UNIT 11 HORMONES

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11.1 INTRODUCTION

The survival of multicellular organisms depends on their ability to adapt to a constantly changing environment. Further, the most characteristic property which even human beings possess is their ability to adapt to ever changing scenario, minute to minute, day to day and generation to generation. Thus intercellular (between various cells) communication mechanisms are necessarily required for this adaptation. The nervous system and the endocrine system provide this intercellular, organism-wide communication. In fact there is a remarkable convergence of these two regulatory mechanisms. They are now even being viewed as an integrated neuroendocrine system.

The physiology of the nervous system and the endocrine system is discussed in Unit 9 and Unit 11 of the Applied Physiology Course. Hence it would help you to go through these units. As you go through the Unit on endocrine glands, you would realize that the endocrine system is composed of the endocrine glands, the so called 'ductless glands' whose secretions pass directly into the blood stream. The secretion of the endocrine gland is called the 'hormone'. Here, in this unit our focus is on hormones. What are hormones? How do we classify them? What are the components involved in the mechanism of hormone action? What is the role of hormones in our body? These are a few aspects discussed in this unit. Since our discussion at this point is the detailed study of hormones, brief information about the endocrine system is also given below.

Objectives

After going through this unit, you will be able to:

- define and classify hormones,

- discuss the regulation of the endocrine system,
- list and explain the various components involved in the mechanism of hormone action,
- compare the mode of signal generation of the two groups of hormones,
- discuss the role of second messengers, and
- describe the biochemical role of each hormone in the body.

11.2 THE ENDOCRINE SYSTEM

The endocrine system, as we mentioned above, is composed of the endocrine glands, the so called 'ductless glands' whose secretions pass directly into the blood stream. The secretion of the endocrine gland is called the 'hormone'. The word hormone is derived from a Greek term that means *to arouse to activity*. As classically defined, a hormone is *a substance that is synthesized in one organ and transported by the circulatory system to act on another tissue.*

However this original description is too restrictive because it is now known that hormones can act on adjacent cells (paracrine action) and even on the cell in which they were synthesized (autocrine action) without entering the systemic (general) circulation. Thus today the term hormone refers *to any substance in an organism that carries a signal to generate some sort of alteration at the cellular level.* Accordingly, since hormones carry signals or messages, they are also called '*messengers*' or specifically *'first messengers'.* Hence if a particular chemical reaction has to take place in a cell, one or the other hormone has to give this message to that cell.

A diverse array of hormones – each with distinctive mechanisms of action and properties of biosynthesis, storage, secretion, transport and metabolism – has evolved to provide homeostatic responses. Hence, the hormones may also be viewed as regulators and the levels of various hormones regulate specific cellular processes. Let us learn about this regulatory mechanism next.

11.3 REGULATION OF ENDOCRINE SYSTEM

What regulates the regulators? The regulation originates in the brain/central nervous system (CNS). The CNS receives inputs from many internal and external sensors about danger, hunger, dietary intake, blood composition and pressure, for example and orchestrates the production of appropriate hormonal signals by the several endocrine tissues of the body. This results in what is called the *hormonal cascade system*. Figure 11.1 shows the chain of command in the hormonal signaling hierarchy. A stimulus originates in the external environment or within the organism. The CNS senses the stimulus and this signal may be transmitted as an electrical pulse or as a chemical signal or both. The signal is forwarded to the hypothalamus situated at the base of the brain. The hypothalamus, which is an endocrine gland, secretes the appropriate hormone called the *releasing hormone* in nanogram (ng) amounts. The releasing hormone is carried by blood to the *anterior pituitary* (also called *adenohypophysis*), another endocrine gland. This is the first target of the environmental or interior signal. (In some cases, the posterior pituitary or neurohypophysis is involved.) The anterior pituitary secretes the hormone called *trophic hormone* or *tropin* in microgram (mcg) quantities. (Greek *tropos* means 'turn'). The trophic hormone is carried by blood to its appropriate endocrine gland which gets stimulated. The endocrine gland which is the second target then synthesizes its specific hormone in milligram (mg) amounts. Through blood, this specific hormone travels to specific tissue(s), the ultimate target and brings about the characteristic

effects. Thus this signal pathway originates in the brain and culminates in the ultimate target cell. The hypothalamus of the brain is the coordination center of the endocrine system. It receives and integrates messages from the central nervous system.

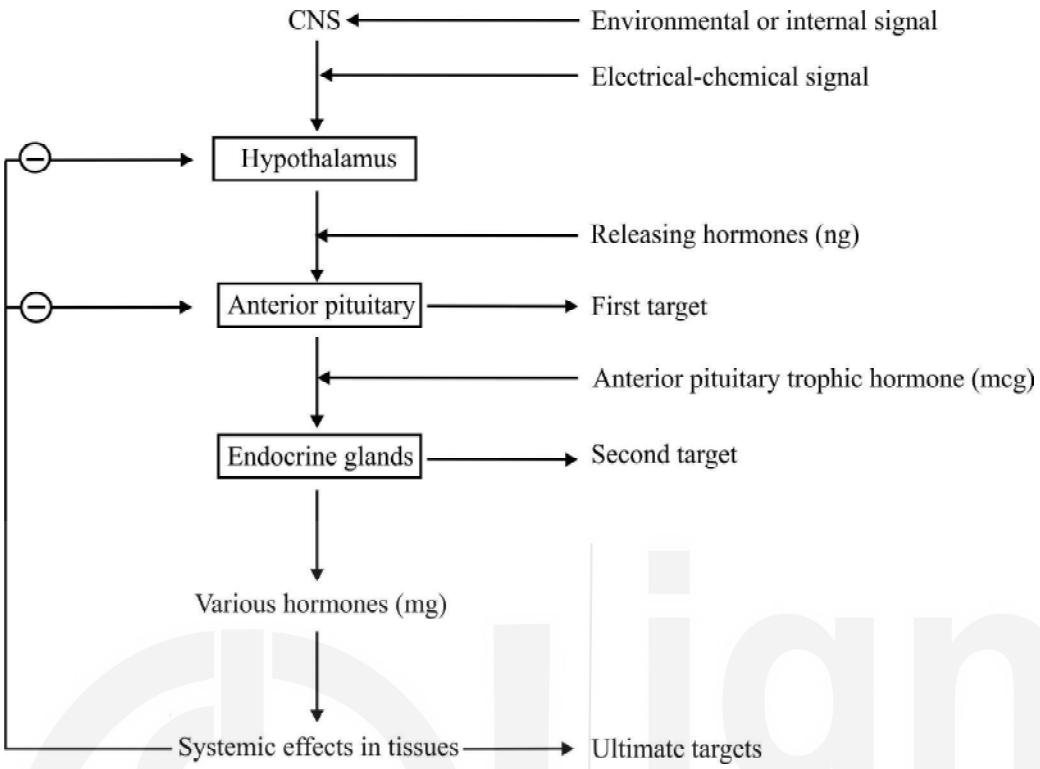

Figure 11.1: General sequence of events in hormonal cascade system

For your better understanding, a specific example is given in Figure 11.2. If there is an infection or haemorrhage or hypoglycemia or the person perceives fear or pain, electrical-chemical signals are generated which are received by the central nervous system. CNS in turn passes on the signals to the hypothalamus. It secretes the *corticotropin-releasing hormone (CRH)* which goes to the anterior pituitary. The anterior pituitary in turn secretes the *adrenocorticotropic hormone (ACTH)* which goes to the adrenal cortex (the outer layer of the adrenal gland) and triggers the release of the specific hormone, *cortisol*. Cortisol, the ultimate hormone, acts in many types of target cells to alter their metabolism. In liver cells (hepatocytes), one of the actions of cortisol is to increase the rate of gluconeogenesis (synthesis of glucose). This ensures that the body gets enough fuel to overcome the adverse situation.

