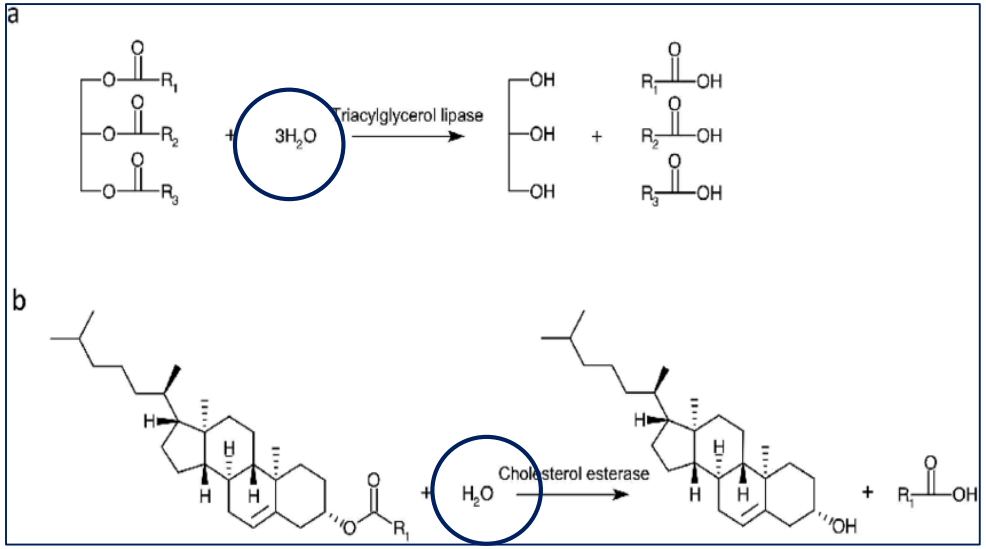
1. Oxidation: the molecule loses two electrons with 2H+ or gains an O2.
2. Reduction: the molecule gains two electrons with H or loses one O2.

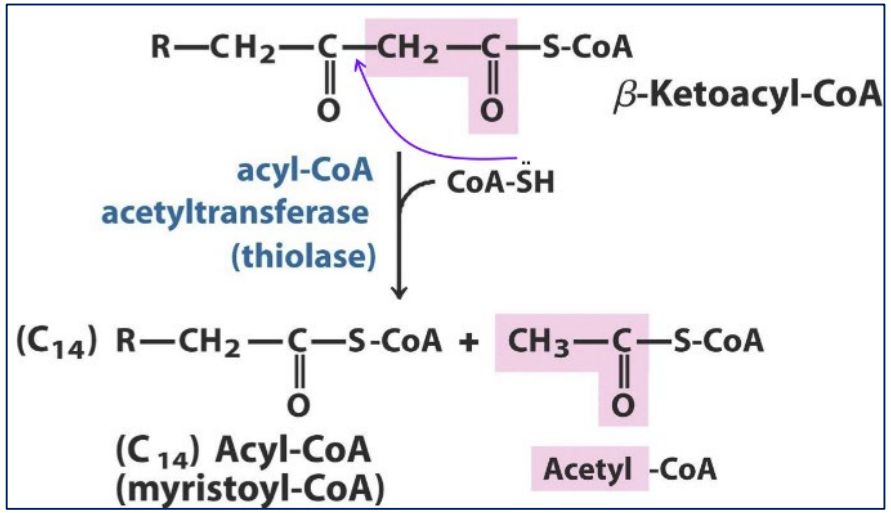
1. OXIDIZING AGENT: ELECTRON ACCEPTOR
2. REDUCING AGENT: ELECTRON DONOR

HYDROLYSIS OR THIOLYSIS REACTIONS

Digestion breakdown of lipid esters by H2O: lipases, cholesterol esterase



Coenzyme A-SH mediated thioester breakage

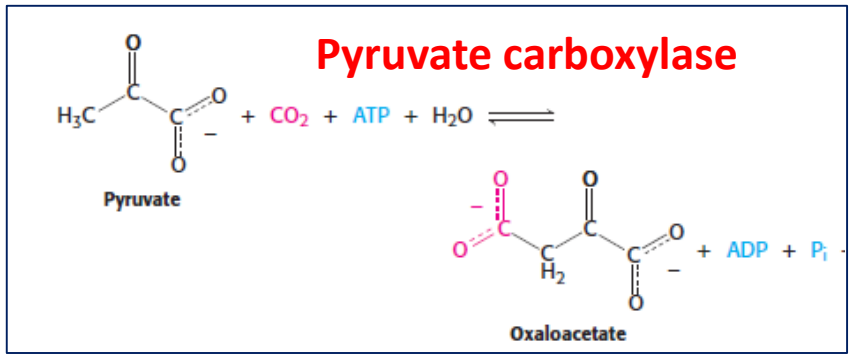


Lehninger, 7th Ed., Biochemistry

TYPES OF CHEMICAL REACTIONS OF METABOLISM

ADDITION REACTIONS: ATP-coupled ligation

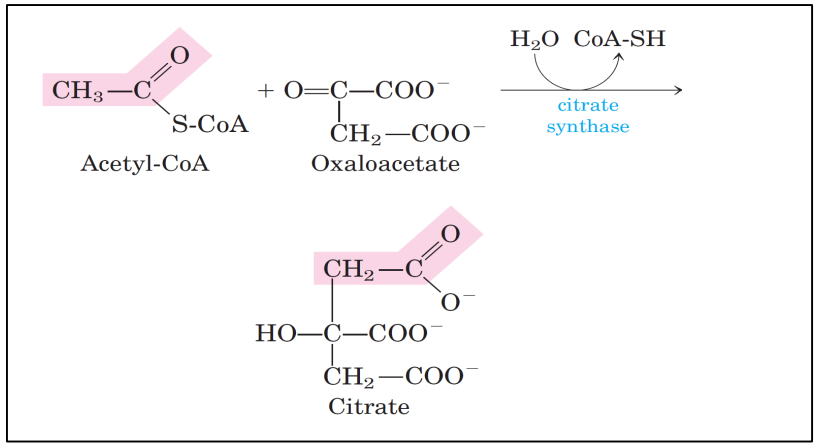
BINDING BY USING ATP AND FORMING C-C SKELETON BONDS



CONDENSATION REACTIONS

CITRATE SYNTHASE

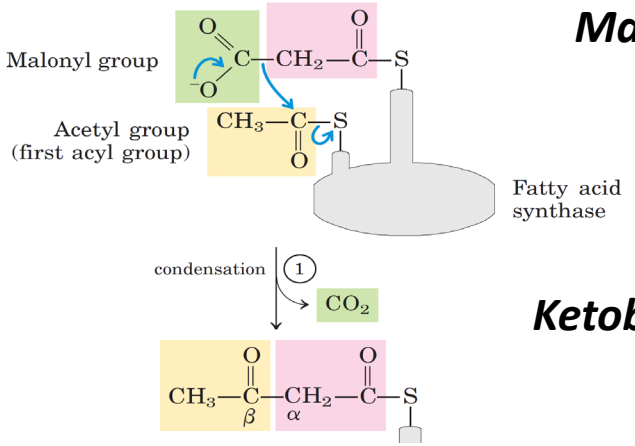
Condensation of AcetylCoA with Oxaloacetate to produce citrate



REACTIONS THAT ELIMINATE GROUPS

decarboxylation

FATTY ACID SYNTHESIS



Malonyl-ACP + ACETYL

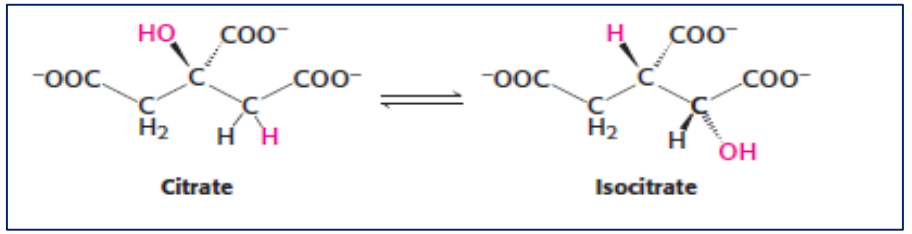
UNFAVORABLE CONDENSATION

Ketobutyryl intermediate+ CO2

ISOMERIZATION REACTIONS

ACONITASE

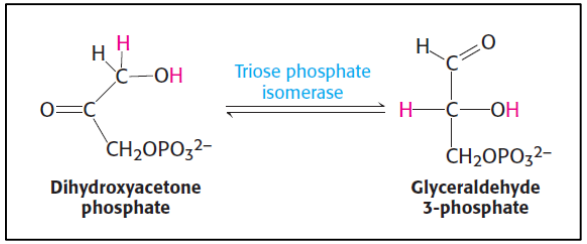
Isomerization of citrate to ISOCITRATE



Lehninger, 7th Ed., Principles of Biochemistry

TRIOSA P ISOMERASE

Isomerization of G3P



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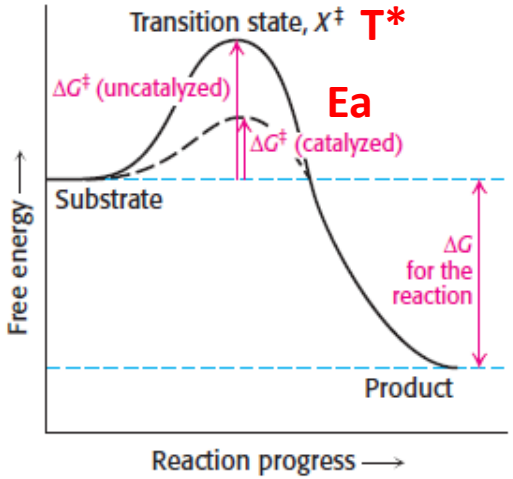
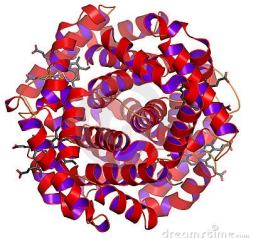
THE CHEMICAL REACTIONS OF SSVV METABOLISM

METABOLISM REACTIONS ARE PERFORMED BY ENZYMATIC CATALYSIS



NEED FOR EFFICIENCY SPECIFICITY AND SPEED/IMMEDIACY: ENZYMES

THE FUNCTIONAL STRUCTURE OF ENZYMES ENABLES ENZYMATIC CATALYSIS



ΔG >0 ENDERGONIC, UNFAVORABLE
ΔG <0 FAVORABLE, EXERGONIC
ΔG = 0 IN EQUILIBRIUM

EUKARYOTIC COMPARTMENTALIZATION: SEPARATES OPPOSITE METABOLIC PATHWAYS

1. **Importance in eukaryotic cells with GREATER COMPLEXITY.**
2. **GREATER REGULATION of metabolism processes.**
3. **COORDINATION between catabolic and anabolic pathways.**
4. **DISTRIBUTION OF FUNCTIONS in organelles.**
5. **Occurrence in multicellular living organisms: NEED FOR COORDINATION.**

Nuclei: replication, transcription.
Mitochondria: β oxidation, c. Krebs, oxidative phosphorylation.
Cytosol: glycolysis, lipid biosynthesis, protein and aas synthesis.
ER: synthesis of membrane, glycosylation and secretion of proteins. Lipoprotein synthesis.

Lehninger, 7th Ed., Principles of Biochemistry

Stryer, 7th ed., Biochemistry

LESSON 18. INTERMEDIATE AND BIOENERGETIC METABOLISM (II)

E-mail: herminia.gonzalez@uv.es

Herminia González Navarro 2022

INDEX

ENERGY FROM FOOD IS EXTRACTED IN THREE PHASES BY OXIDATION

Hans Krebs described these THREE PHASES.

The first phase is **preparation.** Large molecules in food are broken down into smaller units. DIGESTION occurs in the digestive system.

PROTEINS
CARBOHYDRATES → **BROKEN DOWN INTO BIOMOLECULES:**
FATS **AAS, MONOSACCHARIDES, GLYCEROL, FATTY ACIDS**

In the second phase, simple biomolecules are converted into acetyl CoA.

BIOMOLECULES → **AcCoA + a low amount of ATP**

In the third phase, complete oxidation of acetylCoA occurs to produce ATP. This third stage consists of the **citric acid cycle (Krebs cycle) and oxidative phosphorylation.**

AcetylCoA produces 3 NADH, 1 FADH2, and 1 GTP in the Krebs cycle.

