Faculty of Medicine 2012

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Date : March - 17th - 2013

lecture no. : 5

PHYSIOLOGY

Sheet

Medical Committee
The University of Jordan

Price :

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Last time we were talking about receptors and at the end we talked about some properties of Hormone-Receptor binding/interaction.

The H-R interaction :

- **Is specific**
- **affinity**
- **There's saturation because the binding sites are occupied.**
- **Binding of the hormone to the receptor is reversible, forming H-R complex when there is a high concentration of hormone and when there is less hormone the H-R will dissociate and form back H + R.**
- **When hormone binds to its receptor there is a special functional model for that hormone.**

We talked about receptor types:

1. **Channel-linked receptors: ionotropic that's related to ion channels (cationic or anionic channels).**
2. **Enzyme-linked receptors:**

Protein kinase : for phosphorylation

Neurotrophins

3. **G-protein-coupled receptors: they are called metabotropic receptors .**
4. **Intracellular receptors: these are for lipid-soluble hormones.**

TODAY we're going to talk about 2nd messenger targets:

Second messengers could be c-AMP , Ca^{2+}, or phospholipids DAG

***SECOND MESSENGER TARGETS:**

- **Enzymes:**

  When c-AMP is increased, it goes and modulate the phosphorylation through protein kinases.

  Phosphorylation could do activation or inactivation

- **Protein kinases: there're three protein kinases :**

Protein kinase-A : (c-AMP dependent protein kinase)

Protein kinase-B : (Ca^{2+}/calmodulin dependent protein kinase)

Protein kinase-C :(Ca^{2+}/phospholipids dependent protein kinase)

- **whatever the protein kinase is …… it will end with phosphorylation of protein**
- **protein phosphatases: (in opposite to kinases)**

they dephosphorylate proteins

- **phosphatases might be activated by Ca^{2+}/Calmodulin, this will end with the decrease of phosphorylation**

TYPES OF SECOND MESSENGERS: (slides # 3, 4)

1. **Calcium (Ca^{2+}):**

- **The target of calcium is calmodulin**
- **Each calmodulin molecule can bind to 4 atoms of Ca^{2+}**
- **Calmodulin is almost found in every cell, but it is not active unless it's bounded to 4 Ca^{2+} atoms**
- **Calmodulin : cal ..... calcium, modulin ….. it modulates the activity of some thing**
- **So calmodulin (when it's bound to Ca^{2+}) modulates protein kinase-B , which is (calcium/calmodulin dependent protein kinase)**

2. **Cyclic nucleotides: (c-AMP and c-GMP)**

- **The targets for these ones are also protein kinases:**
  - **C-AMP dependent protein kinase**
  - **C-GMP dependent protein kinase**

3. **Diacylglycerol and inositol triphosphate :**

- **In the membrane we have phospholipids**

- **Phospholipase means it acts on phospholipids**
- **Phospholipase-C removes one acyl group ending with 2 acyls left in the glycerol.**
  - **The glycerol ….. 3 carbon atoms (3 acyl groups)**
- **One of the acyl groups is removed by phospholipase-C , two are left , then what's going to be formed is diacylglycerol DAG**
- **Also there's a formation of IP_3 (inositol triphosphate)**
- **DAG + Ca^{2+} …….. they go and activate protein kinase-C**
- **From where Ca^{2+} comes? Ca^{2+} comes from:**
  1. **The extracellular compartment**
  2. **The ER (endoplasmic reticulum)**
- **How it comes from ER ?the IP_3 that's formed goes to the ER and opens Ca^{2+}-channels, Ca^{2+} goes out from ER (according to the electrochemical gradient)**
- **Ca^{2+} with the DAG go and activate protein kinase-C**

HORMONES THAT USE 2nd MESSENGERS: (slide # 5)

- **Water-soluble hormones, (almost they cannot pass through plasma membrane) use 2nd messengers**
- **Ex: catecholamines (epinephrine , norepinephrine) , polypeptides, protein hormones, glycoprotein hormones.**
- **these (the water-soluble hormones) bind to receptor protein on the target cell's plasma membrane.**
- **Signal-transduction mechanism: actions are mediated by these 2nd messengers(2nd messengers are mediators)**
- **The extracellular hormones are transduced into intracellular 2ndmessengers**
- **One hormone could use more than one type of 2nd messengers: ex: catecholamine….. it could use c-AMP 2nd messengers, also it could acts on other 2nd messengers (Ca^{2+} second messenger for example)**