From Figures 11.1 and 11.2, it is clear that in the hormonal signaling hierarchy, at each level, a small signal elicits a large response. The initial electrical signal to the hypothalamus results in the release of a few nanograms of CRH which elicits the release of a few micrograms of corticotropin. Corticotropin acts on the adrenal cortex to cause the release of milligrams of cortisol, for an overall amplification of at least a millionfold. This is called the *hormonal cascade system*. The hormonal cascade system amplifies a specific signal. Thus the cascade mechanism means that small amounts of an extracellular compound can affect large number of intracellular enzymes without crossing the plasma membrane or binding to each target protein.

At each level of a hormone cascade, there is the possibility of feedback inhibition of earlier steps in the cascade, an elevated level of the ultimate hormone or one of the intermediate hormones inhibits release of the earlier hormones in the cascade from the hypothalamus or pituitary. This ensures that a product is made (or released) only until the necessary concentration is reached.

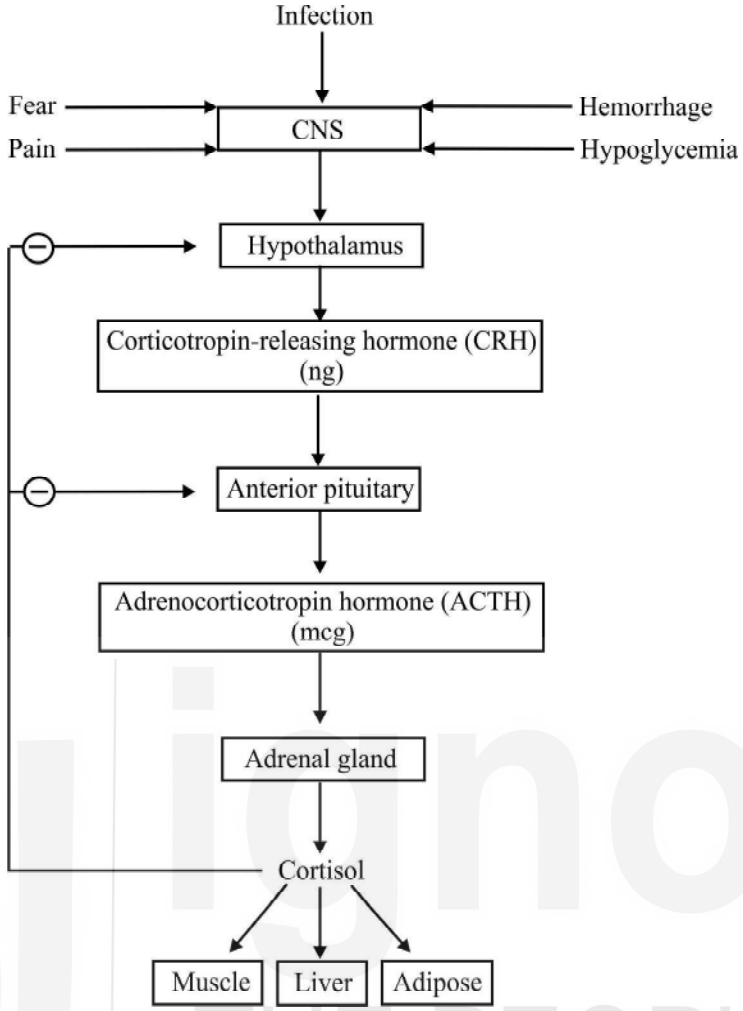

Figure 11.2: Hormone cascade system for cortisol

Not all hormone-producing cells are a part of such long cascades. Insulin release by the pancreas for example, is largely regulated by the level of glucose in the blood supplied to the pancreas.

The section above presented a brief insight into the endocrine glands and the substance called *hormone* secreted by the endocrine glands. So we are now familiar with the word hormone and we know how the endocrine system is regulated. Next, we shall learn about the mechanism of hormonal action. But, first take a break and recapitulate what you have learnt so far. Answer the questions given in the check your progress exercise 1.

Check Your Progress Exercise 1

1) Define the following:

   a) Endocrine system

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   .....

   b) Hormone

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   .....

2) Fill in the blanks:

   a) Hormones carry signals, hence they are called ..... .

   b) The anterior pituitary secretes the hormone ..... .

   c) Corticotropin releasing hormone is secreted by the ..... .

3) What do you understand by the hormonal cascade system? Give the general sequence of events in the hormonal cascade system.

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11.4 MECHANISM OF HORMONE ACTION

Even the brief insight into the endocrine system along with its regulation, presented in the section above, must have impressed upon you the complexity of this endocrine system. Accordingly, you would realize that the mechanism of action of the hormones is not a very simple one. It is for this reason that detailed information on this aspect has only been obtained in the last few decades, despite the fact that the functions of many of the major hormones had been described much earlier. However, it is now well known that the mechanism of hormone action involves many sequential steps and requires the participation of various components, each having a well-defined role. These components are discussed next.

11.4.1 The Target Cell Concept

There are about 200 types of differentiated cells in humans. Only a few produce hormones, but virtually all the cells in the human body are target of one or more of the over 50 known hormones. It was thought that hormones affected a single cell type or only a few kinds of cells and that a hormone elicited a unique biochemical or physiologic action. However, a hormone can affect several different cell types. Further, more than one hormone can affect a given cell type and hormones can exert many different effects in one cell or in different cells.

11.4.2 Hormone Receptors

Hormones are present at very low concentrations in the extracellular fluid, which is generally in the range of 10^{-15} to 10^{-9} mol/L. This concentration is much lower than that of the many structurally similar molecules like sterols, amino acids, peptides, proteins etc. and other molecules that circulate at concentrations in the range of 10^{-5} to 10^{-3} mol/L. Hence target cells must distinguish not only between different hormones present in small amounts but also between a given hormone and the 10^{6} to 10^{-9} excess of other similar molecules. This high degree of discrimination is provided by cell-associated recognition molecules called *receptors*. Thus a target cell has the ability to selectively bind a given hormone to its specific receptor. Hormones initiate their biologic effects by binding to specific receptors. Accordingly, hormone-induced actions are terminated when the hormone dissociates from the receptor. The characteristics of receptors are discussed next.

Characteristics of receptors

All receptors have at least two functional domains-

- a recognition domain that binds the hormone, and

- a region that generates a signal that couples hormone recognition to some intracellular function.

The coupling (signal transduction) occurs in two ways depending upon the chemical nature of the hormone-

- polypeptide and protein hormones and the catecholamines (like epinephrine and norepinephrine) bind to receptors located in the plasma membrane and thereby generate a signal that regulates various intracellular functions, which is often by changing the activity of an enzyme.
- steroid, retinoid and thyroid hormones react with intracellular receptors and this hormone-receptor complex directly provides the signal, generally to specific genes whose rate of transcription is thereby affected. In fact, it is now known that these hormone receptors have several functional domains. These sites are-
  - i) which binds the hormone
  - ii) which binds to specific DNA regions
  - iii) which is involved in the interaction with other coregulator proteins that result in the activation (or repression) of gene transcription, and
  - iv) which may specify binding to one or more proteins that influence the intracellular trafficking of the receptor.

Thus both *recognition* and *coupling domains* occur on receptors. The dual functions of binding and coupling ultimately define a receptor. It is the coupling of hormone binding to signal transduction, which is also called *receptor-effector coupling* that provides the first step in amplification of the hormonal response. This dual purpose also distinguishes the target cell receptor from the plasma carrier proteins that also bind hormone but do not generate a signal.

The next component involved in the mechanism of hormone action is the hormone itself. Let us learn how they are classified.