Reducing power generates a **PROTON GRADIENT: ATP synthesis.**

INTERMEDIATE METABOLISM

PHASES OF INTERMEDIATE METABOLISM: CATABOLISM

The oxidative metabolism of carbohydrates, fats and proteins.
This is produced **in three stages:**

1. Acetyl CoA Production:

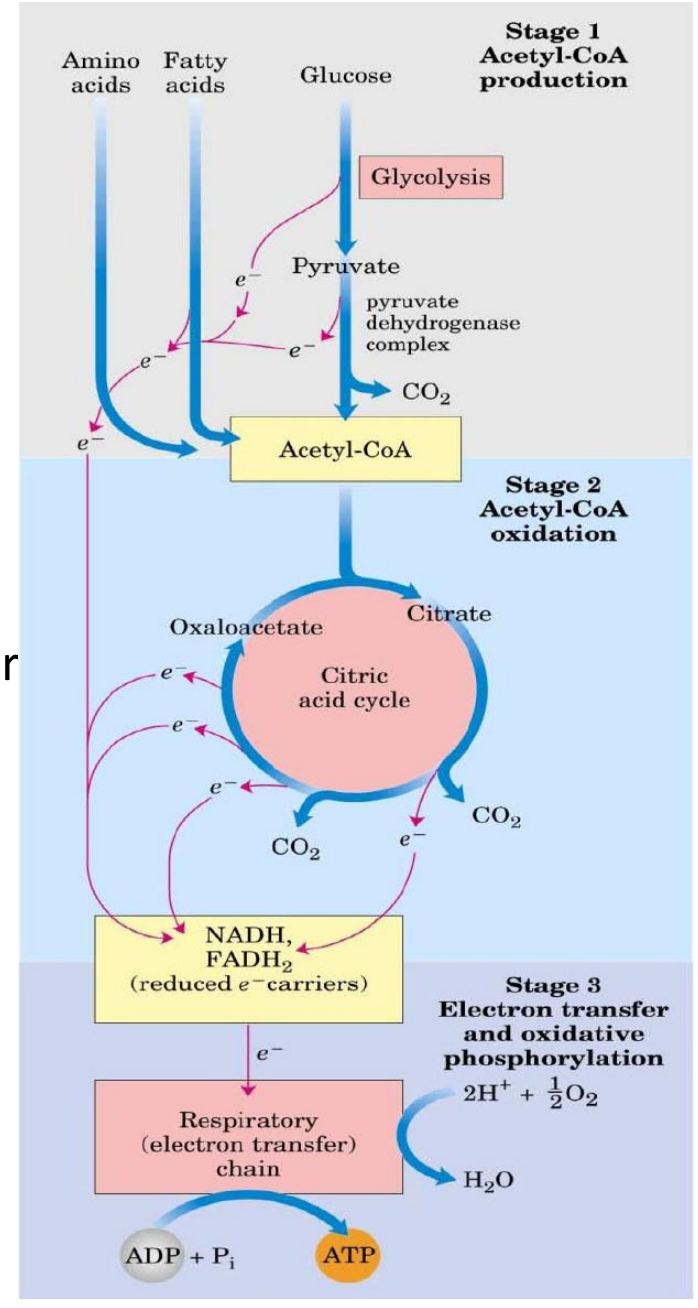
Oxidative **deamination of amino acids.**
Beta oxidation of fatty acids.
Glycolysis.

2. Acetyl CoA Oxidation:

Through the Krebs Cycle (TCA): Direct Power Generation (GTP) and Reducing Power (NADH and FADH2, electron carriers).

3. Oxidative phosphorylation: electron transport (ETC) and ATP synthesis.

The reducing power generated is used to synthesize ATP in the mitochondria by chemiosmotic coupling.



Biochemistry, Lehninger, 7th Ed.

KREBS CYCLE, TRICARBOXYLIC ACID CYCLE, OR CITRIC ACID CYCLE

THE AcCOA RESULTING FROM THE OXIDATION OF CH, FA AND AAS IS INCORPORATED.

Glucose

Glycolysis

PYRUVATE | **AMINO ACIDS** | **FATTY ACIDS**

FA Oxidation

Acetyl CoA

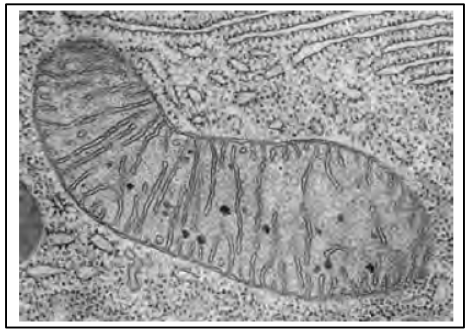
Krebs cycle

Mitochondrial matrix

$2\ CO_2$

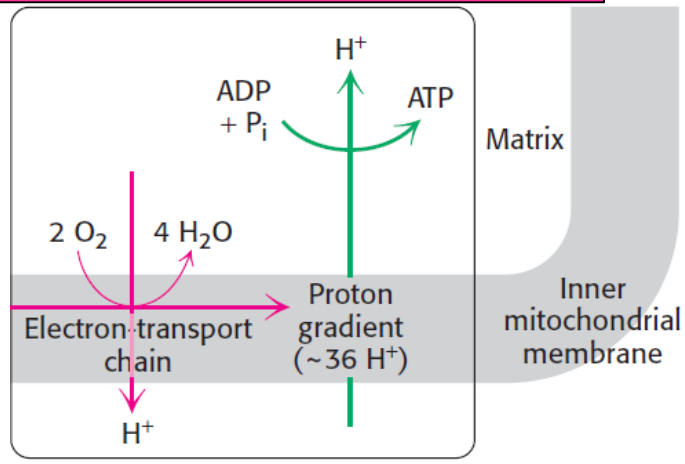
ATP

$8\ e^-$

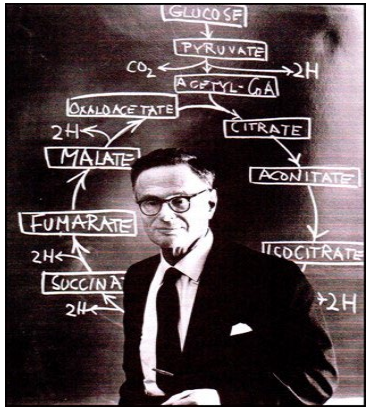


Electron-carrying molecules: 3 NADH, FADH2

OXIDATIVE PHOSPHORYLATION



ETC **ATP SYNTHASE**



Hans Adolf Krebs, 1937

7th edition, *Biochemistry*, JM Berg, JL Tymoczko, L Stryer

Krebs cycle (citric acid cycle or tricarboxylic acid cycle).

1. Cyclic chemical reactions consisting of AcCoA oxidation to **CO2**.

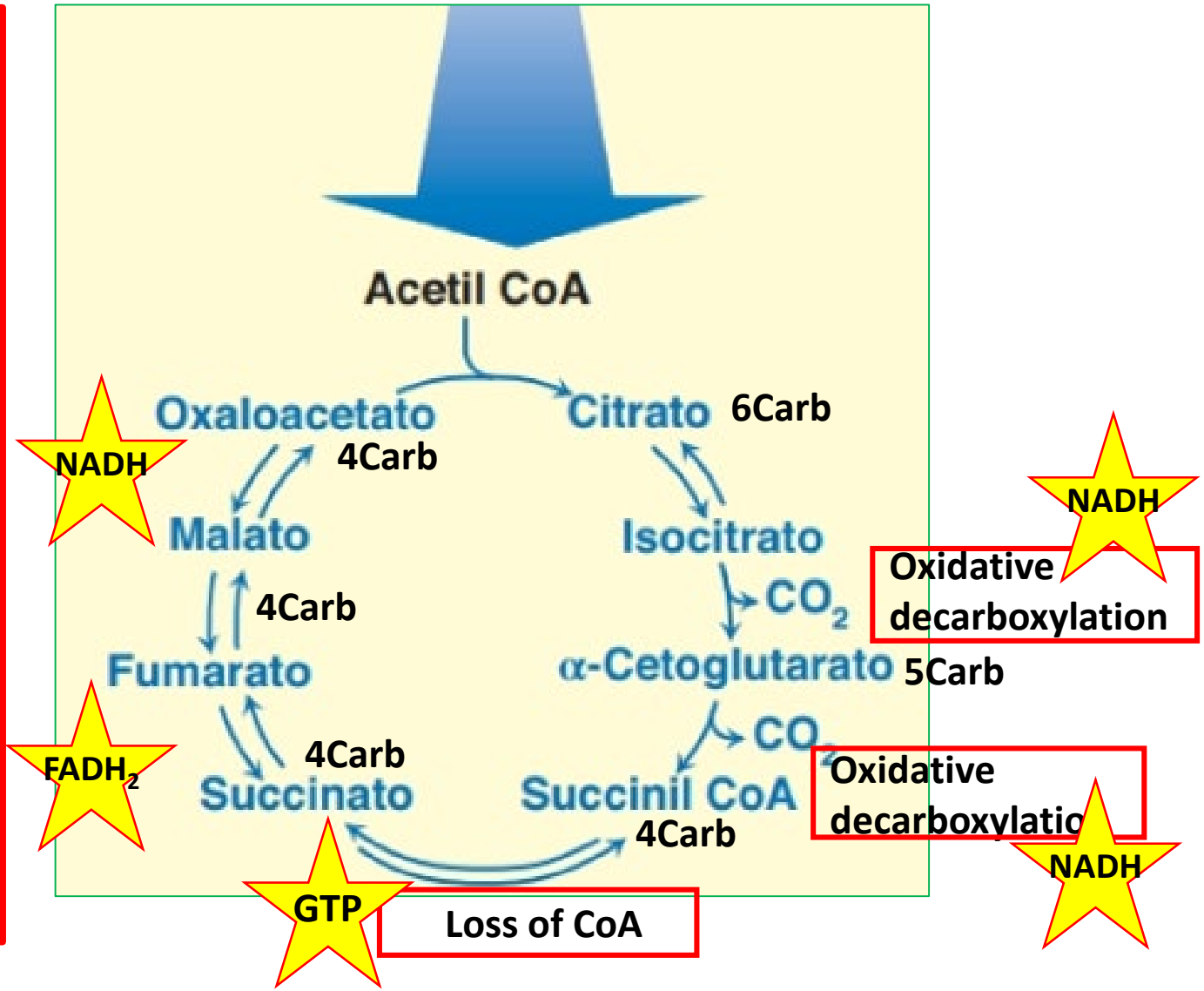
2. Mitochondrial matrix in eukaryotes (aerobic prokaryotic cytosol).

3. Generates 1xGTP and 3xNADH and 1xFADH2 reducing potential.

4. AMPHIBOLIC ROUTE: catalysis is by oxidation of AcCoA but anabolic **by providing precursors of Aas** (Oxaloacetate, α-ketoglutarate).

CITRATE for fatty acid biosynthesis.
OAA for gluconeogenesis.

