Physiology
Sheet **No.**

15

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بسم الله الرحمان الرحيم, اللهم إني أسألك فهم النبيين وحفظ الملائكة المقربين، اللهم اجعل لساني عامراً بذكرك وقلبي بخشيتك، وسري بطاعتك، إنك على كل شيء قدير.

Mechanisms of Hormone Action

The response to any hormones in the cell depends on the type of hormone and the target cell, as different target cells have different effects.

Also, the receptor themselves have a different response to hormones.

So from the groups that we talk about in the previous lectures, we talk about the Lipid-soluble & Water-soluble these are the 2 main groups that determine the location of the receptor.

Lipid soluble hormones: have different options than water-soluble hormones, and the most important one is that they can bind to intracellular receptors (inside the cell) in the cytosol or inside the nucleus, although they sometimes bind to cell surface receptors.

Water-soluble hormones: only have the option to bind to the plasma membrane receptor because they can't cross the membrane, in this way they activate a second messenger {which will transfer the signal inside the cell as the hormone physically doesn't enter the cell}. And what specializes in this type is the capability of amplification of the small signal on the surface of the receptor (as we studied before).

Responsiveness of target cell depends on:

1- Hormone's concentration, sometimes the response is totally different when we have different concentration of the hormones or there must be a specific concentration of the hormone to get a sufficient response.
2- Abundance of target cell receptors

Receptors

Specific membrane proteins which can recognize and bind to corresponding ligand molecules {key and lock match, chemical bond between them}, become activated and transduce a signal to the next signaling molecule.

Like the conductors Cell surface receptors can be **Glycoprotein** (proteins with oligosaccharide chains attached to them) **or Lipoprotein** (lipid-protein complex) **or protein** (without modification). There is variability between it's structure, they are found as integral proteins in the cell membrane.

***Specificity:** The "specificity" of a ligand for a receptor is a description of how favorable the binding of the ligand for the receptor is compared with its possible binding to other types of receptors that may also be present.

-أن يكون الارتباط بين المستقبل والمادة الكيميائية اقوى ارتباطاً من ارتباطه بمستقبل آخر

***Affinity:** "Affinity" simply refers to how strong the binding is between receptor and certain ligand (we express it mathematically as judged by K association or K dissociation and ΔGo).

"High affinity" refers to very strong binding (large negative ΔGo and a very small Kd) And the concentration needed for the ligand to bind to the receptor is small as the affinity is high.

Dissociation constant(Kd): refers to the concentration of a ligand that is required to occupy the receptors by a certain ligand.

"Low affinity" means that more concentration of the ligand is needed to occupy the receptors (because of the weak binding) and thus Kd is high and the opposite is said for high affinity.

Association constant is also called “affinity” constant,

Dissociation constant is also called “binding “constant.

Receptors determine response

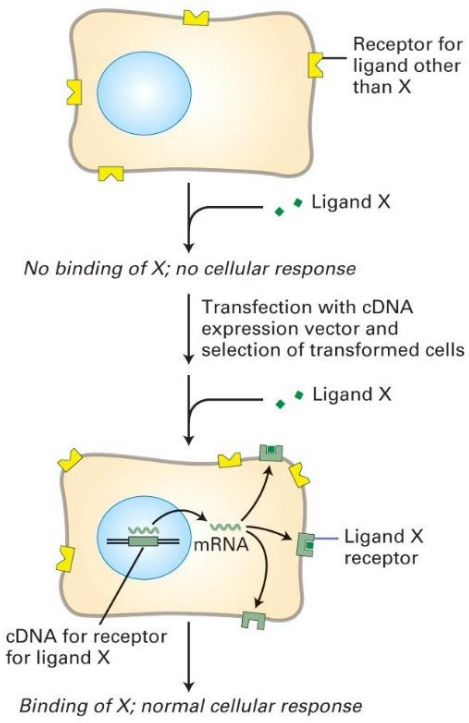
No receptor - no response

In this figure, we have a cell that has receptors for a ligand other than X.

Ligand X can’t affect this cell because it can’t bind to any receptors (because its specific receptors are not found on the surface of this cell).

Transfection of this cell with a DNA expression vector (basically we insert a gene that is transcribed and translated to produce the ligand X receptors) and this will cause the cell to be affected (response) by ligand X binding to its receptors.