11.4.3 Classification of Hormones

Hormones can be classified in several ways according to chemical composition, solubility properties, location of receptors and the nature of signal used to mediate hormonal action within the cell. One of the most common systems of classification is based on the location of receptors and the mechanism of action of the hormone. According to this system, the hormones are grouped into 2 major classes – *Group I* and *Group II*. The classification is given in Table 11.1. We have included only a few hormones in the list, those we are very familiar with. There are many more hormones which are known.

Table 11.1: Classification of hormones according to their mechanism of action

Group I-Hormones that bind to intracellular receptors
• Thyroid hormones (T3 and T4) • Glucocorticoids • Mineralocorticoids • Retinoic acid • Calcitriol (1,25 dihydroxy-D3) • Androgens • Oestrogens
Group II- Hormones that bind to cell surface receptors
A - The second messenger is cAMP • Glucagon • Calcitonin • Parathyroid hormone

- α_2-Adrenergic catecholamines
- β-Adrenergic catecholamines
- Thyroid-stimulating hormone (TSH)
- Antidiuretic hormone (ADH)
- Adrenocorticotropic hormone (ACTH)
- Human chorionic gonadotropin (HCG)

B - The second messenger is cGMP

- Atrial natriuretic factor

C - The second messenger is calcium or phosphatidyl inositol or both

- Acetylcholine
- α_1-Adrenergic catecholamines
- Oxytocin
- Antidiuretic hormone (ADH)
- Cholecystokinin

D - The second messenger is a kinase or phosphatase cascade

- Insulin
- Growth hormone
- Prolactin

Each group of hormones that are listed in Table 11.2 has distinct properties. The hormones in Group I are *lipophilic* or *fat-soluble*. After secretion, these hormones associate with plasma transport or carrier proteins. This overcomes the problem of their insolubility in the aqueous medium of the plasma. At the same time, it prolongs the plasma half-life of the hormone since they cannot be eliminated easily when bound to proteins. The relative percentages of bound and free hormone are determined by the binding affinity and binding capacity of the transport proteins. The free hormone, which is the biologically active form, readily traverses (crosses) the lipophilic (lipid containing) plasma membranes of all cells. The receptors for Group I hormones are present either in cytosol or nucleus of target cells. It is here that the hormone-receptor complex is formed. It is thought that this complex, the *ligand-receptor complex,* is the intracellular messenger which conveys the message brought from the CNS to the specific cell.

The hormones in Group II are *hydrophilic* or *water-soluble*. They cannot cross the lipophilic plasma membrane. Hence they bind to the plasma membrane of the target cell. Their receptors are located in the plasma membrane. Such hormones that bind to the surfaces of cells communicate with intracellular metabolic processes through intermediary molecules called *second messengers*. The hormone itself is called the *first messenger*. These second messengers are generated as a consequence of the ligand-receptor interaction. For example, when epinephrine binds to the plasma membrane of certain cells, the concentration of cyclic AMP (cAMP) increases. Hence cAMP mediates the effects of many hormones. Hormones listed in Group II A of Table 11.2 use cAMP as the second messenger. The general characteristics of group I and group II hormones are given in Table 11.2. As can be seen in Table 11.2, GMP (cGMP) is used as second messenger by atrial natriuretic factor (Group II B). Many hormones use ionic calcium (Ca^{2+}) or phosphatidyl inositol (or both) as the second messenger. These hormones have been classified in Group II C (refer to Table 11.2). You have read about phosphatidyl inositol in chemistry of lipids (Unit 2). The intracellular messenger for Group II D hormones is a protein kinase-phosphatase cascade. You have come across such a cascade in glycogen metabolism.

Table 11.2: General characteristics of group I and group II hormones

Characteristic	Group I hormones	Group II hormones
Type of hormone	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport Proteins	Yes	No
Plasma half-life	Long (hours to days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	Second messenger-cAMP, cGMP, Ca, phosphoinositols, kinase cascades

Having learnt about the hormones, next, we will see how the hormone action brings about the signal transduction, which is the next component in the mechanism of hormone action.

11.4.4 Signal Transduction

The homeostatic adaptations an organism makes to a constantly changing environment are mainly achieved by altering the activity and amount of proteins. This in turn is brought about by the action of hormones. A hormone-receptor interaction results in generation of an intracellular signal that can:

i) regulate the activity of a select set of genes, which will alter the amount of certain proteins in the target cell or

ii) affect the activity of specific proteins including enzymes and transporter or channel proteins. (Cell membranes have channels or passages for movement of molecules).

The signal can influence the location of proteins in the cell and can affect general processes such as protein synthesis, cell growth and replication. These changes may be brought about by influencing gene expression. The signal transduction that occurs as a result of hormone action ultimately affects homeostatic mechanisms in the body. Figure 11.3 shows hormonal response to any stimulus. The stimulus can be a challenge or a threat to the organism, to an organ, or to the integrity of a single cell within that organism. Recognition of the stimulus is the first step in the adaptive response. In the case of an organism as a whole, this generally involves the nervous system, as well as, various senses including sight, hearing, pain, smell, touch. At the cellular level, recognition involves physicochemical factors such as pH, oxygen tension, temperature, nutrient supply, osmolarity and even production of undesirable metabolites. Accordingly one or more of hormones would be secreted which will bring about the desired adaptive responses.

So from our discussion above it is clear that the action of every hormone is mediated through the generation of a signal. Let us get to know more about the signal generation component next. But, before doing so we shall try to recapitulate what we have studied so far. Answer the questions given in the check your progress exercise 2 and check your progress so far.

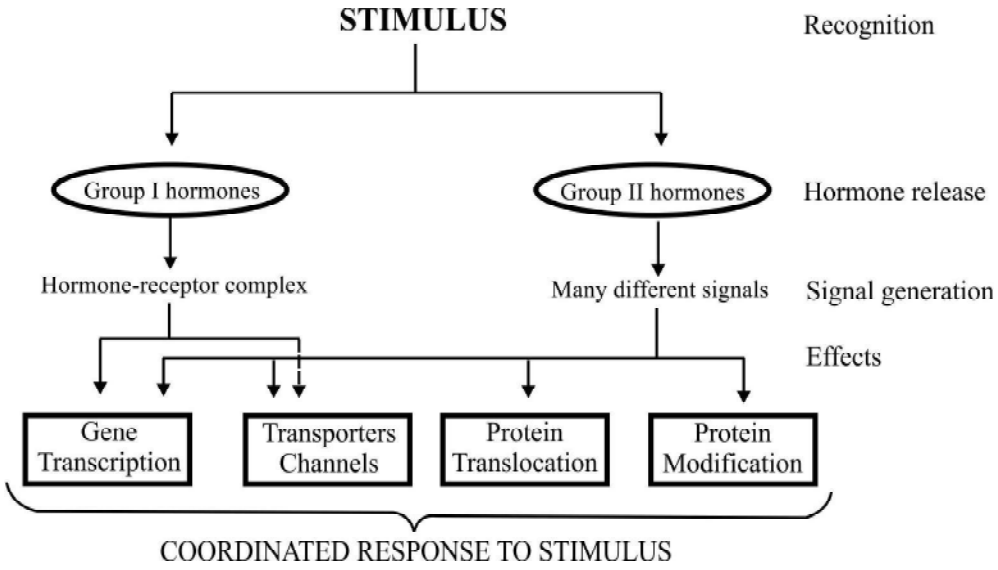

Figure 11.3: Response of group I and group II hormones to a stimulus

Check Your Progress Exercise 2

1) What is a receptor? What is its role in maintenance of hormonal action?

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2) Give the simple classification of hormones based on the mechanism of action.

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3) Match the items in Column A with the items in Column B.