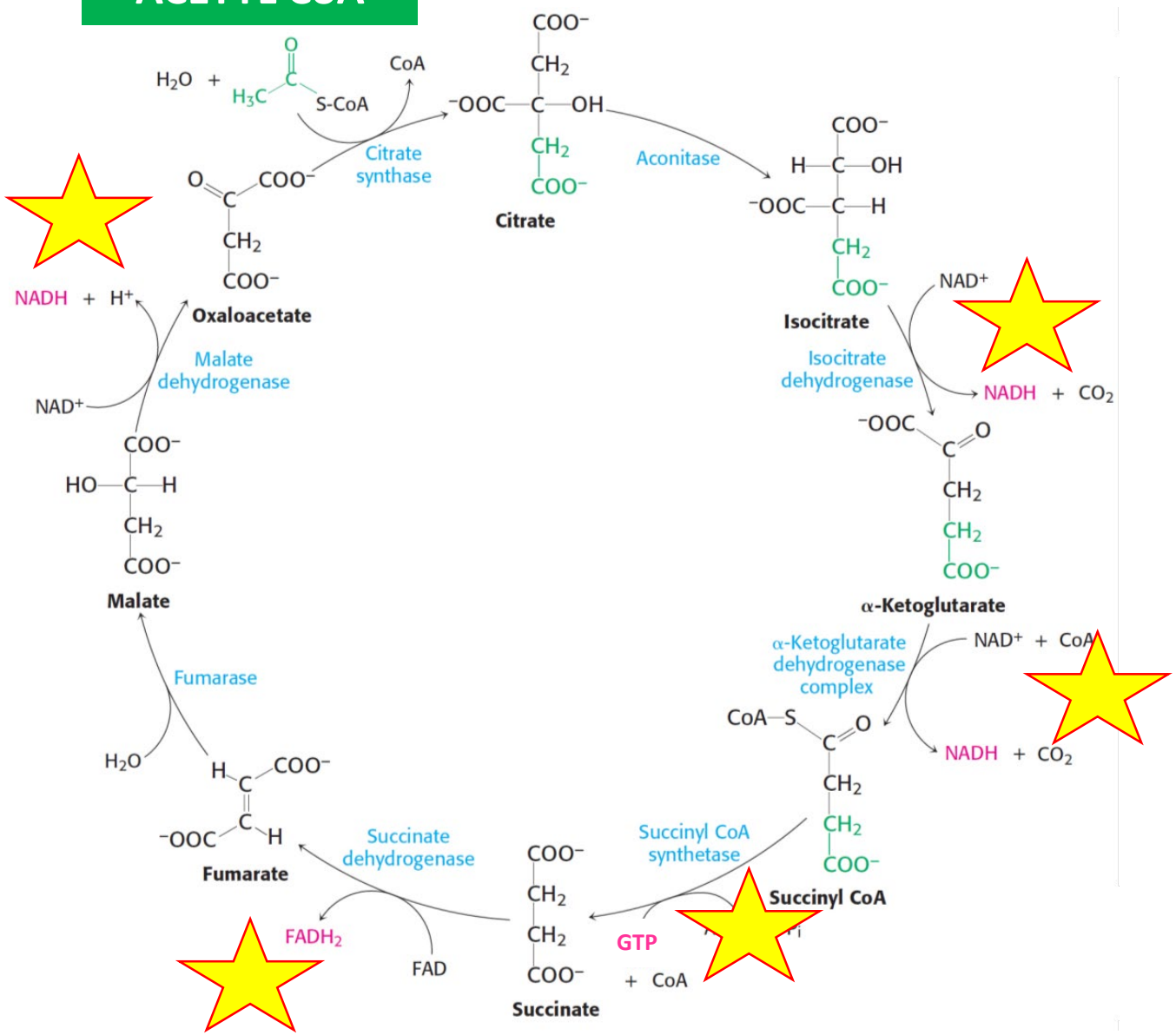
5. Regulated by substrate availability and product inhibition (**ENERGY NEEDS**).



Ferrier, Biochemistry, 7th ed., Lippincott

KREBS CYCLE

ACETYL CoA



7th edition, *Biochemistry*, JM Berg, JL Tymoczko, L Stryer

CITRATE SYNTHASE

Energy of the S-CoA is used for condensation of the Ac with OAA.

ACONITASE

Isomerization of the citrate to ISOCITRATE.

ISOCITRATE DEHYDROGENASE

CO2 production and NAD+ reduction to NADH.
Generation of α-KETOGLUTARATE.

α-KETOGLUTARATE DEHYDROGENASE

CO2 production (decarboxylation) and NAD+ reduction to NADH; incorporation of HSCoA.
Generation of SuccinylCoA.

SUCCINIL CoA SYNTHETASE

GTP production and release of HSCoA; production of SUCCINATE.

SUCCINATE DEHYDROGENASE

Production of FADH2 and FUMARATE.

FUMARASE

Hydration with an H2O molecule and one MALATE molecule production.

MALATE DEHYDROGENASE

OAA regeneration and NADH production.

KREBS CYCLE ENERGY BALANCE

THE NET BALANCE OF THE CYCLE IS:

Acetyl-CoA + 3 NAD^+ + FAD + GDP + Pi + 2 H_2O → CoA-SH + 3 (NADH + H+) + FADH2 + GTP + 2 CO_2

The two carbons of **Acetyl-CoA are oxidized to CO2**, and the energy is released:

-Chemical energy: **GTP** (substrate-level phosphorylation) (GTP + ADP→GDP + **ATP**) **NUCLEOSIDE DIPHOSPHATE KINASE**

-Reducing power (high-potential electrons): 3 **NADH y $FADH_2$** → **ELECTRON TRANSPORT CHAIN**

EACH MOLECULE OF ACETYL CoA WILL RESULT IN:

-1 GTP + 3 NADH + 3 H_+ + 1 $FADH_2$ + 2 CO2

THE MOLECULES WITH REDUCING POTENTIAL WILL ENTER IN THE OXIDATIVE PHOSPHORYLATION (OXPHOS):

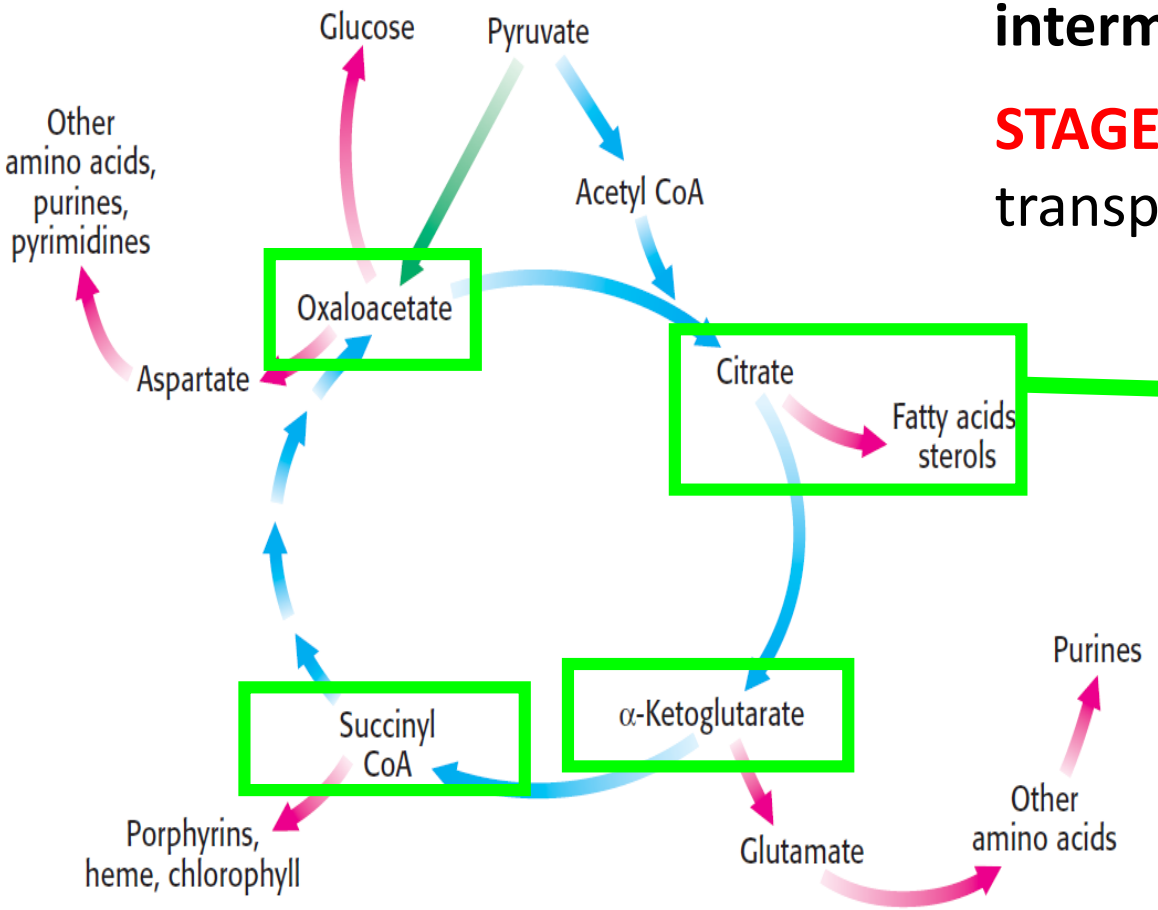
-NADH: 2.5 molecules of ATP (3 x 2.5 = 7.5)

-$FADH_2$: 1.5 molecules of ATP

-**Total:** 7.5 ATP + 1.5 ATP + 1 GTP = **10 ATP equivalents**

ANAPLEROTIC AND CATAPLEROTIC REACTIONS OF THE KREBS CYCLE

The Krebs cycle provides intermediates for the BIOSYNTHESIS of important molecules. This process is called CATAPLEROSIS.



CATAPLEROSIS produces a depletion of metabolic intermediates.

STAGE 1: Exit of the AcCoA from the mitochondria; transport of **citrate.**

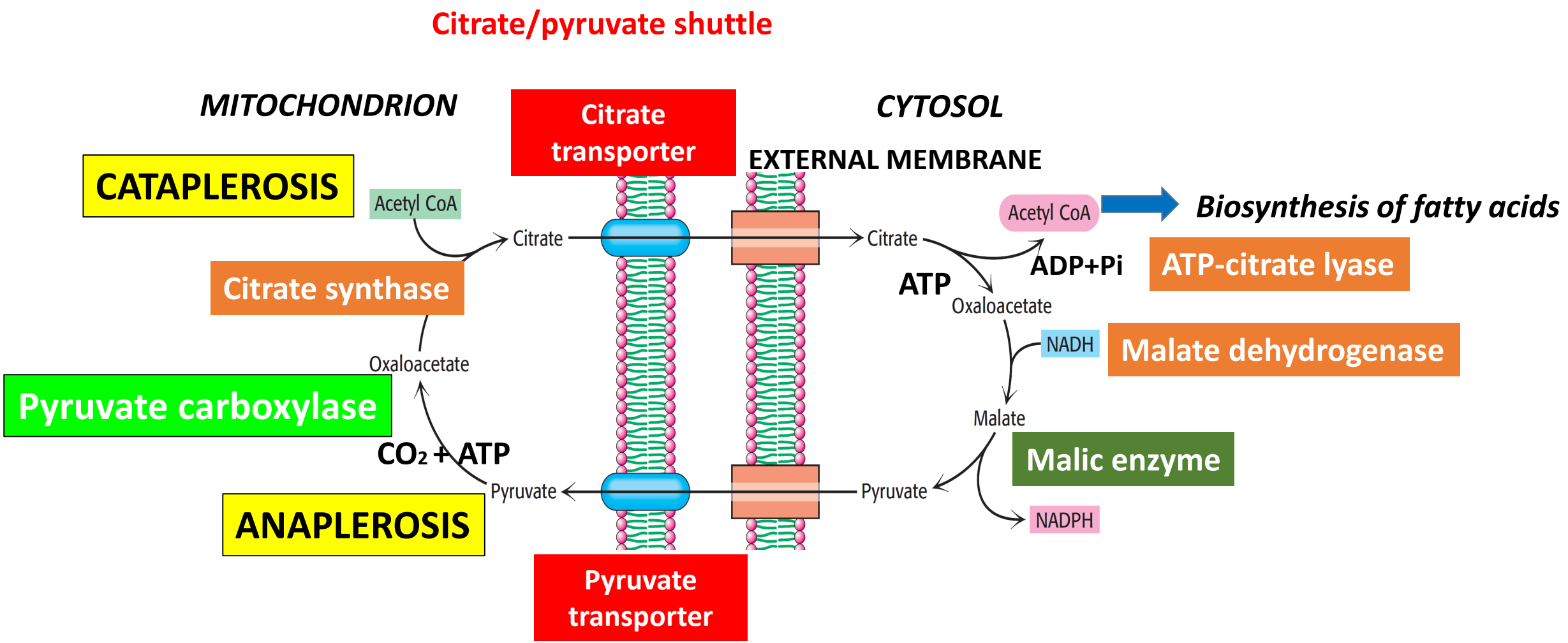
FATTY ACID BIOSYNTHESIS

Citrate/pyruvate shuttle

ANAPLEROTIC REACTIONS ARE NEEDED

Stryer, 7th ed., Biochemistry

FATTY ACID BIOSYNTHESIS. STAGE 1: AcCoA EXIT FROM THE MITOCHONDRIA



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ANAPLEROTIC REACTIONS OF THE KREBS CYCLE

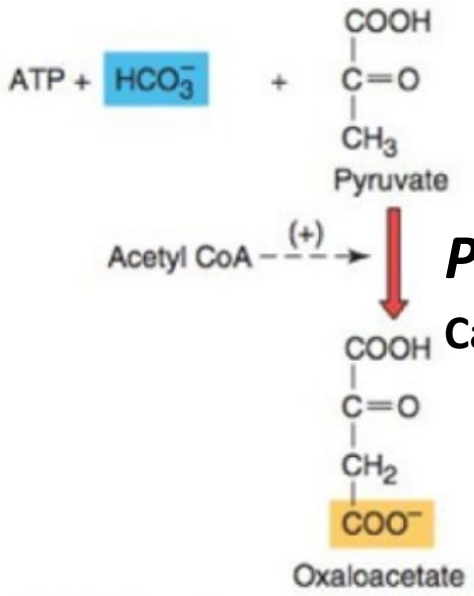
1. These are anabolic reactions that generate metabolic intermediates of the Krebs cycle.