It depends on : 1. How it activates

It depends also on 2. The cell that's going to be activated

ADENYLATE CYCLASE- C-AMP: (slide # 7)

- **Polypeptides hormone or glycoprotein, they bind to their receptors on the membrane causing (if their receptors are coupled to G-protein) dissociation of α-subunit**
- **The α-subunit goes and activates adenylate cyclase**
- **Adenylate cyclase will convert ATP into c-AMP**
- **Now c-AMP will go and bind to inhibitory subunit of the c-AMP dependent protein kinase**
- **Once the c-AMP binds to the inhibitory subunit of the protein kinase-A , the inhibitory subunit dissociates and protein kinase-A becomes activated and it goes and phosphorylates proteins**
- **Activation of phosphorylation might activate enzymes or inhibit enzymes (it depends)**

Explanation of the figure in slide # 7

- **This is the hormone binds to the receptor, the receptor is coupled to the G-protein**

  Just to remind you how the G-protein becomes active:

  GDP is replaced by GTP

- **Activation of the G-protein**

- **The activation of G-protein causes the dissociation of the α-subunit , one of the mechanisms is that the α-subunit goes and activates adenylate cyclase**
- **Adenylate cyclase converts ATP into c-AMP + PP_i**
- **PP_i …… inorganic phosphate (2 phosphates)**
- **C-AMP ….. goes to the inhibitory subunit of protein kinase-A to be activated**
- **Protein kinase goes and phosphorylates proteins**
- **Modulation of the enzymes present in the cell**
- **Alteration of metabolism of the cell**
- **How the process is terminated:**

The process is terminated by conversion of c-AMP into AMP by specific phosphodiesterase … once the c-AMP is destroyed the effect is terminated

- **There're phosphodiesterases specific for c-GMP , called the c-GMP dependent phosphodiesterase.**

So each one has specific phosphodiesterase

- **As we said in the last lecture : the importance of the 2^{nd} messenger is amplification.**

G-PROTEIN-COUPLED RECEPTORS: (slide #9)

- **Single molecule binds to G-protein-coupled receptors, G-protein activates, turn on adenylate cyclase …etc. at the end we get too many intracellular responses.**

PHOSPHOLIPASE-C :

- **Ca^{2+} and phospholipids are kinds of 2^{nd} messengers**

- **Phospholipids in the membrane are broken down by phospholipase-C**
- **What activates phospholipase-C : it could be the G-protein system (the α-subunit goes and activates phospholipase-C)**
- **From its name (phospholipase-C) : it works on an internal acyl group, not on a peripheral one. It acts on phospholipids**
- **triacylglycerol + phospholipase-c >>>> diacylglycerol + IP_3**
- **Triacylglecerol has 3 acyl groups (3 carbons) from fatty acids**
- **We said previously that catecholamines work on c-AMP here they work on phospholipase-C**
- **Epinephrine (catecholamine) binds to α-adrenergic receptor, activates G-protein, the G-protein activates phospholipase-C**
- **IP_3 diffuses to the ER causing release of Ca^{2+}(by interaction with the receptors of the membrane of ER)**
- **DAG that's released activates protein kinase-C)**
- **When any protein kinase (A,B,C) is activated , it causes phosphorylation of specific proteins (depending on the action of the hormone)**

****Calcium – calmodulin : (slides # 12, 13 ,14)**

Slide 12: it is a G-protein system

- **Activation of phospholipase-C might end with too many Ca^{2+} in the cytoplasm (through IP_3 formation)**

- **Now Ca^{2+} that's released is bounded to calmodulin , causing activation of another protein kinase called protein kinase-B**

Sometimes the action is stimulation of the three protein kinases , but each protein kinase has specific site for phosphorylation of the protein , and these specific sites on the protein that is phosphorylated also have specific actions.

Slide 13: this is calmodulin,it has 4 binding sites , it becomes active when it's bounded to Ca^{2+} it goes and activates protein kinase.