Column A	Column B
i) Group I hormones	a) protein kinase-phosphatase cascade
ii) Group II hormones	b) cAMP
iii) Second messenger of group IIa	c) lipophilic
iv) Second messenger of group IIb	d) hydrophilic
v) Second messenger of group IIc	e) cGMP
vi) Second messenger of group IId	f) Calcium and phosphatidyl inositol

4) Briefly explain the hormonal response to a stimulus.

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The next component involved in the mechanism of hormone action is *signal generation*. Let us learn about it.

11.4.5 Signal Generation

Even though action of every hormone is mediated through the generation of a signal, there are great differences in the kind of signal generated and the manner in which it occurs. The difference is determined by the nature of the hormones involved i.e. group I hormones or the group II hormones. Let us get to know more about this aspect next.

Group I Hormones

The ligand-receptor complex is the signal for group I hormones. These hormones which are lipophilic, easily diffuse through the plasma membrane of all cells and encounter their specific, high-affinity intracellular receptors in target cells. As already mentioned, these receptors can be located in the cytoplasm or in the nucleus of target cells. The hormone-receptor complex undergoes, first, an *activation reaction*. This can occur by the following two mechanisms :

- In the case of glucocorticoid hormones, the receptors are present in the cytoplasm of the target cells as illustrated in Figure 11.4. These receptors are bound to a protein called *heat shock protein 90* (hsp 90). When the hormone binds to the receptor, there is dissociation of hsp 90 from the receptor. This is an essential step before the glucocorticoid receptor can be translocated into the nucleus of the cell. In fact the receptor itself contains nuclear localization sequences which help in this process of translocation from the cytoplasm to nucleus. The activated receptor then moves into the nucleus. It binds with high affinity to DNA at a specific sequence called the *hormone response element (HRE)*. When the particular hormone is a glucocorticoid, this region is also specifically called *glucocorticoid response element (GRE)* as shown in Figure 11.4. Once the activated hormone-receptor is bound to HRE, one or more proteins which act as coactivators also bind to this region resulting in accelerated gene transcription.

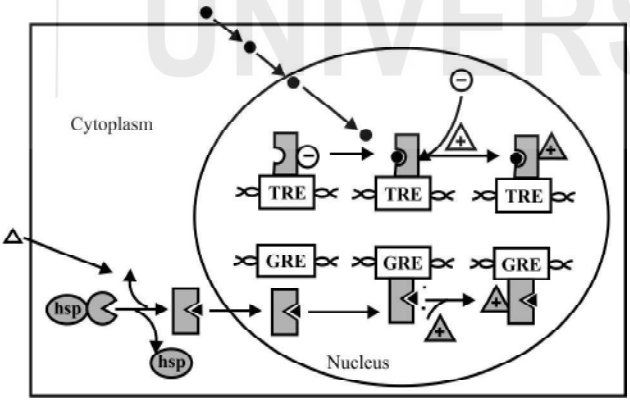

Figure 11.4: Regulation of gene expression by Group I hormones

- Thyroid hormones and retinoids diffuse from the extracellular fluid across the plasma membrane and go directly into the nucleus. In this case, the respective receptor is already bound to the HRE which can be also called *thyroid response element (TRE)* if we are talking of thyroid hormone. Figure 11.4 above highlights this element. However this DNA-bound receptor fails to activate

transcription because it is complexed with a corepressor. In fact the receptor-corepressor complex is an active repressor of gene transcription. But when the hormone binds to this complex, there is dissociation of the corepressor. Additionally, the hormone-receptor complex is now able to bind to one or more coactivators with high affinity. This ultimately results in the acceleration of gene transcription.

As you already know when gene transcription takes place, specific mRNA is produced and specific protein is synthesized and metabolic processes are influenced. Action of each hormone is very specific. Further, the hormone affects less than 1% of the genes, mRNA or proteins in a target cell. However, the effect produced can be profound. Apart from exerting their effect on modulating gene transcription, hormones can act at any step in the information pathway as shown in Figure 11.5.

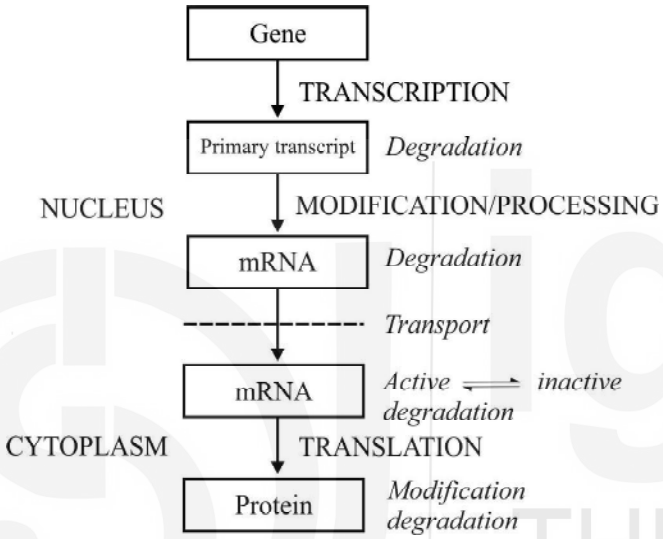

Figure 11.5: The information pathway

Next, let us see how signals are generated by the action of group II hormones.

Group II Hormones

Group II hormones being water soluble cannot cross the plasma membrane. Hence they have their receptors in the plasma membrane and thus have to use intracellular messenger molecules to communicate their message to the cell. These molecules called *second messengers* are the intracellular signals they generate. Many of these second messengers affect gene transcription, as well as, many other processes in the cell. Receptors of Group II hormones work in collaboration with a specific protein called *G Protein*. Hence these receptors are also called *G protein-coupled receptors* or *GPCR*. The G protein is called the *transducer*. After the hormone (first messenger) binds to its specific receptor on the surface of the target cell, the signal is passed through the membrane located G protein transducer to a membrane-bound effector. The action of the effector molecule generates an intracellular second messenger, which is usually a small molecule or ion like cAMP, cGMP, Ca^{2+} and phosphatidyl inositides. The diffusible second messenger carries the signal to its ultimate destination, which may be in the nucleus, an intracellular compartment or the cell cytosol resulting in specific cell response. This general mechanism of signal transduction is shown in Figure 11.6.

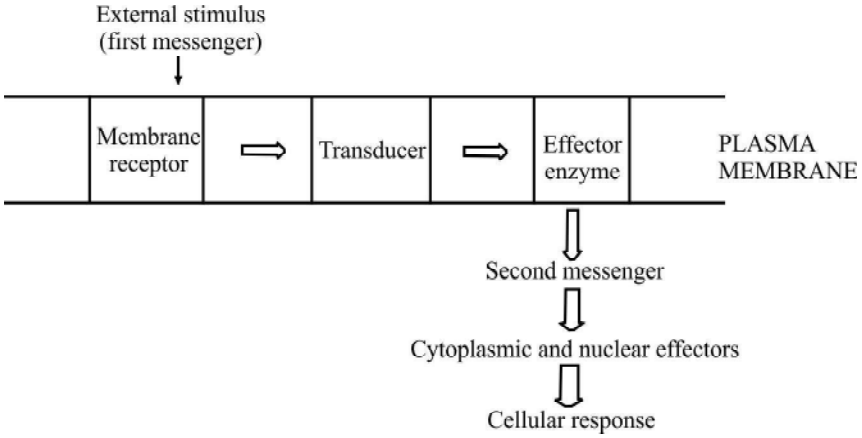

Figure 11.6: General mechanism of signal transduction

As discussed earlier, an important feature of signaling pathways is *amplification*. In this case, a single hormone-receptor complex can react with a number of transducer molecules, each of which can activate several molecules of effector protein. This will form several molecules of second messenger which can activate many kinase molecules, which in turn will catalyze the phosphorylation of many target proteins. This series of amplification events results in a cascade effect. The cascade mechanism means that small amounts of an extracellular compound can affect large numbers of intracellular enzymes without crossing the plasma membrane or binding to each target protein.