Anaplerotic means the action of filling (from Greek).

2. There are four reactions:

1. Pyruvate carboxylase: this is activated by Acetyl-CoA (cumulative) when quantities of OAA are low. It is **most important** in anaplerotic reactions and is located in the mitochondria.

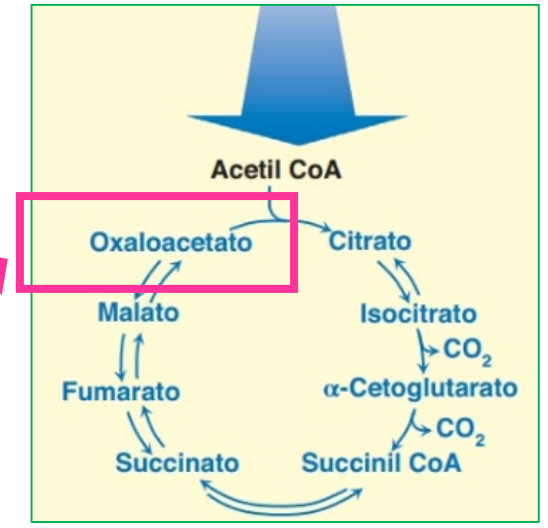
When AcCoA levels are very high, there is not enough OAA to CONDENSE and form CITRATE.
THE CYCLE DOES NOT WORK.



PYRUVATE CARBOXYLASE

Carboxylation of PYR using the coenzyme BIOTIN

PYRUVATE



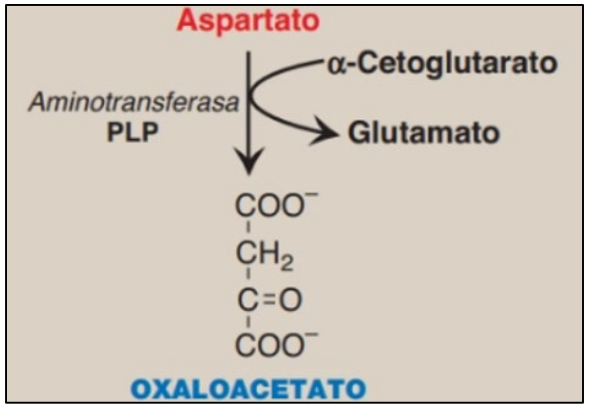
Devlin, Textbook of Biochemistry with Clinical Applications, 7th ed.

Ferrier, Biochemistry, 7th ed., Lippincott

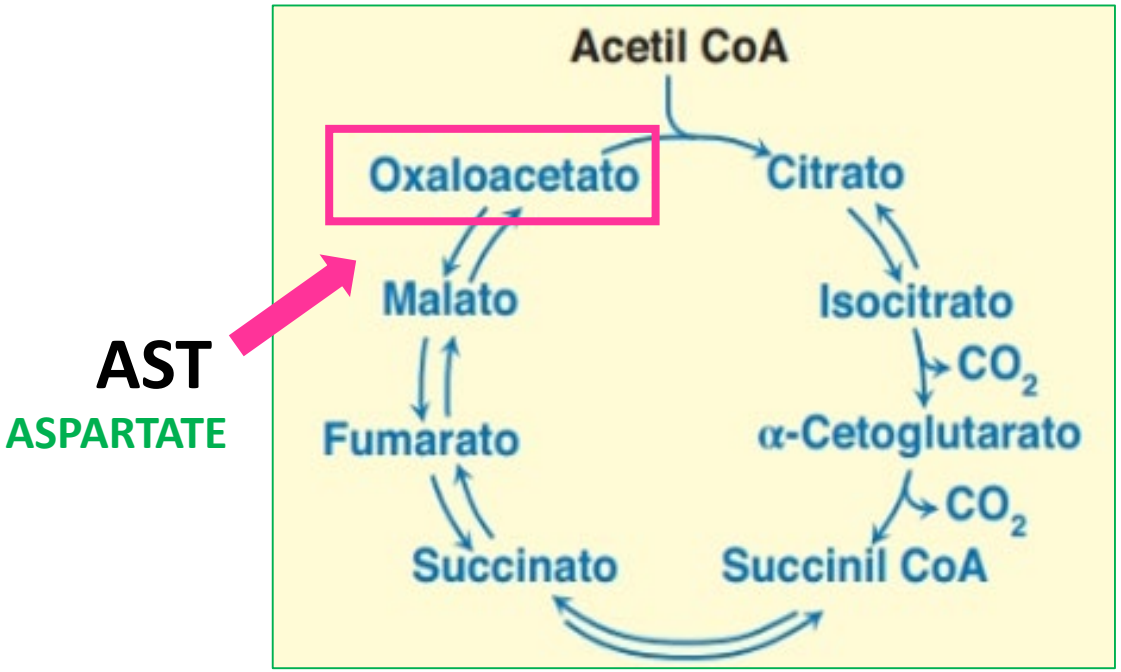
ANAPLEROTIC REACTIONS OF THE KREBS CYCLE

2. Aspartate aminotransferase (AST):

Transamination from aspartate to α-ketoglutarate.



(REMOVAL OF AMINO GROUPS FROM ASPARTATE)

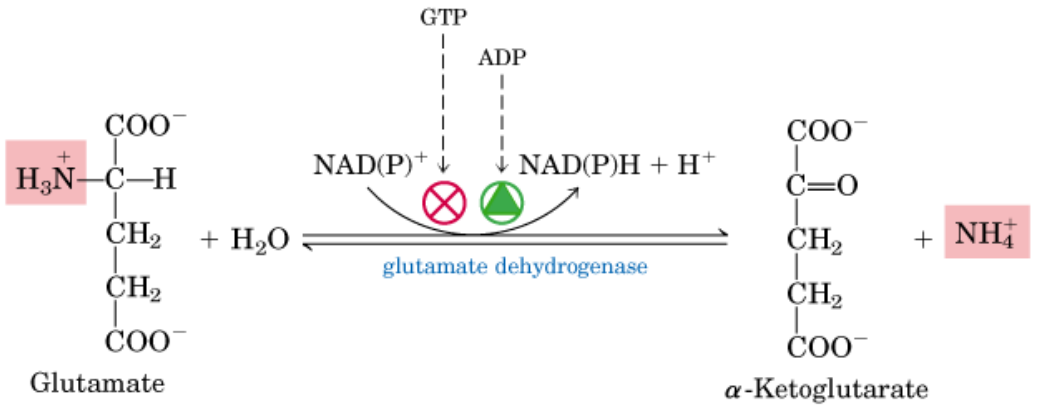


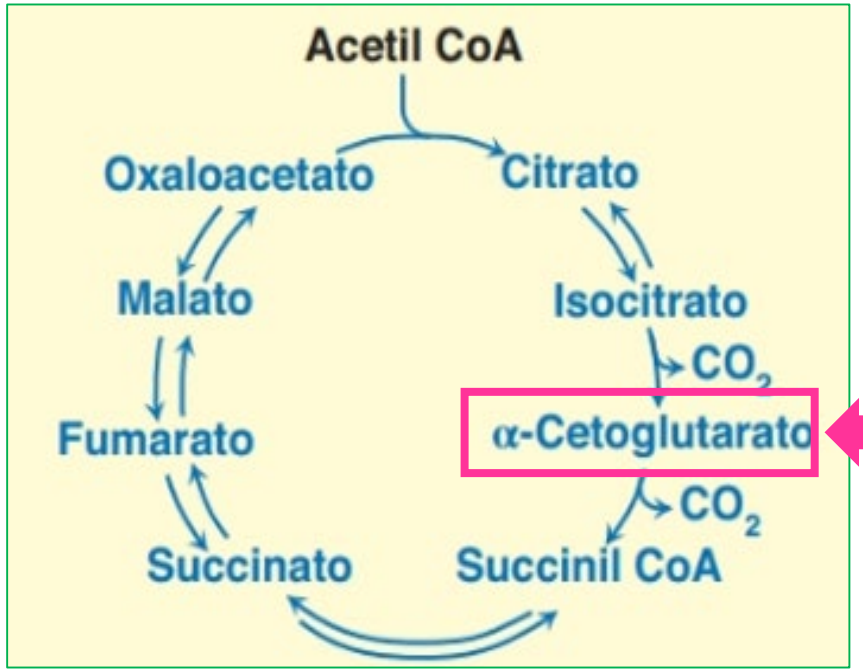
Ferrier, Biochemistry, 7th ed., Lippincott

ANAPLEROTIC REACTIONS OF THE KREBS CYCLE

3. Glutamate dehydrogenase: Oxidative deamination from glutamate.

(REMOVAL OF AMINO GROUP FROM GLUTAMATE)





GDH

GLUTAMATE

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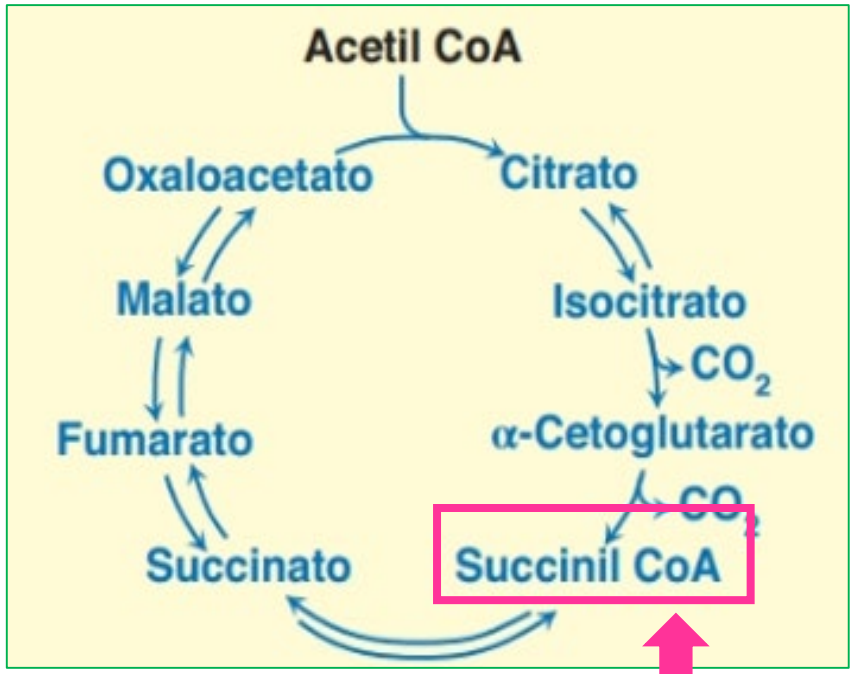
ANAPLEROTIC REACTIONS OF THE KREBS CYCLE

4. Methyl malonyl-CoA mutase and propionyl CoA carboxylase:

β OXIDATION OF ODD-CHAIN FATTY ACIDS.