When we don’t have a specific receptor for a hormone in a certain cell, that hormone would not affect that cell.



This figure shows the importance of the specificity of ligand-receptor binding.

ligand

A small molecule that binds specifically to a larger one (receptor), {not a must to be a receptor it can bind for example to an enzyme and here we call it a substrate}; for example, a hormone is a ligand for its specific protein receptor.

- **Membrane receptors**

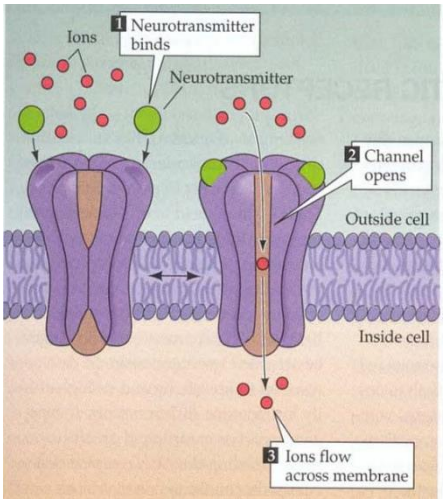
  Membrane Glycoprotein or sometimes lipoproteins

The only option for the water-soluble ligand

- **Intracellular receptors**

  Can be in Cytosol or Nuclei

  DNA binding protein

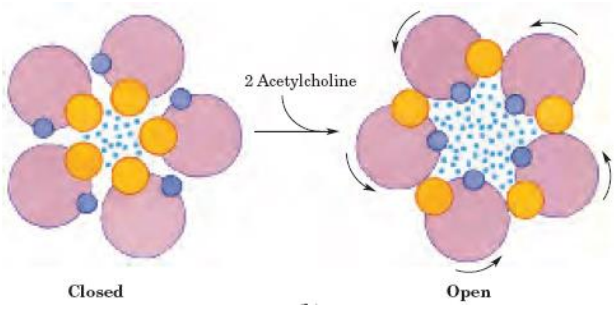


membrane receptors

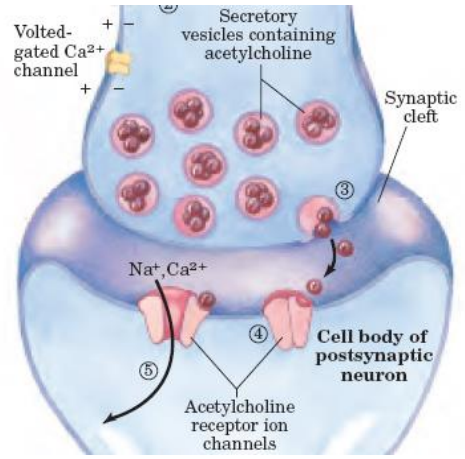
1- Ligand-gated ion channels type (cyclic receptor)

ligand→receptor→ion channel open or close

In this example, when the neurotransmitter (acetylcholine) bind to the **Ligand-gated ion channel** cause action which can be either opening or closing the channel which allows the ions to flow across the membrane.



Example of neurotransmitter binding to the channel causing it to open and allow the ions to flow.



Three major classes of surface receptors for signaling:

A. **Ion-channel linked receptors**.

B. **G-protein linked/coupled receptors**. (**GPCR**)

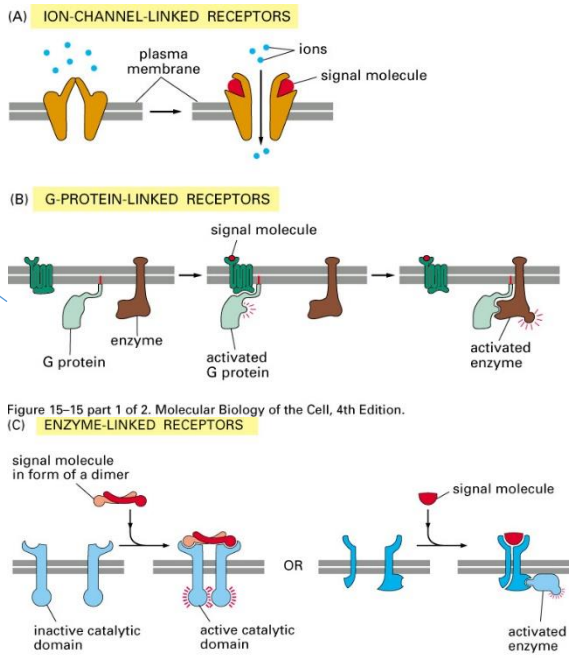


Figure 15–15 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Plasma membrane receptor, classified as transmembrane/integral protein.