In the section above we learnt that Group II hormones work in collaboration with a specific protein called *G Protein* and an intracellular second messenger, which is usually a small molecule or ion like cAMP, cGMP, Ca^{2+} and phosphatidylinositides. These are the other important components of the mechanism of hormone action. Let us get to know a bit more about these components, next.

11.4.6 G Protein-Coupled Receptors (GPCR)

Receptors of Group II hormones have seven domains (areas) spanning the plasma membrane. This is shown in Figure 11.7. The seven domains are depicted as seven interconnected cylinders which extend through the lipid bilayer of the membrane (plasma membrane consists of a protein layer in between two lipid layers). The G protein consists of 3 polypeptides (subunits), each having a different amino acid composition, i.e. it is a heterotrimeric protein. The 3 polypeptides are denoted as α, β and γ in Figure 11.7. The α subunit of G protein is bound to guanosine diphosphate (GDP). The G protein is inactive in this form. Further the G protein as shown in Figure 11.7 is anchored to the plasma membrane but not linked to the receptor.

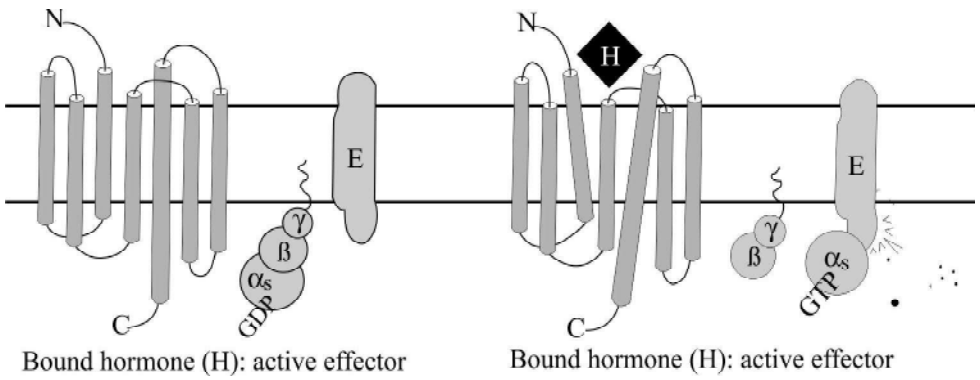

Figure 11.7: G-Protein coupled receptors (GPCR)

When a Group II hormone binds to the receptor, there is presumably a conformational change of the receptor. This has been depicted as tilted membrane-spanning domains in Figure 11.7. Following the conformational change, a GTP molecule replaces the GDP molecule attached to the α subunit. The β and γ subunits then dissociate from the α subunit as shown in Figure 11.7. The β and γ subunits however are always associated (βγ). These changes result in activation of the G protein. The α subunit along with the attached molecule of GTP then binds to the effector molecule (E) which is also present on the plasma membrane. The effector can be the enzyme adenylyl cyclase, Ca^{2+}, Na^{+}, K^{+} or Cl^{-} channels, the enzyme phospholipase C or the enzyme cGMP phosphodiesterase.

The α subunit has intrinsic (built-in) GTPase activity. This means it can act as the enzyme GTPase and hydrolyze GTP into GDP and Pi. Once this happens, the protein gets inactivated. The trimeric complex (αβγ) is reformed and is ready for another cycle. Cholera toxin catalyzes the ADP-ribosylation (combining with ADP) of α subunit. This modification disrupts the intrinsic GTP-ase activity and hence the α subunit cannot reassociate with βγ and is therefore irreversibly activated.

There is a large family of G proteins. The α subunits of different G proteins are distinct, but the β and γ subunits are similar and often interchangeable. Humans have 24 α proteins, 5 β proteins and 6 γ proteins.

Next, let us get to know more about the second messengers.

11.4.7 Second Messengers

To understand the second messengers better, let us look at Table 11.1, presented earlier. As you can see, in Table 11.1, Group II hormones are further subdivided on the basis of the intracellular signals (second messengers) they generate. For example, Group IIA hormones function through cyclic AMP, Group IIB hormones function through cyclic GMP and so on. Cyclic AMP, GMP, calcium, phosphatidyl inositols etc. are all second messengers. Let us get to know more about these messengers next, starting with cyclic AMP.

A) ***Cyclic AMP (cAMP)***

Figure 11.8 illustrates the formation of cyclic AMP. As can be seen, it is formed from ATP by the enzyme adenylyl cyclase (effector molecule). Several components comprise a system for the generation, degradation and action of cAMP. These are discussed next.

- *Adenylyl cyclase*

Not all hormones on binding to G proteins activate this enzyme. In the case of some hormones, binding to G proteins results in inhibition of adenylyl cyclase. Such G proteins are referred to as G_i *proteins*. Accordingly G proteins which cause activation (stimulation) of adenylyl cyclase are referred to as G_s *proteins*. Hence Group IIA hormones may be subdivided on the basis of this characteristic as given in Table 11.3.

Table 11.3: Subclassification of Group II A Hormones

Hormones that stimulate Adenylyl cyclase (Hs)	Hormones that inhibit Adenylyl cyclase (Hi)
• Glucagon • Calcitonin • Parathyroid hormone • β-Adrenergic catecholamines • Thyroid-stimulating hormone (TSH) • Antidiuretic hormone (ADH) • Adrenocorticotropic hormone (ACTH) • Human chorionic gonadotropin (HCG)	• Acetylcholine • α_2-Adrenergic catecholamines