INTERMEDIATES of the β oxidation fatty acids

Methyl Malonyl CoA and Propionyl CoA

Ferrier, Biochemistry, 7th ed., Lippincott

REGULATION OF THE KREBS CYCLE

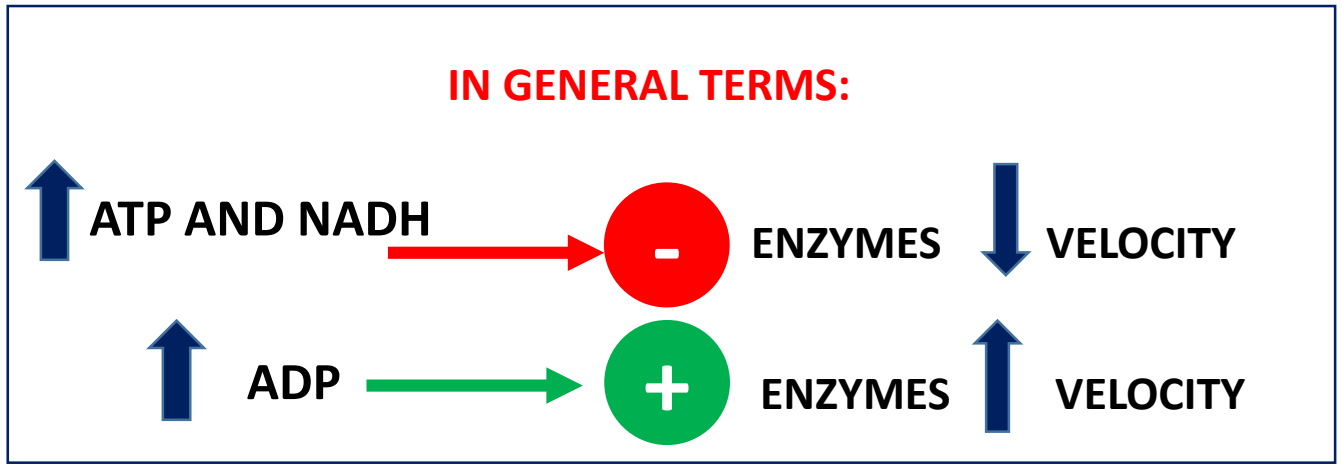
The most important regulatory enzymes (ΔG<0):

1. Citrate synthase: inhibition by the final product, citrate.

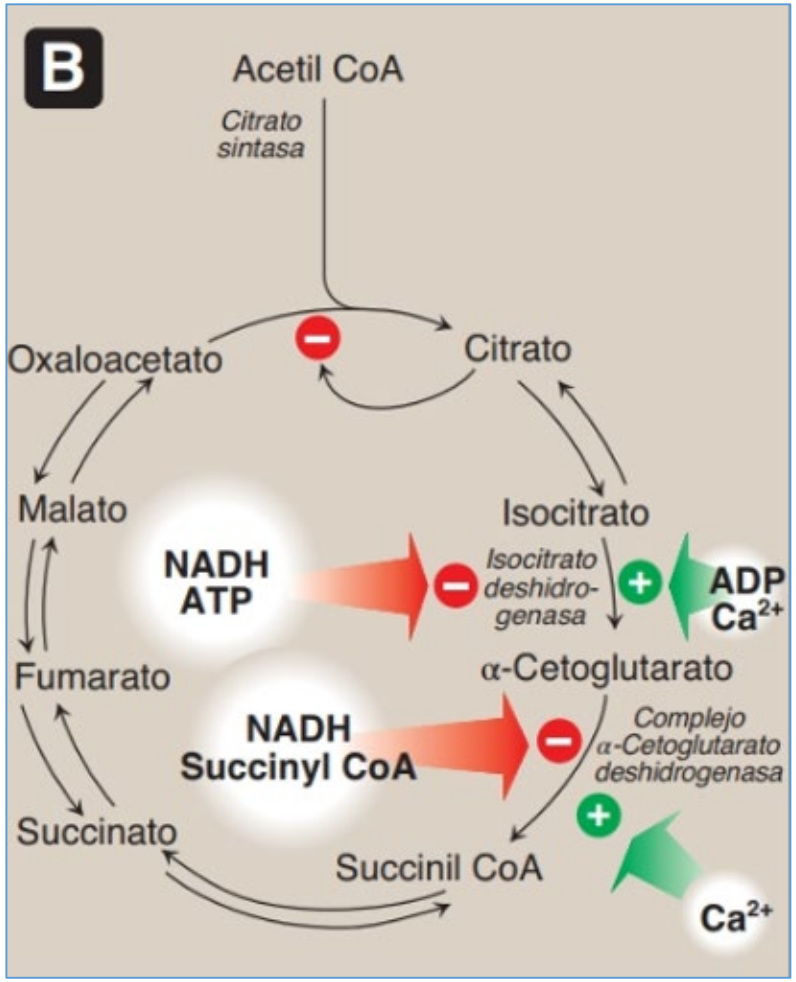
2. Isocitrate dehydrogenase: inhibition by NADH (competes with the NAD+) and ATP (allosteric); activation by ADP (allosteric), Ca2+.

3. α-ketoglutarate dehydrogenase complex: inhibition by NADH and SuccinylCoA (products); **activation by Ca2+.**

Ca2+, a secondary messenger of cellular activation.



Regulation of the Krebs cycle



Ferrier, Biochemistry, 7th ed., Lippincott

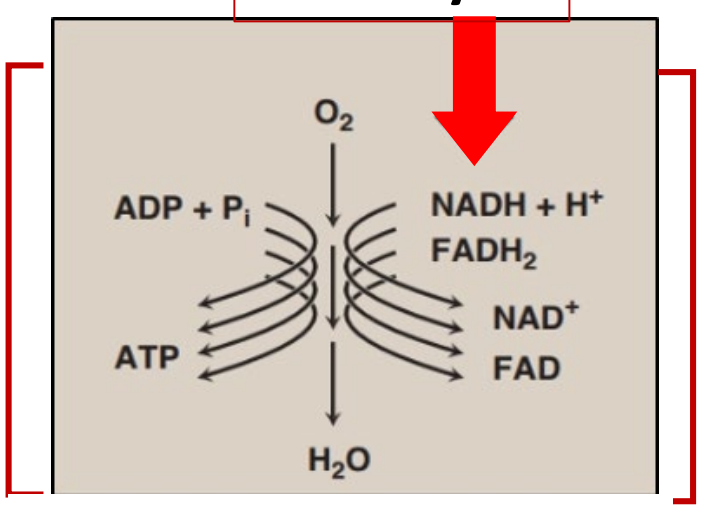
ELECTRON TRANSPORT CHAIN AND ATP SYNTHESIS
OXIDATIVE PHOSPHORYLATION (OXPHOS)

MITOCHONDRIAL MATRIX: oxidation of pyruvate, amino acids and fatty acids (by β-oxidation) and the Krebs cycle.

FATTY ACID OXIDATION (AcCoA)
CARBOHYDRATE OXIDATION (PYRUVATE/AcCoA)
OXIDATION OF AAS (ASPARTATE-OAA AND GLUTAMATE-αKETO)

Krebs cycle

ATP SYNTHESIS



OXIDATIVE PHOSPHORYLATION

The **ETC** is located in the **inner mitochondrial membrane** and is the common pathway.

Electrons derived from energetic molecules flow into oxygen (O2), reducing it to H2O.

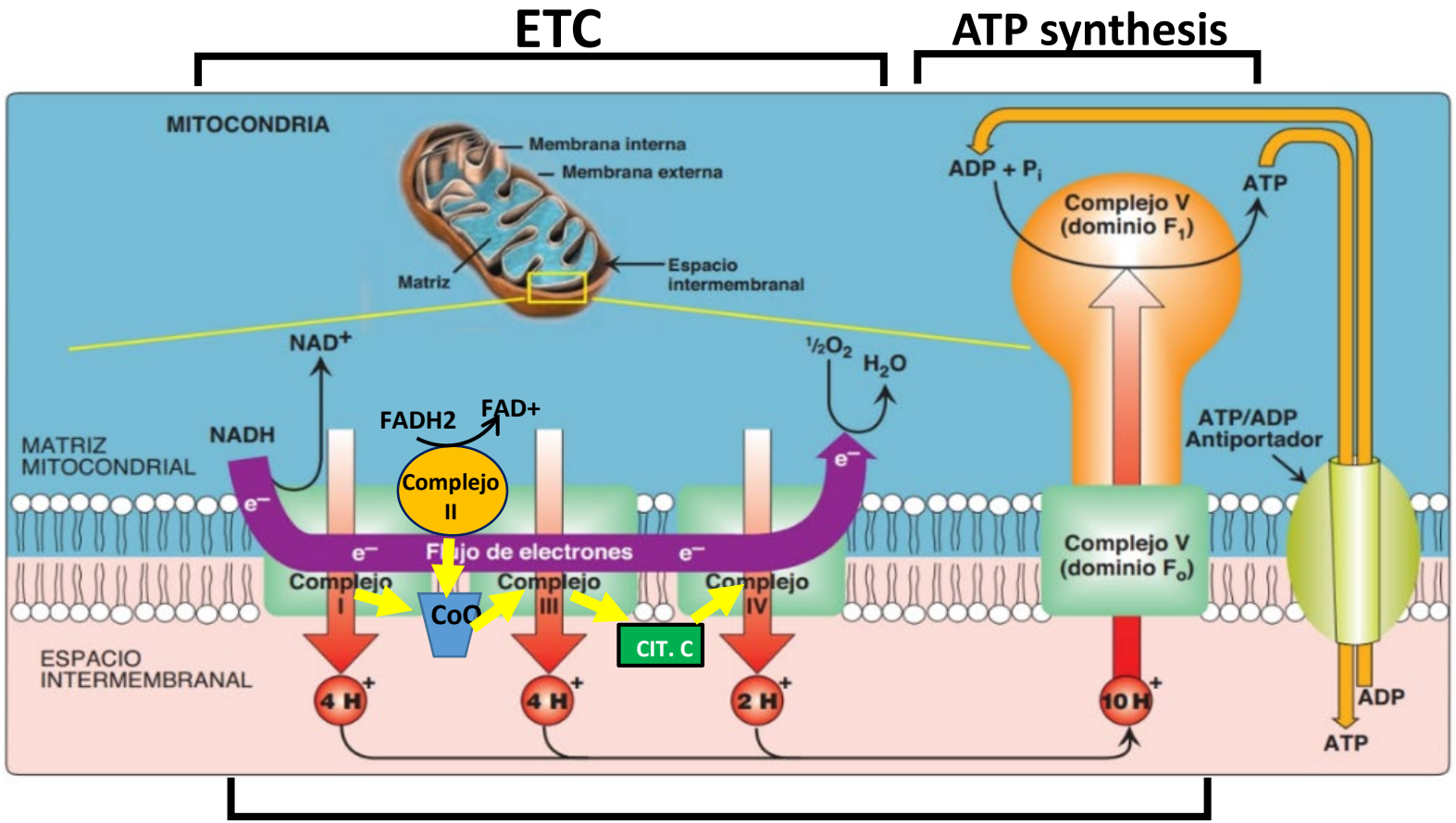
Transport of electrons between complexes with oxidoreduction centers.

Ferrier, Biochemistry, 7th ed., Lippincott

ELECTRON TRANSPORT CHAIN AND ATP SYNTHESIS

The flow of electrons from NADH and FADH2 is carried out by oxidation-reduction reactions.

As electrons flow, they **lose energy** that is used to **pump H+** into the intermembrane space.



