Signal Transduction via Cell Membrane Receptors

• These are the pathways that become activated by hormones signals that cannot diffuse through the plasma membrane

• They need to interact first with a membrane receptor before the signal transduction pathway can be started

• The hormone is called the first messenger, and the intracellular product produced by the action of the activated receptor is called the second messenger.

• Only the second messenger will alter cellular events (thus if something inhibits the production of the 2nd messenger, there will be no effect).

G-protein coupled receptors

• G-protein coupled receptors work in relay to pass on the action to the inside of the cell via activation of membrane bound enzyme
The hormone is considered as the 1st messenger.

A second messenger is a non-protein product, produced by the activation of a specific enzyme via the G-protein, and released inside the cell.

Produced and released into the cell, the 2nd messenger can now activate and influence other cellular events.

These cellular events that become activated are cell specific:
- Release of calcium from SER in smooth muscle
- Activation of lipases in adipose tissue
- Opening of ion channels in cardiac tissue
- ……..

Concept of 1st and 2nd Messengers

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Two major kinds of G-protein coupled Receptors

Two important G-protein pathways can be distinguished

They are different by the fact that the G-protein activates a different target protein (enzyme).

**System 1**: Activation of an enzyme that uses ATP as a substrate and produces cyclic AMP as a product.

**System 2**: Activation of an enzyme that uses Phosphatidyl Inositol Phosphates (PIP’s) as a substrate.

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**System 1: The adenylate cyclase system**

In this system the target enzyme is **Adenylate Cyclase**. This enzyme converts ATP into cyclic AMP (cAMP)

\[
\text{ATP} + \text{H}_2\text{O} \rightarrow \text{c-AMP} + \text{PP}_i
\]

**Adenylate Cyclase**

*Note*: other receptors and G-proteins activate enzymes called Phosphodiesterases, that result in the break down cAMP to AMP. (what would their purpose be?)
Receptors, G-proteins and Adenylate Cyclase

Catecholamines
ACTH
FSH
LH
Glucagon
PTH
TSH
Calcitonin

Active Protein Kinase A will phosphorylate specific proteins and alter the state these proteins (activate or de-activate)!

Protein Kinases & Phosphorylation

A protein Kinase is an enzyme that adds a phosphate group to a protein. By doing so, it can for example activate ("wake-up") a dormant protein (such as an enzyme).

A protein Phosphatase is an enzyme that removes the phosphate group from protein. By doing so, it reverses the previous action and puts the enzyme back to ‘sleep’!
Amplification Effect of cAMP

The activation of Adenylate Cyclase by a hormone has a fast amplification effect. This example shows how fast a little Glucagon can result in the release of a whole lot of glucose!

![Diagram]

Terminating cAMP effects

Because of the fast amplification effect of cAMP, it needs to be terminated in order to prevent it from going out of control.

This is done by:

- Activation of Phosphodiesterase enzymes (remember, PDE break down cAMP)

- Activation of Phosphatase enzyme that de-phosphorylate phosphorylated proteins.

- Activation of an inhibitory G protein that turns off the adenylate cyclase.

These enzymes are controlled via activation or inhibition by means via of different hormones-receptor interactions.
Activation and Inactivation of Adenylate Cyclase

Whereas some specific receptors (thus with specific hormones) are coupled to stimulatory G proteins (and thus activate), some receptors (binding other hormones) are coupled to inhibitory G proteins. These turn off the AC enzyme and/or activate PDE. This ends the previous activation of cellular events and is a way to “switch off” a turned on event.

Examples:
- Epinephrine and norepinephrine (β receptors)
- Calcitonin
- Parathyroid hormone
- ADH, ACTH, FSH, LH, TSH
- Glucagon

Enhanced breakdown of cAMP

PDE

Reduced enzyme activity

In some instances, G protein activation results in decreased levels of cAMP in the cytoplasm. This decrease has an inhibitory effect on the cell.

G-protein coupled Receptors and Phospholipase C

Whereas the target enzyme in System 1 is Adenylate Cyclase, the target enzyme in System 2 is Phospholipase C!

System 1: Activation of an enzyme that makes cyclic AMP

System 2: Activation of an enzyme that makes Phosphatidyl Inositol Phosphates (PIP’ s).
G-protein coupled Receptors and Phospholipase C

What reaction does Phospholipase C catalyze?

It acts on phospholipid membrane components called Phosphatidyl Inositol Bi Phosphates (PIP₂).

\[ \text{PIP}_2 \rightarrow \text{Diacylglycerol} + \text{Inositol TriPhosphate} \] 

(DAG) \hspace{1cm} (IP₃)

DAG and IP₃ are thus your second messengers!

G-protein coupled Receptors and Phospholipase C

What effects do DAG and IP₃ have?

**DAG**
- DAG activates a class of Protein Kinases called PK-C
- PK-C’s will phosphorylate and activate proteins
- Can for example phosphorylate Calcium channels and open them

**IP₃**
- Acts on the smooth ER
- Results is that calcium will be released into the cytoplasm
- Calcium in turn will bind to and activate calmodulin
- Activated calmodulin can now activate enzymes and other proteins

Effects on Ca²⁺ Levels

- Some G proteins use Ca²⁺ as a second messenger
- Calcium levels in turn will bind to and activate calmodulin
- Activated calmodulin can now activate enzymes and other proteins

Examples:
- Epinephrine and norepinephrine (α₁ receptors)
- Oxytocin
- Regulatory hormones of hypothalamus
- Several eicosanoids
The interaction of a hormone with a receptor is like a hit and run mechanism.