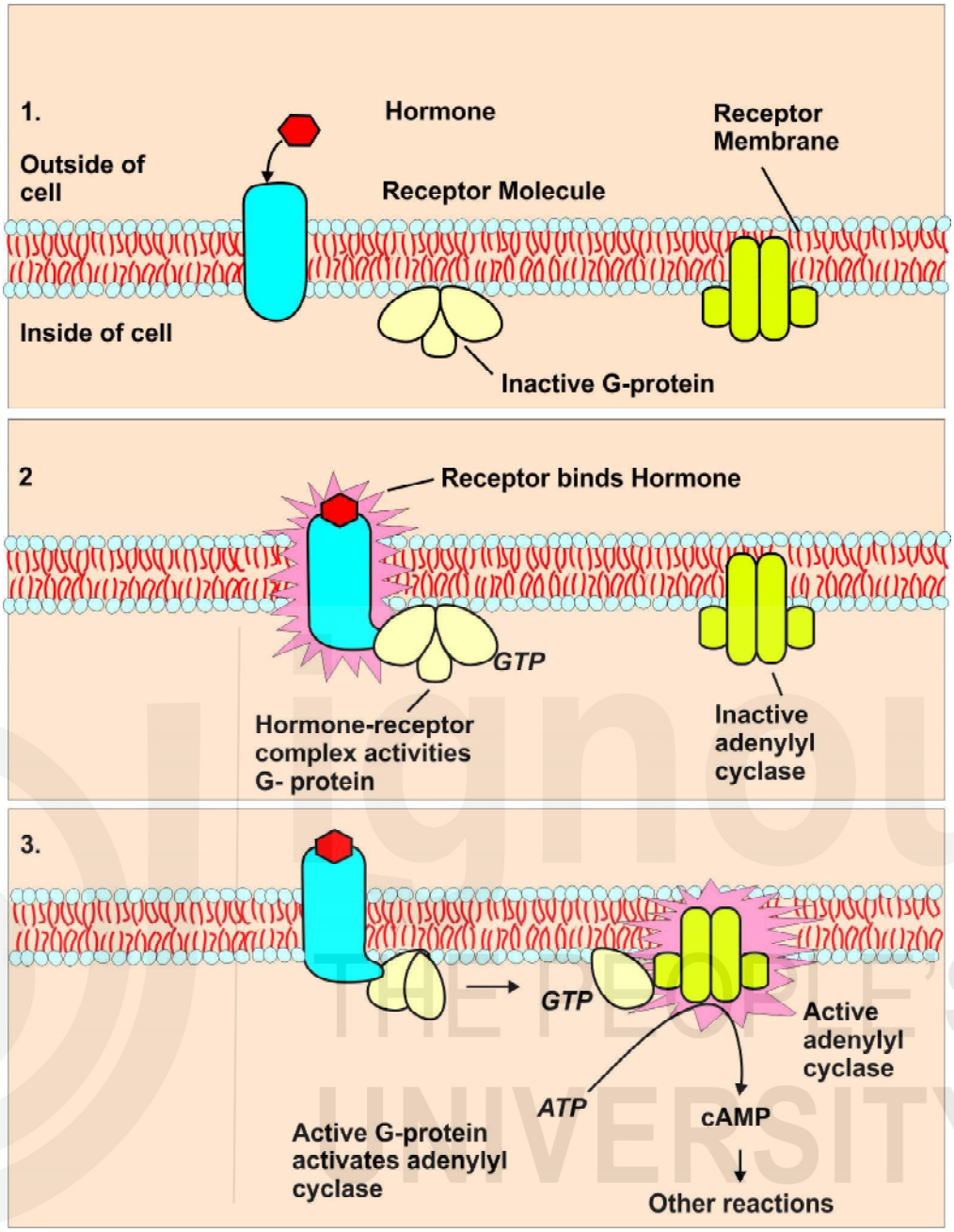

Figure 11.8: Formation of cyclic AMP

Thus two parallel systems have been identified, a stimulatory (s) and an inhibitory (i) system. Further each system consists of a receptor R_s or R_i, and a regulatory complex protein G_s and G_i. As discussed earlier, G_s and G_i are each trimers composed of α, β and γ subunits. However the α subunit in G_s differs from that in G_i. Hence they are designated α_s and α_I respectively. Both α_s and α_i bind to guanine nucleotides. GTP activates α_s and α_i and GDP inactivates α_s and α_i. There is a large family of G proteins.

The α subunits and the βγ complex have actions independent of those on adenylyl cyclase. Some forms of α_i stimulate K^+ channels and inhibit Ca^{2+} channels and some α_s molecules have the opposite effects. Some members of the G family activate the phospholipase C group of enzymes. The βγ complexes have been associated with K^+ channel stimulation and phospholipase C activation. G proteins are involved in many important biologic processes in addition to hormone action. GPCRs are implicated in a number of diseases and are major targets for pharmaceutical agents.

- *Protein Kinase*

Ligand binding to a cell-surface receptor almost invariably results in the activation of protein kinases. These enzymes catalyze the transfer of a phosphoryl group of ATP to various protein substrates. Some proteins are activated by phosphorylation, whereas, others are inactivated. The cAMP produced by the action of adenylyl cyclase, binds to a protein kinase called *protein kinase A (PKA)* that is a heterotetrameric molecule. It is a serine-threonine protein kinase, catalyzes phosphorylation of the hydroxyl group of specific serine-threonine residues in target enzymes. This phosphorylation can be reversed by the action of protein phosphatases, which catalyze hydrolytic removal of the phosphoryl groups.

Protein kinase A consists of two regulatory subunits (R) and two catalytic subunits (C) in a configuration of R_2C_2. On binding with cAMP, the following change takes place:

$$4 \text{ cAMP} + R_2C_2 \longrightarrow R_2 \cdot (4 \text{ cAMP}) + 2 \text{ C}$$

The enzyme protein kinase A has no enzymatic activity when present in the configuration R_2C_2. However binding of cAMP by R dissociates R from C as shown in the equation above. This frees the C subunit and becomes active. The active C subunit catalyzes the transfer of the γ (last) phosphate of ATP to serine or threonine amino acid residues in a variety of proteins resulting in the formation of phosphoproteins.

- *Phosphoproteins*

The effects of cAMP in eukaryotic cells are all thought to be mediated by protein phosphorylation-dephosphorylation, principally on serine and threonine residues of protein molecules as discussed above. The control of any of the effects of cAMP, including such diverse processes as carbohydrate and fat metabolism, ion transport, enzyme induction, gene regulation, cell growth and replication etc. could be conferred by a specific protein kinase, by a specific phosphatase, or by specific substrates for phosphorylation. These substrates help define a target tissue and are involved in defining the extent of a particular response within a given cell.

- *Phosphodiesterases*

The ability to turn off a signal-transduction pathway is an essential element of all signaling processes. Actions caused by hormones that increase cAMP concentration can be terminated by the action of phosphodiesterases. They catalyze the hydrolysis of cAMP to 5'-AMP. The presence of these hydrolytic enzymes ensures a rapid turnover of the signal (cAMP) and hence a rapid termination of the biologic process once the hormonal stimulus is removed. There are at least 11 known members of the phosphodiesterase family of enzymes.

Having studied about cyclic AMP, we move to the other second messenger, cyclic GMP.

B) ***Cyclic GMP (cGMP)***

It is also an intracellular signal. It is made from GTP by the enzyme *guanylyl cyclase*. The *atriopeptins*, a family of peptides produced in cardiac atrial tissues, cause natriuresis (excretion of Na^+ in urine), diuresis (increased excretion of urine), vasodilation and inhibition of secretion of the hormone, aldosterone. These peptides bind to and activate the membrane-bound guanylyl cyclase. This results in an increase of cGMP by as much as 50-fold and brings about the above mentioned effects. The increased cGMP activates cGMP-dependent protein kinase (PKG), which in turn phosphorylates a number of smooth muscle proteins. This then results in relaxation of smooth muscle and vasodilation. Termination of this effect is brought about by the action of the enzyme *cGMP phosphodiesterase* which hydrolyzes cGMP to 5'-GMP.

Next, we shall learn about the role of calcium and phospatidylinositols as second messengers in the mechanism of hormone action.

C) ***Calcium or Phosphatidylinositols***

First let us get to know about the role of calcium.

Calcium

Several hormones act through calcium as second messenger. Ionized calcium is also an important regulator of a variety of cellular processes, including muscle contraction, blood clotting, enzyme activity and membrane excitability. The extracellular Ca^{2+} concentration is about 5mmol/L and is very rigidly controlled. Although substantial amounts of calcium are associated with intracellular organelles such as mitochondria and endoplasmic reticulum, the intracellular concentration of free or ionized calcium (Ca^{2+}) is very low: 0.05-10 μmol/L. Inspite of this large concentration gradient and a favourable electrical gradient, Ca^{2+} is restrained from entering the cell. A considerable amount of energy is expended to ensure that the intracellular Ca^{2+} is controlled, as prolonged elevation of Ca^{2+} in the cell is very toxic. The class IIC hormones, about which you have already studied in Table 11.1, by binding to receptors that are themselves Ca^{2+} channels, enhance membrane permeability to Ca^{2+} and thereby increase Ca^{2+} influx. Hormones also indirectly promote Ca^{2+} influx by modulating the membrane potential at the plasma membrane. Ca^{2+} can also be mobilized from the endoplasmic reticulum, and possibly from mitochondrial pools.