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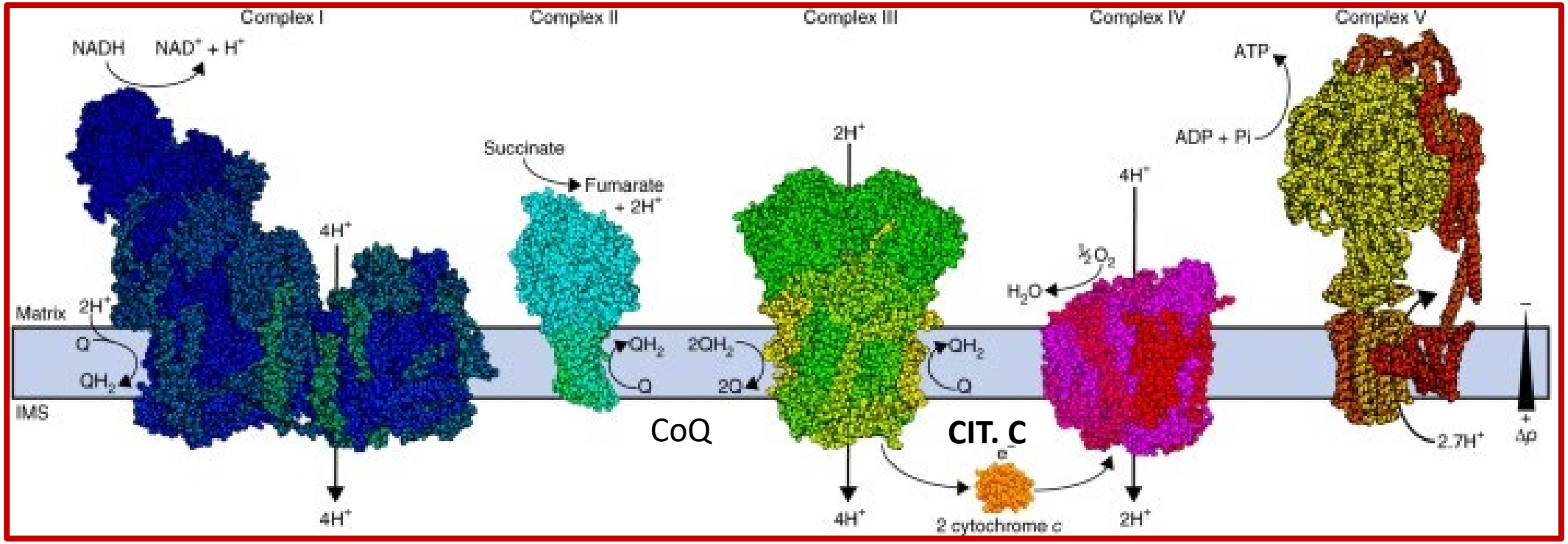
ELECTRON TRANSPORT CHAIN AND ATP SYNTHESIS: I-V COMPLEXES



NADH DH (Q OXIDOREDUCTASE)

DH SUCCINATE (Q OXIDOREDUCTASE)

CYTOCHROME BC1 (Fe) Cytochrome c reductase

CYTOCHROME A A3 (Cu) Cytochrome c oxidase

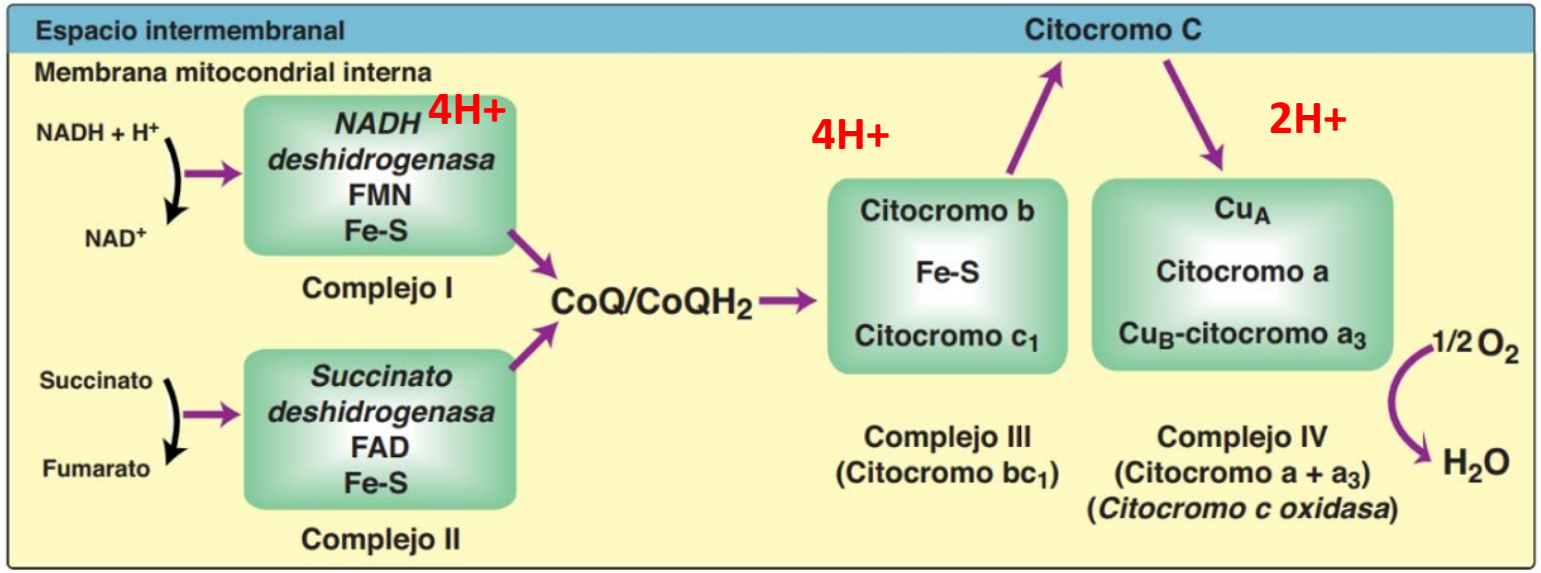
ELECTRON TRANSPORT CHAIN: I-IV COMPLEXES

COMPLEX I is a complex NADH oxidoreductase (DEHYDROGENASE): the free H+ plus the hydride ion (2 electrons + 2 H+) from NADH are transferred to the Complex **Coenzyme Q.** The flow of the e- causes the **translocation of 4H+.**

COMPLEX II: DOES NOT TRANSLOCATE H, SUCCINATE Q OXIDOREDUCTASE OR SUCCINATE DH generates FADH2; the e- from FADH2 move by a FeS (**Iron–sulfur**) protein to the **Coenzyme Q.**

COMPLEX III: CYTOCHROME BC1 receives e- from **Coenzyme Q** and transfers them to cytochrome c (intermembrane space); **4H+ are pumped.**

COMPLEX IV: with cytochromes a + a3 that receive the e- from cytochrome c and transfer the electrons to the O2 in order to reduce it. **Pumps 2H+.**



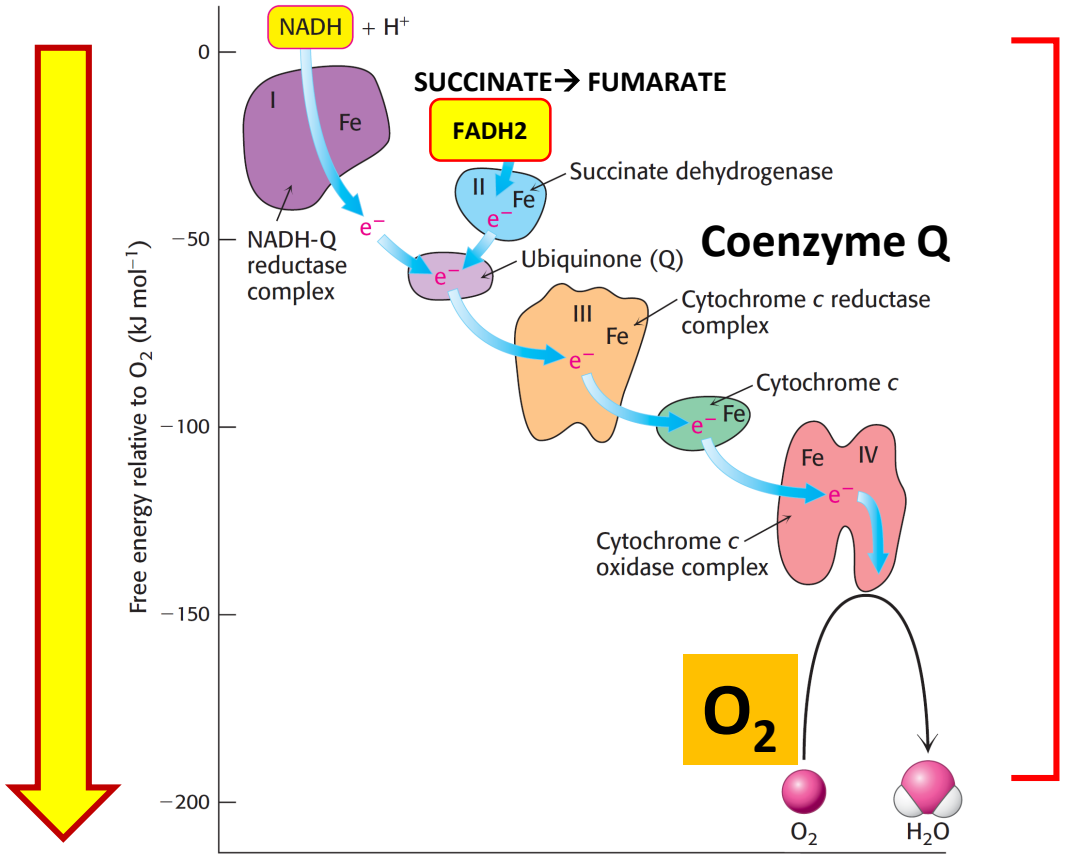
Ferric (Fe3+) to ferrous (Fe2+) form

Ferrier, Biochemistry, 7th ed., Lippincott

ELECTRON TRANSPORT CHAIN: DECREASE IN FREE ENERGY

FREE ENERGY

ΔG<0



Oxide-reduction reactions in which e- lose energy.

The energy released by the transfer of e- results in the **pumping of H+ against gradient** into the intermembrane space.

This pumping **establishes an electrochemical gradient.**

Generation of H2O by the reduction of O2.

PROTON GRADIENT

PROTON GRADIENT FORCE: the H+ will be returned to the MATRIX (exergonic process) used to generate ATP (endergonic).

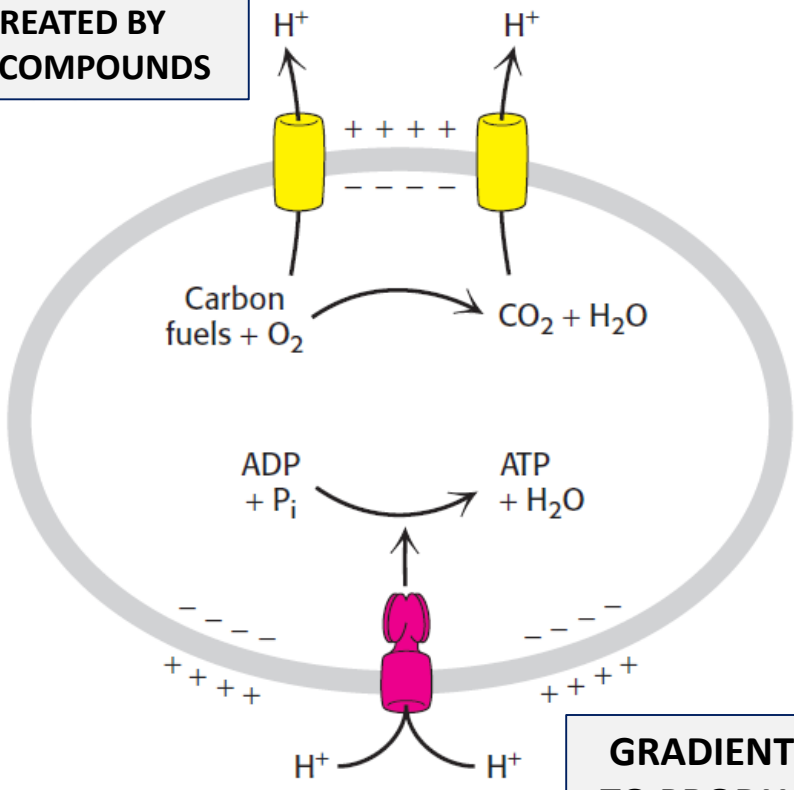
PRODUCTION OF ATP COUPLED TO ION GRADIENT

ELECTROCHEMICAL POTENTIAL in the form of proton gradient is an effective mechanism for storing free energy.

Oxidation of fuel molecules, oxidative phosphorylation and photosynthesis (ETC) create ion gradients that are used for the synthesis of most ATP in cells (up to 90%).

Ion gradients are versatile mechanisms for coupling thermodynamically unfavorable reactions to favorable ones.

GRADIENT CREATED BY OXIDATION OF COMPOUNDS



GRADIENT USED TO PRODUCE ATP

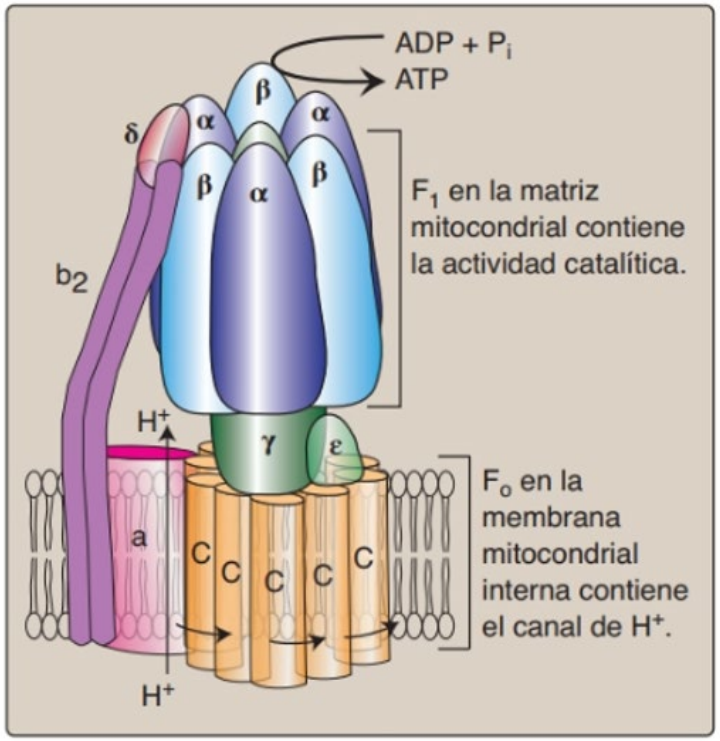
EXAMPLE: The electrochemical potential of a gradient can be used to transport nutrients such as sugars and amino acids into cells.