Has a unique structure of 7 transmembrane helical domains.

Linked to a G-protein, when the ligand binds to the receptor the G-protein will interact with the receptor which causes activation of the G-protein, then the G-protein will go to its effector.

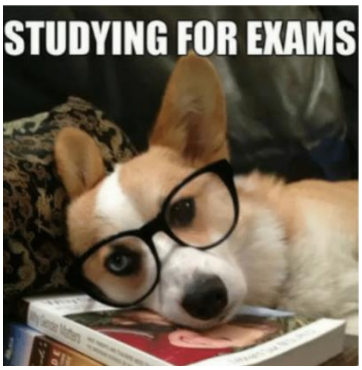
<u>The effector can be an enzyme, or a channel.</u>

If it is an enzyme, it will be activated and produce product from substrate, and this product can be the second messenger which will carry the signal inside the cell which will effect on different proteins inside the cell and get the affect of the hormone.

C. **Enzyme-linked receptors**:

They are linked to enzymes either the enzymatic activity is within the receptor we call it intrinsic.

Or the enzymatic activity in another enzyme binds to the receptor causing it to be activated.



♡ Don't give up♡

G-protein -coupled receptors (GPCR):

largest family of cell surface receptors; present in all eukaryotes; ex: adrenergic receptors, opioid receptors.

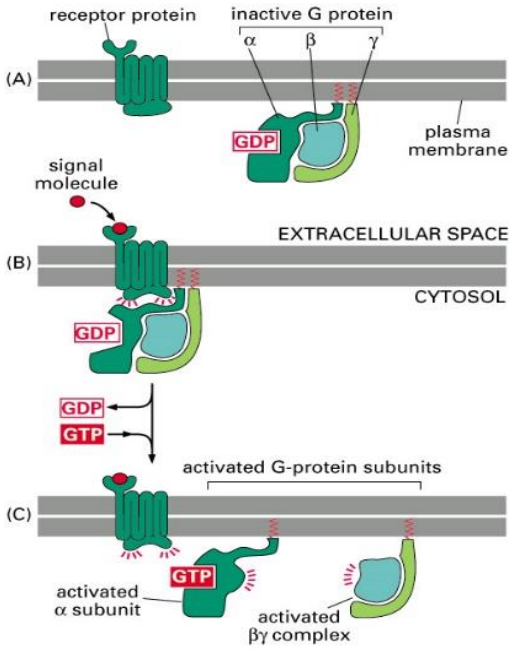


Figure 15–28. Molecular Biology of the Cell, 4th Edition.

1. Overview:

a. 7 trans-membrane spanning helical domains.

b. Act as receptors for many different ligands including **Neurotransmitters** (NT), **Hormones** (H) or even **light**.

c. Large amount of receptor diversity, but common mechanism of action.

d. Transmit signals to intracellular targets via G proteins {complex subunit made from **α, β, γ**}

e. Targets are plasma membrane bound enzymes or ion channels.

2. Mechanism of Activation of GPRs:

a. Binding of ligand to extracellular domain of GPRs induces conformational change that allows cytosolic domain of the receptor to bind to inactive G protein **{α subunit}** at inner face of the plasma membrane (PM).

b. This interaction activates the G protein, which dissociates from the receptor

c. Activated G protein α subunit can now bind GTP instead of GDP, causing dissociation into activated α vs. $\beta\gamma$ subunits. Each of these can go on to activate target proteins**.** {Active α subunit will bind to GTP instead of GDP, when it bind to GTP it is capable of dissociate from both the receptor and Gβ,γ complex and become active and free. Active because it binds with GTP and free because it dissociated from the receptor and can move in the membrane and now it will go to a target. Also the $\beta\gamma$ subunits when it dissociate from the α subunit it can be activated and bind to a target protein which can be the same target as the α or another target}.

Most signal molecules targeted to a cell bind at the cell surface to **receptors** embedded in the **plasma membrane.**

the plasma membrane (e.g., steroid hormones) interact with intracellular receptors.