- The more hormones present, the more hit and run effects
- If a receptor has a higher affinity, it causes a hormone to stay on the receptor longer and thus keep the triggering action going.
- The more receptors on a cell, the easier it is for a hormone to find a receptor

When a hormone dissociates (stops interacting) from a receptor it can jump on a new receptor and start the trigger again.

This lasts until the hormone (messenger) is destroyed or removed.
Once the desired effect is obtained, the hormone concentration is reduced via:

- inhibition or attenuation of production of the hormone through negative feedback
- breakdown via degrading enzymes or removal via diffusion
- when located in the blood stream, the hormone can be removed by the action of kidney and/or liver

Concentration of a molecule can be adjusted quickly only if the lifetime of the molecule is short. Lifetime of most hormones is very short!

Regulation Of Receptors

Because of their importance and their interaction with cell receptors, hormones are present in very small quantities and only released when needed or when induced by specific stimuli. via stringent feedback cycles.

Abundance of Receptor are regulated as well by physiological feedback systems.

**Up-regulation.**

When a cell is not being targeted by a lot of hormones due to a shortage of messengers (or when the presence of antagonists block the action of the receptors), the receptor numbers tend to increase.

**Down-regulation.**

When there is an abundance of a certain hormone (resulting in over-stimulation), the number of cellular receptors for that hormone tend to decrease over time.
Control of Hormone Release

- Endocrine Activity is controlled by Endocrine Reflexes
- **Endocrine Reflexes are the** Functional counterparts of neural reflexes
  - In most cases, controlled by negative feedback mechanisms
    - Stimulus triggers production of hormone, the direct or indirect effects of the hormone reduce intensity of the stimulus (and reduces hormone production)
  - This keeps the hormone within a certain functional range and variations in concentration are kept within a narrow desirable range

Control of Hormone Release

- Hormones are synthesized and released in response to:
  - Humoral stimuli
  - Neural stimuli
  - Hormonal stimuli
Humoral Stimuli

- **Humoral stimuli** – secretion of hormones in direct response to changing blood levels of ions and nutrients
  - Example: concentration of calcium ions in the blood
    - Declining blood $\text{Ca}^{2+}$ concentration stimulates the parathyroid glands to secrete PTH (parathyroid hormone)
    - PTH causes $\text{Ca}^{2+}$ concentrations to rise and the stimulus is removed

Neural Stimuli

- **Neural stimuli** – nerve fibers stimulate hormone release
  - Example: Preganglionic sympathetic nervous system (SNS) fibers stimulate the adrenal medulla to secrete catecholamines
Hormonal Stimuli

- Hormonal stimuli – release of hormones in response to hormones produced by other endocrine organs

- Example:
  - The hypothalamic hormones stimulate the anterior pituitary
  - In turn, pituitary hormones stimulate targets to secrete still more hormones

Nervous System Modulation

- The nervous system modifies the stimulation of endocrine glands and their negative feedback mechanisms

- For example, control of blood glucose levels
  - Normally the endocrine system maintains blood glucose
  - Under stress, the body needs more glucose
  - The hypothalamus and the sympathetic nervous system are activated to supply ample glucose
Hormone-Target Cell Interaction

There are three types of hormone interaction:

- **Permissiveness** – one hormone cannot exert its effects without another hormone being present
- **Synergism** – more than one hormone produces the same effects on a target cell
- **Antagonism** – one or more hormones opposes the action of another hormone

General Endocrine disorders

Many of the endocrine disorders are due to malfunctioning glands or malfunctioning feedback systems.

In simple endocrine reflexes, only one hormone is involved

We will cover some complex feedback systems where more than one hormone is involved.

In the latter case, the definition of a trop(h)ic hormone becomes important: it is a hormone whose only function is to regulate the release of another hormone!
1. **Hypo-secretion**

- Gland secretes too little hormone
- If the gland itself is not functioning properly
  \[ \rightarrow \text{primary hypo-secretion} \]
- If the gland is normal but there is a problem with the tropic hormone that stimulates the gland
  \[ \rightarrow \text{secondary hypo-secretion} \]
- If the tropic-hormone releasing gland is normal but something is missing that results in secretion of the tropic hormone
  \[ \rightarrow \text{tertiary hypo-secretion} \]
General Endocrine disorders

2. **Hyper-secretion**

- Primary hyper-secretion  
  gland is secreting too much hormone on its own

- Secondary hyper-secretion  
  over-stimulation of a gland by the tropic hormone  
  (thus too much tropic hormone is made/present)

Most hyper-secretions result from endocrine-cell tumors

General Endocrine disorders

3. **Hypo- and hyper-responsiveness**

In both conditions, nothing is actually wrong with the secretion of the hormones but the response is abnormal

- Hypo-responsiveness can be due to
  - Deficient receptors or lack of receptors
  - Deficient membrane proteins that interact with an otherwise normal receptor (e.g. G-proteins or the target enzymes of the alpha subunits)
  - Lack or deficiency of enzymes that turn pro-hormones into active hormones

- Hyper-responsiveness is most often due to an abnormal up-regulation of receptors for the hormone.