ATP SYNTHESIS

PROTON GRADIENT generates an ELECTROCHEMICAL POTENTIAL by the difference in concentration of H+ for transport in favor of gradient.

The H+ will be returned to the MATRIX (exergonic process) used to generate ATP (endergonic).
The H+ gradient will produce the synthesis of ATP.

ATP SYNTHASE/COMPLEX V



Ferrier, Biochemistry, 7th ed., Lippincott

ATP synthase (F0F1 ATPase or complex V)
REQUIRES 3-4 H+ by ATP.

The chemiosmotic coupling hypothesis (1961) was developed by Peter D. Mitchell, who received the Nobel Prize in 1978.

https://www.youtube.com/watch?v=LQmTKxI4Wn4

REGULATION OF OXIDATIVE PHOSPHORYLATION

-The rate of oxidative phosphorylation depends on **the cell's energy needs**.
-The most important regulator is ADP which is related with the metabolic energy needs.

ADP regulation is called **RESPIRATORY CONTROL**. ATP synthase activity is required for coupling to work.

The consumption of O2 by the mitochondria depends on the ADP present.

Catabolic pathways have a regulation coupled to oxidative phosphorylation by the cellular energy charge (EC).

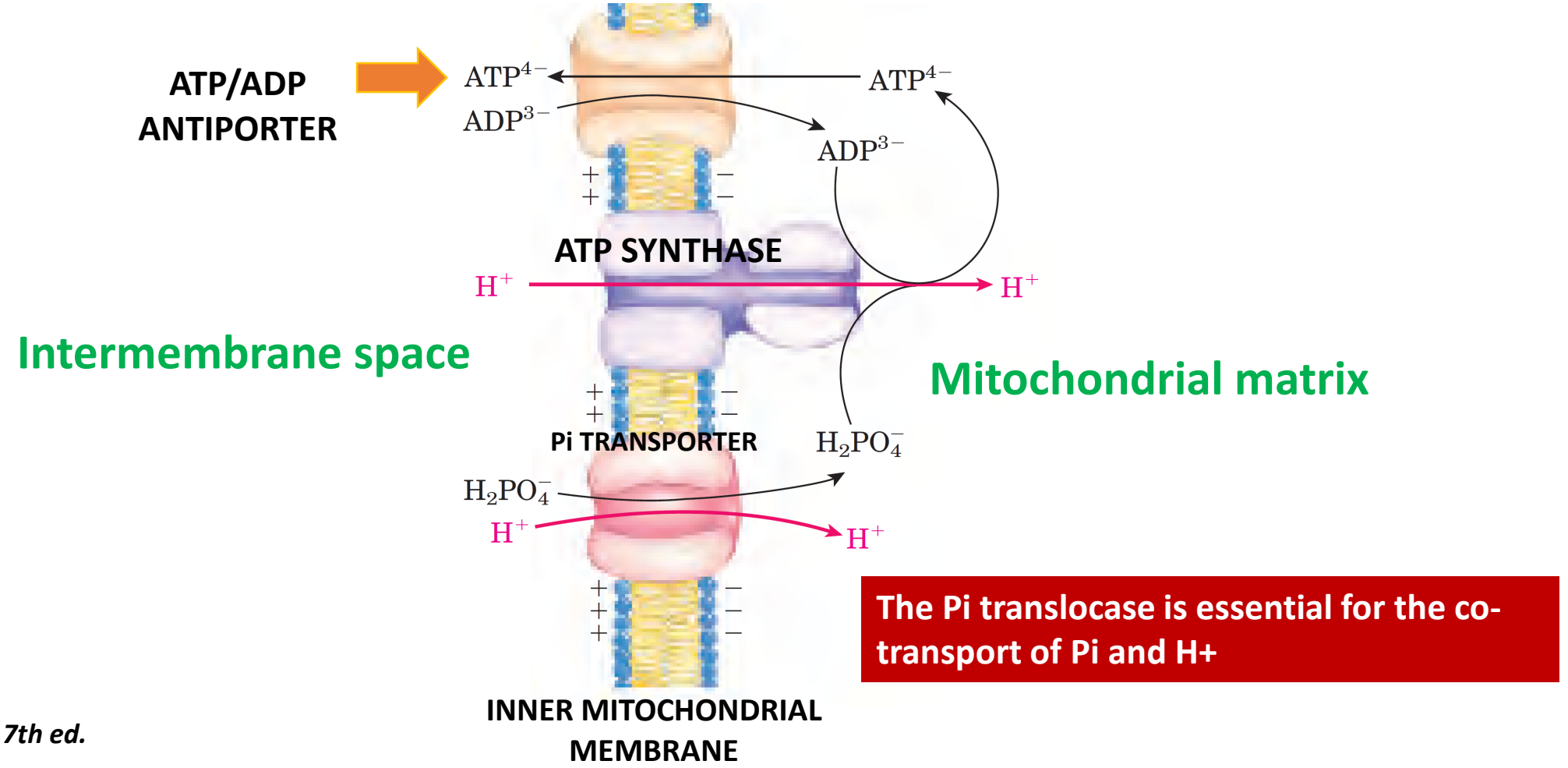
The EC in most cells ranges from 0.80 to 0.95.

Cellular energy charge

$$\frac{([ATP] + [ADP]/2)}{([ATP] + [ADP] + [AMP])}$$

TRANSPORT OF ATP TO CYTOSOL: ATP TRANSLOCASE

-The mitochondrial inner membrane contains distinct transport systems. FOR ATP/ADP AND Pi.
-One of the most important of these is the **ATP-ADP translocase**, which is also known as **ADENINE NUCLEOTIDE TRANSLOCASE.**
-This enables strongly charged ATP and ADP molecules to be mobilized across the inner membrane.



The Pi translocase is essential for the co-transport of Pi and H+

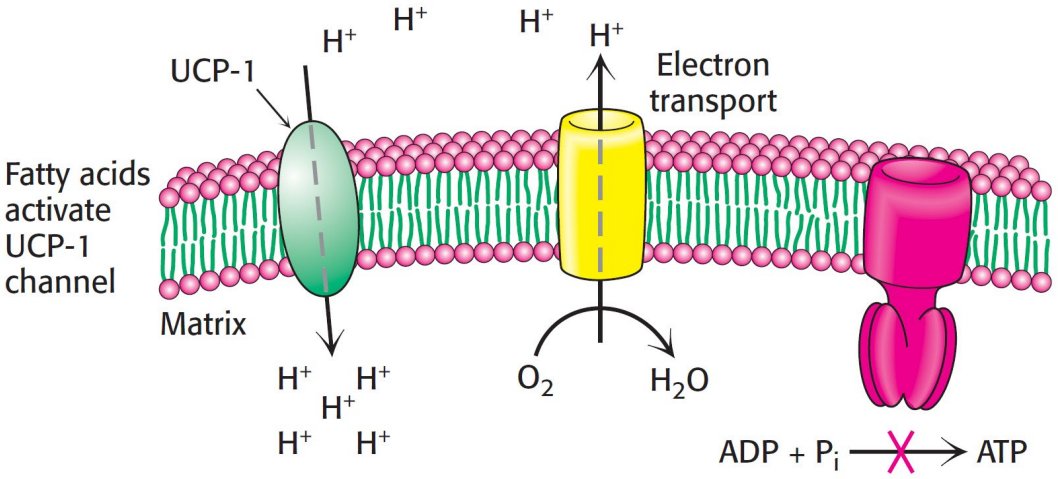
Biochemistry, Lehninger, 7th ed.

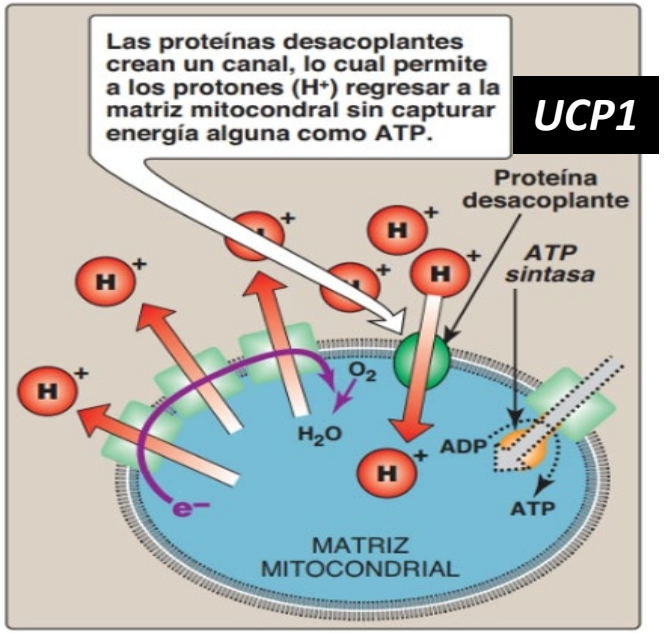
DECOUPLING OXIDATIVE PHOSPHORYLATION TO PRODUCE HEAT

Protein decoupling by UCP1 (**thermogenin, uncoupling protein**): inner mitochondrial membrane of mammals IN BROWN OR BROWN FAT.

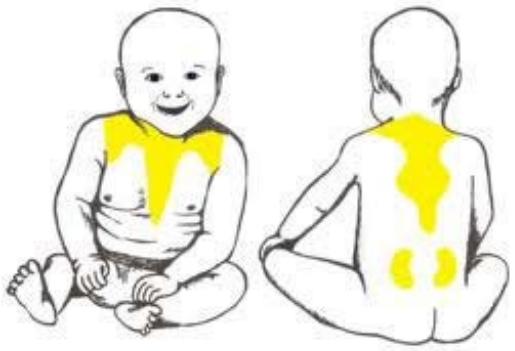
Transport H+ and energy is used in thermogenesis. Induced by catecholamines (**ADRENALINE**), whose production is stimulated by cold in the hypothalamus.

TEMPERATURE DROP: release of hormones leads to the production of free fatty acids from triacylglycerols, which in turn activates thermogenin, UCP1.