A large family of **cell surface receptors** have a common structural motif, **7 transmembrane a-helices**.

Rhodopsin

Rhodopsin was the first G-protein coupled receptor to be discovered. its 7-helix **structure** confirmed by X-ray crystallography (in retina, low light vision). It has no ligand it is activated by light.

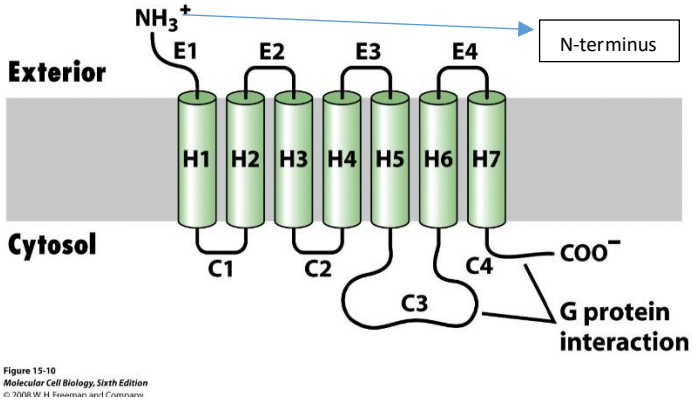


Figure 15-10
Molecular Cell Biology, Sixth Edition
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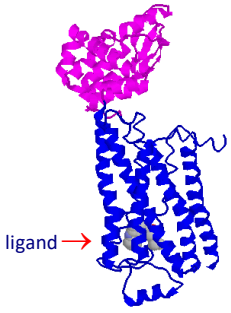
β-adrenergic receptor is activated by epinephrine & norepinephrine.



β-Adrenergic Receptor

G Protein Signal Cascade

The signal is usually passed from a 7-helix receptor to an intracellular G-protein

Seven-helix receptors are thus called GPCR, or G-Protein-Coupled Receptors.

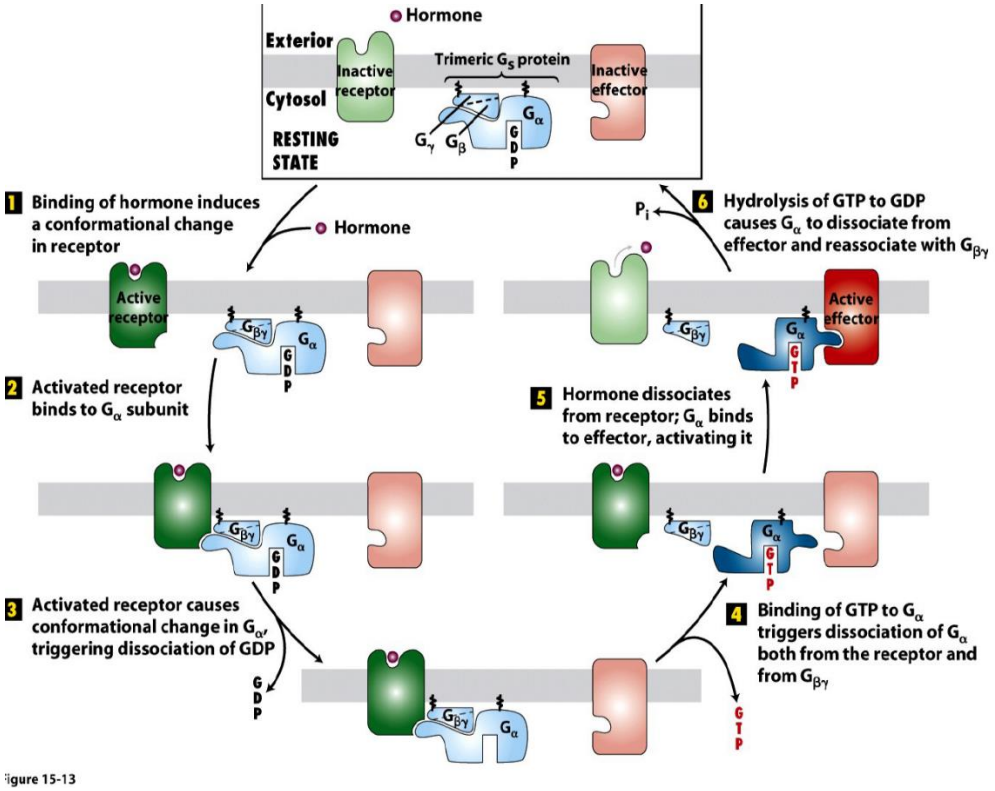
Approximately 800 different GPCRs are encoded in the human genome but they all have the same mechanism of actions.