Once calcium enters the cell, it brings about its effect through the calcium-dependent regulatory protein *calmodulin*. Calmodulin has four Ca^{2+} binding sites. When all these sites are attached to, there is a marked conformational change of the molecule. This allows calmodulin to activate enzymes and ion channels. The interaction of Ca^{2+} with calmodulin is conceptually similar to the binding of cAMP to protein kinase A and the subsequent activation of protein kinase A. Calmodulin is one of numerous subunits of complex proteins and is particularly involved in regulating various kinases and enzymes of cyclic nucleotide generation and degradation. Some of the enzymes regulated directly or indirectly by Ca^{2+}, probably through calmodulin is given in Table 11.4.

Table 11.4: Enzymes regulated directly or indirectly by Ca^{2+} through calmodulin

- Adenylyl cyclase
- Ca^{2+}- dependent protein kinases
- Ca^{2+}- Mg ATPase
- Cyclic nucleotide phosphodiesterase
- Phosphorylase kinase

Next, let us look at the role of phosphatidylinositols.

Phosphatidylinositols

Some signal must provide communication between the hormone receptor on the plasma membrane and the intracellular Ca^{2+} reservoirs. This is provided by two molecules, both derived from a plasma membrane phospholipid, phosphatidylinositol 4,5-bisphosphate. When hormones like antidiuretic hormone, acetylcholine and α_1-type catecholamines bind to their respective receptors on the cell surface, the signal is transduced through the G protein. The active GTP-bound form of the G protein activates the effector enzyme phospholipase C. This enzyme catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate to inositol triphosphate and 1,2-diacylglycerol. Both these intermediates are second messengers that transmit the original signal to the interior of the cell.

Inositol triphosphate diffuses through the cytosol and binds to a calcium channel in the membrane of the endoplasmic reticulum. This binding causes the calcium channel to open for a short time, releasing Ca^{2+} from intracellular storage sites in the endoplasmic reticulum into the cytosol. Accumulation of high levels of Ca^{2+} in the cytosol results in the activation of Ca^{2+}-calmodulin-dependent kinases and many other Ca^{2+}-calmodulin-dependent enzymes. These then modify substrates and thereby alter physiologic responses.

1,2-diacylglycerol is capable of activating the enzyme, protein kinase C, whose activity also depends upon Ca^{2+}. Protein kinase C can phosphorylate specific proteins to form the corresponding phosphoproteins which then bring about cellular responses.

Signaling via the inositol-phospholipid pathway just discussed, is turned off in several ways. First, when GTP is hydrolyzed, the G protein returns to its inactive form and no longer stimulates phospholipase C. The activities of the two second messenger molecules, inositol triphosphate and 1,2-diacylglycerol are also transient. They are rapidly converted to inactive intermediates. The calcium signal is also short-lived since Ca^{2+} is pumped back into the lumen of the endoplasmic reticulum when the channel closes.

Finally, let us study about the last second messenger i.e. protein kinase cascade.

D) ***Protein kinase cascade***

Many growth factors operate by a signaling pathway that includes a multifunctional transmembrane protein called *tyrosine kinase*. The receptor, transducer and effector functions are all found in this protein. As the name suggests, the kinase preferentially phosphorylates tyrosine residues. Phosphorylation of tyrosine residues is not common (< 0.03% of total amino acid phosphorylation) in mammalian cells. Binding of the ligand to an extracellular domain of the receptor activates tyrosine-kinase catalytic activity in the intracellular domain, by *dimerization* (combination of two units) of the receptor. When the two receptor molecules associate, each tyrosine-kinase domain catalyzes the phosphorylation of specific tyrosine residues of its partner, a process called *autophosphorylation*. This initiates a complex series of events. The phosphorylated receptor next phosphorylates various receptor protein substrates, again on tyrosine residues. There are at least four such substrates. The phosphorylated substrates then bind to specific domains of a variety of proteins that are directly involved in mediating the different effects of the hormone. This entire sequence sets off a cascade of events in the cell. It is now well known that the hormone insulin works through such a receptor.

To end the tyrosine kinase cascade effect, phosphoryl groups are removed from both the receptors and their protein targets by the action of protein tyrosine phosphatases. These enzymes play an important role in regulating the tyrosine-kinase signaling pathway.

You may have found the discussion above on mechanism of hormone action and signal transduction a bit tough. We must tell you that only a brief outline (for easy understanding) has been given in the above discussion on mechanism of hormone action and signal transduction. Extensive research conducted in this area has shown that the whole process is extremely complex involving the interplay of a host of receptor proteins, intermediates, regulators and coregulators. We hope you must have understood the mechanism involved. If not, we suggest you go through this section again, step by step, and recapitulate. This information you would see is the basis for your understanding the biochemical role of different hormones discussed next.

Check Your Progress Exercise 3

1) What do you understand by G protein-coupled receptors?

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2) Briefly explain the general mechanism of signal transduction.

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3) List the different second messengers used in the mechanism of hormone action.

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11.5 BIOCHEMICAL ROLE OF HORMONES

Before we get to know about the role of hormones, let us quickly review where the various hormones are synthesized. Hormones are synthesized in a variety of cellular arrangements. You may already know that some are synthesized in specialized organs designed solely for this specific purpose – like *thyroid* (triiodothyronine), *adrenal* (glucocorticoid and mineralocorticoid) and the *pituitary* (TSH, growth hormone, ACTH etc). Some organs are designed to perform two distinct but closely related functions: like the *ovaries* produce mature oocytes, as well as, the reproductive hormones *estradiol* and *progesterone*. Hormones are also produced in specialized cells within other organs – like *small intestine* (glucagon-like peptide), *kidney* (angiotensin II). Synthesis of some hormones requires the parenchymal cells of more than one organ – like the skin, liver, kidney are required for the production of 1,25 dihydroxy D_3 or calcitriol.

Now then, what is the role of hormones in our body? Let us find out.

The functions of hormones vary widely. A hormone may bring about its effect in a specific cell type, tissue or organ. Or a hormone can cause changes in more than one cell type, tissue or organ. A hormone can also have one effect in one tissue and a totally opposite effect in another tissue. Most hormones exert their influence on more than one reaction/metabolic pathway in the body. Again a certain type of effect can be caused by more than one hormone. Some authors also tend to categorize the biological role of hormones as being predominantly either *physiological* or *biochemical*. Probably these effects are in many cases overlapping. Hence, all this adds to the complexity of hormones as a class of biologically important molecules in the body. Nevertheless, due to painstaking research in the last few decades, the

functions of the various hormones have been spelt out. There are two ways of elucidating the functions of hormones. First is a direct assessment where data has been obtained regarding its activity. Second is by looking at what happens in a state of absence/deficiency of the hormone and attributing the effects to lack of those actions of the hormone.

We will now look at the biochemical role of hormones. Included for your study are some of the major hormones from different endocrine glands. However, you must know, there are many more hormones which have been identified and whose functions have been enumerated. This can call for a separate study altogether. Here our focus is on a few major hormones. We shall take them one by one, starting with the hormones produced by the pancreas.

11.5.1 Pancreas

The two major hormones secreted by the pancreas, as you may already be aware, include insulin and glucagon. Let us get to know about their role.

A) **Insulin**

Insulin is secreted by the α-cells of the islets of Langerhans and was first isolated from the pancreas in 1922 by *Banting* and *Best*. Almost overnight this changed the outlook for the severely diabetic patient from one of rapid decline and perhaps death to that of a nearly normal person. Historically, insulin has been associated with 'blood sugar' and accordingly insulin has profound effects on carbohydrate metabolism. In fact it is now known that insulin affects fat and protein metabolism as much as it does carbohydrate metabolism.