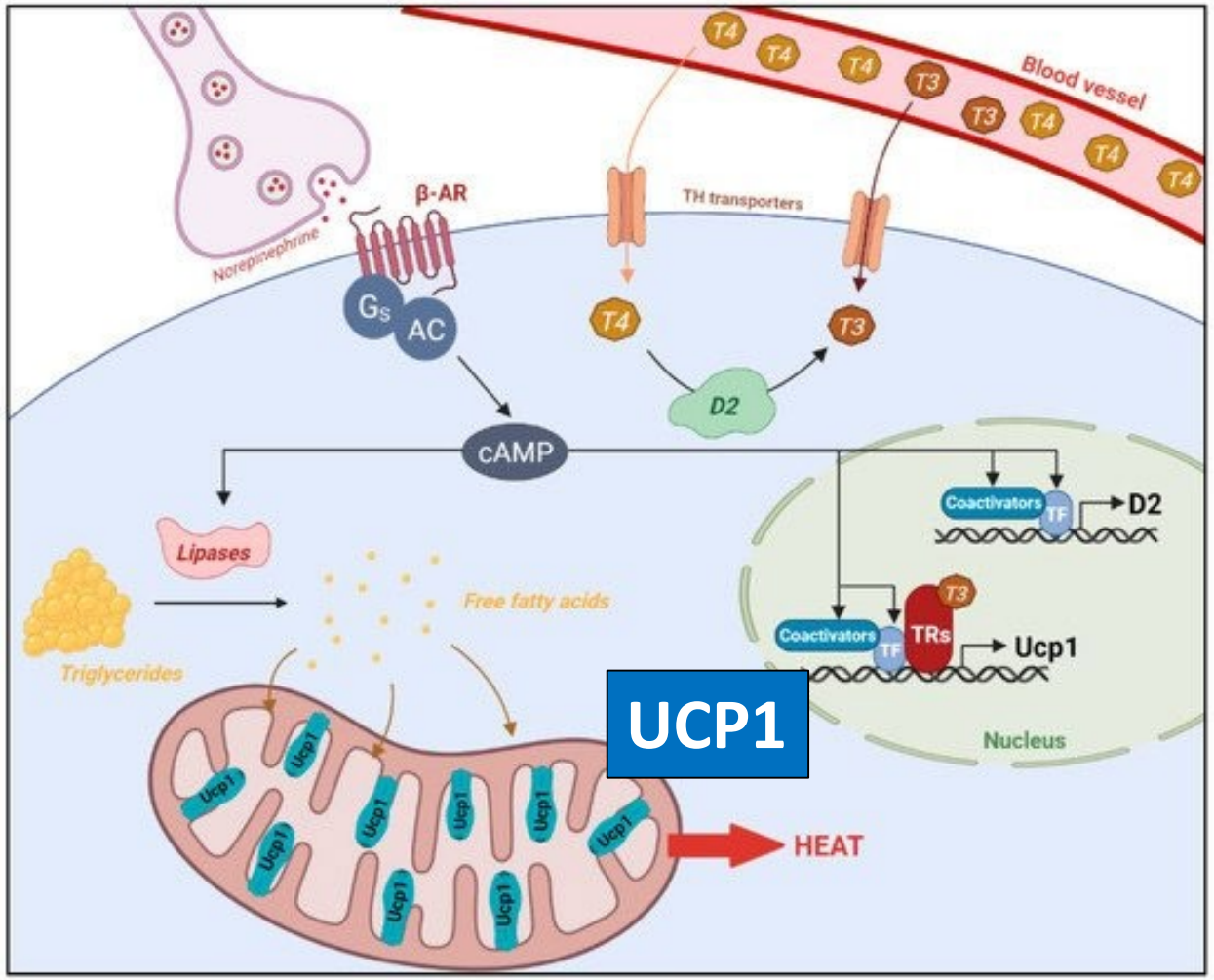




Protein decoupling by UCP1 breaks the proton gradient.



CONTROL OF THERMOGENESIS IN BROWN ADIPOSE TISSUE BY NORADRENALINE: RECEPTORS β-ADRENERGIC AND THE PROTEIN UCP1 (UNCOUPLED PROTEIN 1)



Sympathetic neurons
(TEMPERATURE DROP SIGNAL)

↓

NORADRENALINE (ADRENAL GLAND)

↓

β-ADRENERGIC RECEPTORS: GPCR, AC, cAMP

↓

INCREASED EXPRESSION OF FREE UCP1 AND FA

FREE FA: β-oxidation TO GENERATE ENERGY (AcCoA).

UCP1: decouples ATP production from respiration (from the ETC), which increases mitochondrial activity and HEAT PRODUCTION.

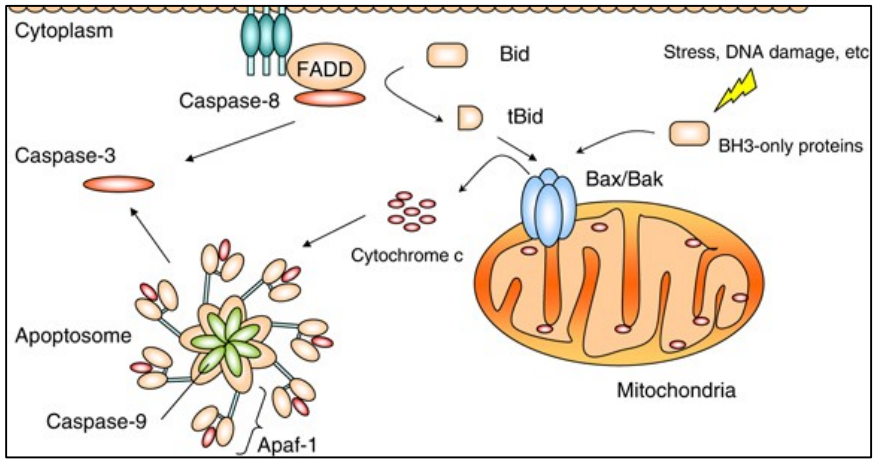
Cells **2021**, *10*(6), 1327; https://doi.org/10.3390/cells10061327

MITOCHONDRIA PLAY A KEY ROLE IN APOPTOSIS, OR PROGRAMMED CELL DEATH

In the course of development, or in cases of significant cell damage, individual cells within multicellular organisms enter into **PROGRAMMED CELL DEATH, OR APOPTOSIS**.

Mitochondria act as a **control center** that regulates **APOPTOSIS, a form of cell death:**

1. **APOPTOSIS** INCREASES THE **PERMEABILITY** OF THE OUTER MEMBRANE OF THE MITOCHONDRIA.
2. **CYTOMCHROME C** LEAVES THE MITOCHONDRIA AND ACTIVATES ANOTHER PROTEIN, APAF-1, WHICH LEADS TO THE APOPTOSOME.
3. THE APOPTOSOME INITIATES A PROTEASE/CASPASE CASCADE.
4. A CASPASE-ACTIVATED DNase CLEAVES THE CELL'S GENETIC MATERIAL.

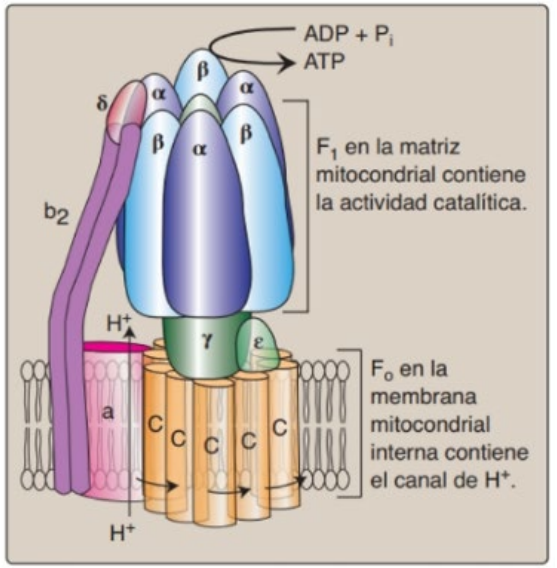


***Oncogene* volume 27**, pp 6194–6206 (2008)

INHIBITION AND PATHOLOGIES RELATED TO OXIDATIVE PHOSPHORYLATION

1. Oligomycin (streptomyces bacteria) is an antibiotic that binds to the F0 domain of ATP synthase. It closes the channel and prevents H+ from entering the matrix.

2. Defects in HEREDITARY oxidative phosphorylation:
-these are more likely as a result of alterations in hereditary mtDNA.



THE MOST-AFFECTED TISSUES will be those with the highest ATP requirements (CNS, skeletal and cardiac muscles, and liver).

EXAMPLES:
MITOCHONDRIAL MYOPATHIES: MUSCULAR ALTERATIONS
LEBER'S HEREDITARY OPTIC NEUROPATHY: neuroretinal and optic nerve damage.

3. Defects in NON-HEREDITARY oxidative phosphorylation:
- a decrease in ATP production occurs **in PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE.**

4. Generation of reactive oxygen species (ROS):
-the final acceptor of e- is the O2 to generate H2O.
-however, a small number of toxic molecules are produced (**the oxygen radicals: O2-, OH**).
-cellular defenses against ROS are SUPEROXIDE DISMUTASE AND GLUTATHIONE PEROXIDASE. These defensive enzymes may decrease their activity with aging.

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STUDY OF METABOLIC PATHWAYS: IMPORTANT ASPECTS

Why? To clearly understand the purpose of the pathway, i.e. which products it aims to obtain, including their performance and energy balance. **PURPOSE**

Where? ORGANELLES AND TISSUES. Consider **LOGICAL COMPARTMENTALIZATION** at all levels: organs/tissues, cellular compartment(s) involved.

How is it produced? What does it need? And what does it generate?

First approach. Keep clearly in mind the pathway's **"GENERAL STRATEGY"** for achieving its objectives, i.e., in general terms, how does the pathway achieve its objectives? Then analyze in greater detail how the pathway develops. This does not involve knowing formulas but the pathway's intermediaries and the enzymes, especially those involved in the regulatory steps.

When? FASTING/FEEDING/HORMONAL REGULATION, ETC.

REGULATION It is very important to clearly understand under what conditions the pathway will work, i.e., how it is regulated. Consider numerous aspects relating to the pathway's key regulatory enzymes and how these are controlled.

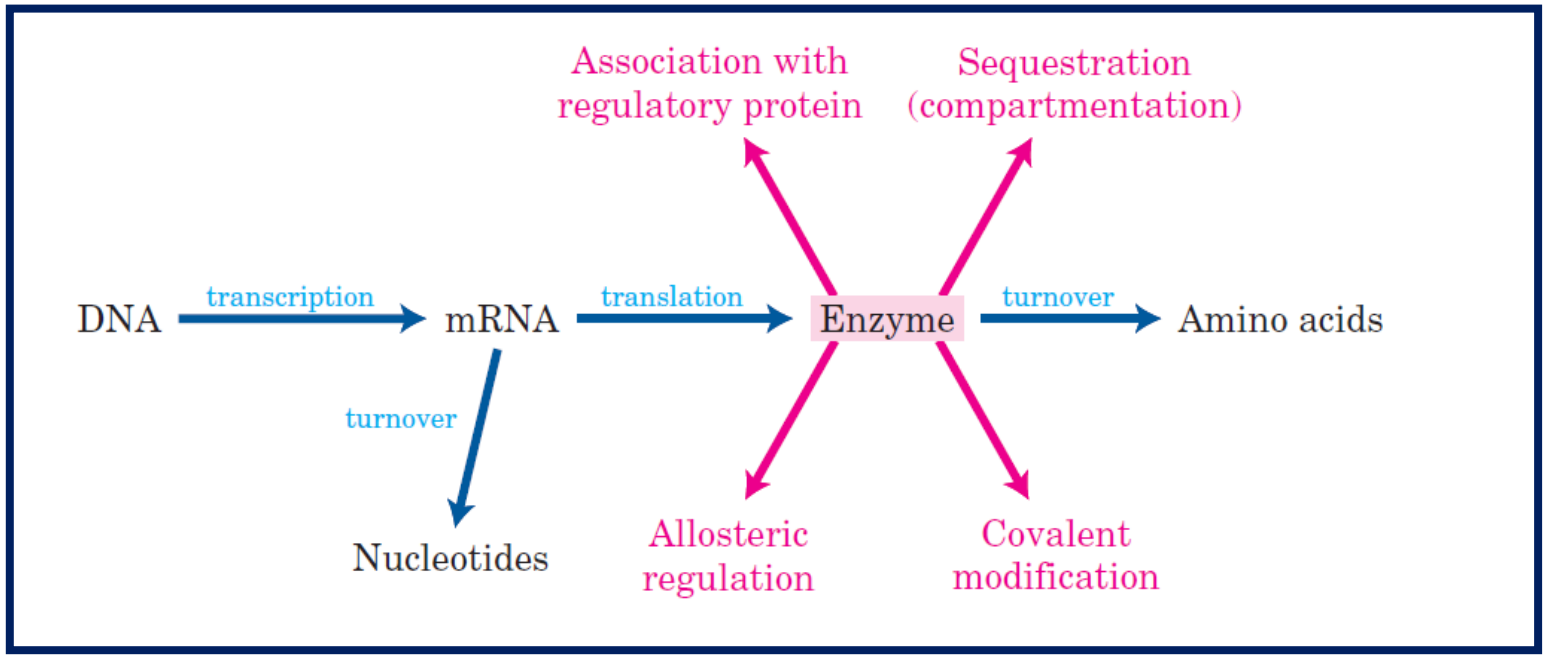
- In the short term (allosteric regulation, substrates or products, isoenzymes, by phosphorylation and dephosphorylation).
- In the long term (regulation of the amount of enzyme), effects that include hormonal action (carbohydrates, insulin, glucagon and adrenaline).

Slow response:

1. Through the regulation of the enzyme synthesis.
2. Through the regulation of the enzyme degradation.

Quick response:

-Reversible or irreversible covalent modifications: phosphorylation, synthesis as zymogens (inactive forms).



PINK: MINUTES, SECONDS **BLUE: HOURS**