زهقت؟

احضر هذا

https://youtu.be/Glu_T6DQuLU

SCAN ME



igure 15-13

<u>Study the figure above carefully</u>;

*The effector is most likely to be an enzyme spanning the plasma membrane.

*Not all types of α subunits activate the corresponding effector and not all of them have the same effector.

*Immediately after Gα activates the effector, it must become inactivated by the hydrolysis of GTP that is bound to it (happen automatically so its automatic hydrolysis) and thus it is replaced by GDP and it rebinds with the Gβ,γ complex {act as an inhibitor for the α subunit}, and that complex will anchor to the plasma membrane and separate from the receptor until there is signal that will bind to the receptor .

*G-proteins are heterotrimeric (means consists of different units), with 3 subunits α, β, γ.

We have many subtypes of Gα, depend on its effect.

*A G-protein that activates cyclic-AMP formation within a cell is called a stimulatory G protein –the first type of G proteins- designated Gs with α subunit Gsα. (s for stimulation)

*The name of the protein that's activated by the stimulatory α subunit and that converts AMP to cAMP is Adenylate Cyclase.

***G_s** is activated, e.g., by receptors for the hormones **epinephrine** and **glucagon**.

*The β-adrenergic receptor is the GPCR for epinephrine.

TABLE 15-1 Major Classes of Mammalian Trimeric G Proteins and Their Effectors*

G_α CLASS	ASSOCIATED EFFECTOR	2ND MESSENGER	RECEPTOR EXAMPLES
$G_{\alpha s}$	Adenylyl cyclase	cAMP (increased)	β-Adrenergic (epinephrine) receptor; receptors for glucagon, serotonin, vasopressin
$G_{\alpha i}$	Adenylyl cyclase K^+ channel ($G_{\beta\gamma}$ activates effector)	cAMP (decreased) Change in membrane potential	α_2-Adrenergic receptor Muscarinic acetylcholine receptor
$G_{\alpha olf}$	Adenylyl cyclase	cAMP (increased)	Odorant receptors in nose
$G_{\alpha q}$	Phospholipase C	IP_3, DAG (increased)	α_1-Adrenergic receptor → Causes vasoconstriction in smooth muscle cells in blood vessels
$G_{\alpha o}$	Phospholipase C	IP_3, DAG (increased)	Acetylcholine receptor in endothelial cells
$G_{\alpha t}$	cGMP phosphodiesterase	cGMP (decreased)	Rhodopsin (light receptor) in rod cells

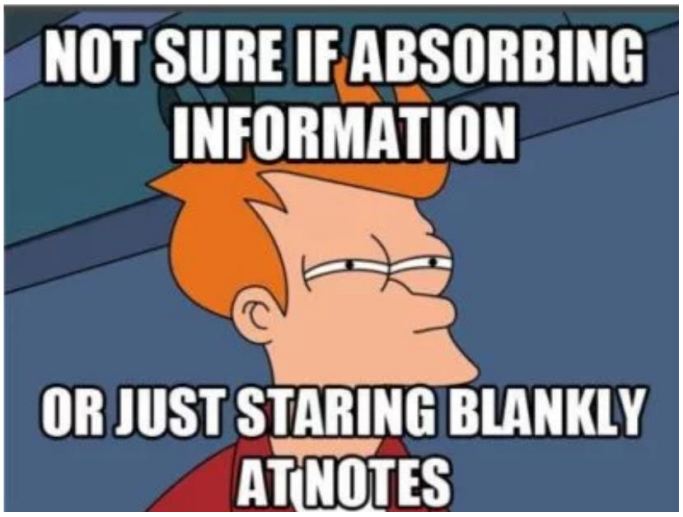
*A given G_α subclass may be associated with more than one effector protein. To date, only one major $G_{\alpha s}$ has been identified, but multiple $G_{\alpha q}$ and $G_{\alpha i}$ proteins have been described. Effector proteins commonly are regulated by G_α but in some cases by $G_{\beta\gamma}$ or the combined action of G_α and $G_{\beta\gamma}$.
IP_3 = inositol 1,4,5-trisphosphate; DAG = 1,2-diacylglycerol.
SOURCES: See L. Birnbaumer, 1992, *Cell* **71**:1069; Z. Farfel et al., 1999, *New Eng. J. Med.* **340**:1012; and K. Pierce et al., 2002, *Nature Rev. Mol. Cell Biol.* **3**:639.