* **The protein kinase is active when it's bound to calcium/calmodulin SO it's called Ca^{2+}/calmodulin dependent protein kinase**
* **Protein kinases do phosphorylation , but they don't phosphorylate the same protein or the same aminoacid of the protein . they have different targets . different targets means different responses.**
* **The protein it phosphorylates could be glycine , histadine , or whatever protein , each has different action.**

Remember kinds of channels : (they are different)

Voltage-gated channels, ligand-gated channels, leaky channels, c-AMP dependent channels

Neurotransmitter release: (slide # 15)

* **There's an action potential in the presynaptic terminal , it opens v-gated Ca^{2+}-channels .**
* **Ca^{2+} enters (down its electrochemical gradient)causing increase in the intracellular Ca^{2+}**
* **Increase in the intracellular Ca^{2+} causes movement of the vesicles to the membrane , fusion with the membrane , and release of the transmitter by exocytosis (could be as hormones or ligands)**
    * **Once the NTs are released they diffuses through interstitial space,binds to there receptors**
    * **Receptors may be coupled to ion channels (cationic or anionic)**
* **Binding of NT to receptor activates the receptor**
* **Activation of the receptor may cause inhibition or stimulation , depending on hyperpolarization or depolarization . they end with response.**

* **Opening cationic channels :**
    - **Opening of Na^+-channels causes depolarization which causes activation .**
    - **Opening of K^+-channels causes hyperpolarization which is inactivation / inhibition.**
* **Is it activation or inhibition ? it depends on :**
    - **The channel that's opened**
    - **How this enzyme is inactivated or terminated**

Transmitter inactivation (terminating of the process):

How ⟶ it depends on the NT

The NT's main way of termination		Other ways (not the main)
Reuptake(recycling)	Catecholamines (EP, NE)	Enzymatic breakdown By amineoxydases
Enzymatic break down	Acetylcholine by(acetylcholinesterases)	Reuptake
hydrolysis (by peptidases)	Protein hormones	Not by reuptake Not by other things

* **acetylcholine (by acetylcholinesterase) >>>> acetyl Co-A + choline**
* **Choline is being reuptaken to be reused**
* **Peptidases are in the interstitial space**
* **Peptidases breakdown peptide bonds**
* **Some NT are reuptaken before arriving to the receptor**

The breaking of the hormone causes dissociation of the H-R complex

NT-Receptor binding : (slide # 17)

- **Receptors are large , dynamic proteins**
- **Dynamic: not static , can increase in number or decrease**
- **Increase is called upregulation, decrease is called down regulation**

2 kinds of postsynaptic receptors:

1. **Ionotropic : they are coupled to ion channels (cationic or anionic)**
2. **Metabotropic: it involves G-protein systems, binding of NT initiates a sequence of inernal mechanisms like 2nd messenger mechanism.**

- **Ionotropic receptors are coupled to ion channels**
- **Metabotropic is coupled to G-protein 2nd messenger mechanism**

NT binding…… membrane potential response

- **An example of ionotropic receptor is acetylcholine**
- **Once it's bound to the receptor , it opens the channel , the channel could be Na^+ , K^+ , Ca^{2+}**
- **So acetylcholine is excitatory in some cells , and inhibitory in others.**
- **What determines whether the NT is excitatory or inhibitory is the type of receptor- coupled channels.**

Acetylcholine in the heart	Acetylcholine in the GI tract
Inhibitory(decreases the heart rate)	Excitatory (increase the movement , secretion)
It's coupled to K^+-channels	It's coupled to Na^+-channels

Ionotropic receptors :

Characteristics: very fast , each is made of subunits in the center there is a channel (receptor of Ach is pentameric >> 5 subunits)

- **If you need something fast …hormone receptors are coupled to ion-channels , because they open and close very fast**
- **If you need slower but prolonged action … you need a 2nd messenger mechanism (like c-AMP activates protein kinase) it has longer duration (the time of H-R interaction)**

Receptors are coupled directly to ion-channels : fast , ionotropic

Second messengers: activation of 2nd kinase:

- **Can work by affecting NT production for long-termed effect**
- **It causes amplification of the process**
- **Other metabotropic receptors :**
- **This receptor has 7 subunits (hepta) :very prolonged**

Slide # 26:

- **We talked previously about primary ligand**
- **Agonist and antagonist… they bind to the same receptor**
- **Agonist…They have the same action like the hormone**
- **Antagonist… they block the active site**
- **Primary ligand and agonist have same response**
- **Antagonists have no response (Blockers)**