Table 15-1
Molecular Cell Biology, Sixth Edition

The rows with arrows are the required ones.

Note: *In Gαi the (i) means that it is inhibitory.

*Notice that if either epinephrine or norepinephrine binds to α2-Adrenergic Receptor, this leads to the inhibition of Adenylyl cyclase decreased cAMP-. While if either one binds to β-Adrenergic receptor then this leads to the stimulation of Adenylyl cyclase increased cAMP . Meaning that the same hormone might cause exact opposite actions and signals depending on the receptor it binds to.



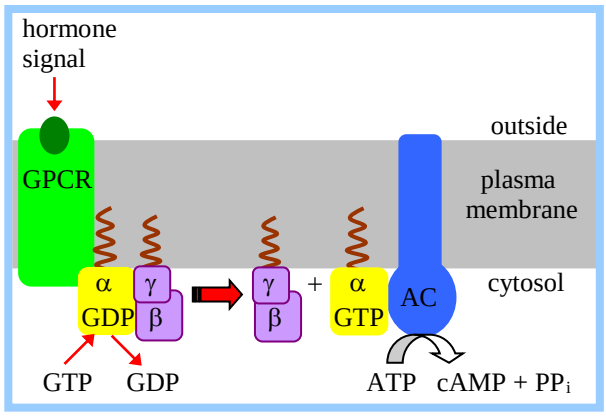
Summary of Hormones signaling pathways:

IP_3	**cAMP**	**cGMP**	**Tyrosine kinase - intrinsic**	**Tyrosine kinase - receptor associated**	**Steroid**
GnRH	FSH	ANP	Insulin	Prolactin	Glucocorticoid
Gastrin	LH	NO (EDRF)	IGF-1	Cytokines (IL-2,6,8)	Estrogen
Oxytocin	ACTH		FGF	GH	Progesterone
TRH	TSH		PDGF		Testosterone
ADH (V_1)	CRH				Aldosterone
Histamine (H_1)	hCG				Vitamin D
Angiotensin II	PTH				T_3/T_4
	Calcitonin				Cortisol
	Glucagon				
	GHRH (can act via IP_3 as well)				

You should memorize the first two columns (IP3 & cAMP columns) for now. Others will be discussed later on.

- In the first column for example, **GnRH** (Gonadotropin-releasing hormone) binds to a 7 transmembrane receptor called the **α2-Adrenergic Receptor**, which is bound to Gαq that dissociates from the Gβ,γ complex and binds with an effector called Phospholipase C that produces IP3

- GHRH (Growth hormone releasing hormone) can act via IP3 (Gq) or via cAMP (Gs)



The α subunit of a G protein binds GTP, & can hydrolyze it to GPD + Pi.

α & γ subunits have covalently attached lipid anchors that bind a G protein to the plasma membrane cytosolic surface.

Adenylate Cyclase (AC) is a transmembrane protein, with cytosolic domains forming the catalytic site.

Adenylate Cyclase is inhibited by Gαi and is activated by Gαs

G Protein Signal Cascade

G-protein coupled receptor bind to the hormone causing the activation of the receptor, the Gα subunit become activated.

Gα has bound GDP and it replaced by GTP. Gα -GTP dissociates from the inhibitory βγ complex & can now bind to and activate Adenylate Cyclase to increase synthesis of cAMP.

Immediately after Gα activates the effector, it must become inactivated by the hydrolysis of GTP that is bound to it (happen automatically) and thus it is replaced by GDP and it rebinds with the Gβ,γ complex and become inactive complex.

THE END

وفي النهاية ما نحن الا بشر قد نخطأ و نصيب فارجوا منكم مسامحتنا عن اي خطأ قد بدر منا سهو

و اتمنى ان تدعوا لنا بدعاء من القلب في هذه الايام الفضيلة.♥♥♥

اللهم إني أستودعك ما قرأت وما حفظت، وما تعلمت، فرده عند حاجتي إليه، إنك على كل شيء قدير.