Insulin is associated with energy abundance. When there is great abundance of energy-giving foods in the diet, especially excess amounts of carbohydrates, insulin is secreted in large quantity. Hence insulin plays an important role in storing the excess energy substances. Thus carbohydrates are stored as glycogen mainly in the liver and muscles and as fats in the adipose tissues. In the case of proteins, insulin has a direct effect in promoting amino acid uptake by cells and conversion of these amino acids into protein. So let us see the effect of insulin on the metabolism of these molecules.

- *Effects on carbohydrate metabolism*

Immediately after a high-carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin. The insulin in turn causes rapid uptake, storage and utilization of glucose by almost all the tissues of the body, but especially by the muscles, adipose tissue and liver. Glucose enters all cells by facilitated diffusion. In muscles, adipose and a variety of other tissues, insulin facilitates glucose entry into the cells by increasing the number of glucose transporter in the cell membrane. The glucose transporter molecule is called GLUT 4. In the liver, glucose induces hexokinase and this increases the phosphorylation of glucose. As a result, the intracellular concentration of free (unphosphorylated) glucose remains low, facilitating the entry of glucose into the cell.

Insulin influences the intracellular utilization of glucose in a number of ways as shown in Figure 11.9. In a normal person, about half the glucose ingested is converted to energy through the glycolytic pathway and about half is stored as glycogen or fat. *Glycolysis* (breakdown of glucose into pyruvate and lactate) decreases in the absence of insulin, and the anabolic processes of *glycogenesis* (synthesis of glycogen) and *lipogenesis* (synthesis of fat) are affected. Only 5% of an ingested glucose load is converted to fat in an insulin-deficient diabetic.

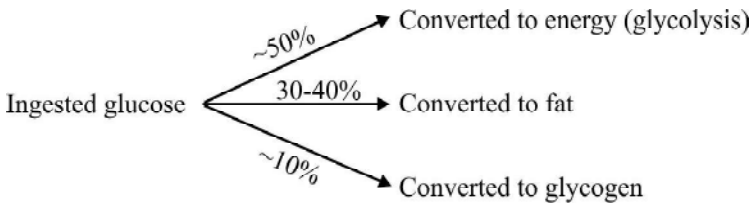

Figure 11.9: Utilization of glucose

Insulin increases hepatic glycolysis by increasing the activity and amount of several regulatory enzymes including *glucokinase*, *phosphofructokinase*-1 (PFK-1) and *pyruvate kinase*. Enhanced glycolysis increases glucose utilization and thus indirectly decreases glucose release into the plasma. Insulin also decreases the activity of the enzyme glucose-6-phosphatase, an enzyme found in liver but not in muscle. Since glucose-6-phosphate cannot cross the plasma membrane of the liver cell (only glucose can), this action of insulin results in the retention of glucose within the liver cell.

In liver and muscle, insulin stimulates the conversion of glucose to glucose-6-phosphate, which then undergoes isomerization to glucose-1-phosphate and is incorporated into glycogen by the enzyme glycogen synthase. You may recall reading about this in Unit 6, under Carbohydrate Metabolism. The activity of this enzyme is stimulated by insulin. This effect is an indirect one. Insulin activates a phosphodiesterase causing hydrolysis and conversion of cyclic-AMP (cAMP) to 5'-AMP. Hence intracellular cAMP levels are decreased leading to low activity of cAMP-dependent protein kinase which normally phosphorylates glycogen synthase. Accordingly glycogen synthase remains in the dephosphorylated active form, promoting glycogen synthesis. Additionally insulin also activates a phosphatase that dephosphorylates glycogen synthase and maintains it in the active form. Low intracellular levels of cAMP also do not promote phosphorylation of phosphorylase, keeping it in an inactive form and decreasing glucose liberation from glycogen. Hence the net effect of insulin on glycogen metabolism is highly anabolic. The glycogen can increase to a total of about 5-6% of the liver mass, which is equivalent to almost 100 g of stored glycogen in the whole liver.

The actions of insulin on glucose transport, glycolysis and glycogenesis occur within seconds or minutes, since they mainly involve the activation or inactivation of enzymes by covalent modulation through phosphorylation or dephosphorylation. A more long-term effect on plasma glucose involves the inhibition of gluconeogenesis by insulin. Many of the gluconeogenic enzymes are activated by glucocorticoid hormones, and to a smaller extent by α- and β-adrenergic agents, angiotensin II and vasopressin. Insulin inhibits these same steps. The key gluconeogenic enzyme, as you have already studied earlier in Unit 6, is *phosphoenolpyruvate carboxykinase (PEPCK)*. Insulin decreases the amount of this enzyme by selectively inhibiting transcription of the gene that codes for the mRNA for PEPCK.

Insulin stimulates lipogenesis from glucose. The net action of all these effects of insulin is to decrease the blood glucose level. In this action, insulin stands alone against a group of other hormones that counteract this effect.

Next, let us study about the role of insulin in lipid metabolism.

- *Effects on lipid metabolism*

As already mentioned above, lipogenesis is promoted by insulin. This is by:

- providing acetyl-CoA and NADPH required in fatty acid synthesis
- maintaining a normal level of the enzyme acetyl-CoA carboxylase, and
- providing the glycerol moiety required for triacylglycerol synthesis.

Thus effect of insulin on fat is anabolic. Insulin is also a potent inhibitor of lipolysis in liver and adipose tissue and thus has an indirect anabolic effect. Since insulin decreases tissue cAMP levels, protein kinase activity is decreased resulting in dephosphorylated form of the enzyme lipase. This is the inactive form and hence cannot cause hydrolysis of fat. In addition, insulin also exhibits direct action of its anti-lipolytic activity. It activates a phosphatase as a result of which the lipase is maintained in a dephosphorylated inactive form. The net effect is decreased levels of free fatty acids, a situation that promotes glucose utilization (free fatty acids have a glucose-sparing action). In patients with insulin deficiency, lipase activity increases, resulting in enhanced lipolysis and increased concentration of free fatty acids in plasma and liver.

Insulin apparently affects the formation or clearance of VLDL and LDL, since levels of these metabolites, and consequently the level of cholesterol, are often elevated in poorly controlled diabetes. Accelerated atherosclerosis, a serious problem in many diabetics, is attributed to this metabolic defect. So now you can appreciate what important role insulin has in lipid metabolism.

Next, we shall look at the role of insulin in protein metabolism.

- *Effects on protein metabolism*

Insulin generally has an anabolic effect on protein anabolism since it stimulates protein synthesis and retards protein degradation. It stimulates the uptake of neutral amino acids into muscle. Among the amino acids, most strongly transported are valine, leucine, isoleucine, tyrosine and phenylalanine. The effects of insulin on general protein synthesis in skeletal and cardiac muscle and in liver are thought to be exerted at the level of mRNA translation. As already discussed, insulin depresses the rate of gluconeogenesis. Because amino acids are quantitatively the most important substrates for gluconeogenesis, the suppression of gluconeogenesis conserves the amino acids in the protein stores of the body. Accordingly, protein wasting is one of the most serious of all the effects of severe diabetes mellitus.

Finally, let us look at the effect of insulin on growth and its synergistic effect with growth hormone.

- *Effect on growth and synergistic effect with growth hormone*

Because insulin is required for synthesis of proteins, it is equally as essential for growth of an individual as is growth hormone. Animal experiments have shown that a depancreatized, hypophysectomized (removal of pancreas and pituitary) rat without therapy hardly grows at all. Administration of either insulin or growth hormone one at a time also causes almost no growth. However a combination of the two hormones results in dramatic growth. Thus it appears that the two hormones – insulin and growth hormone – function synergistically to promote growth, each performing a special function that is separate from that of the other. Probably, a small part of this necessity for both hormones results from the fact that each promotes cellular uptake of different types of amino acids, all of which are required if growth is to be achieved.

Having studied the role of insulin in our body, can you now suggest what would happen if there was a deficiency of insulin in our body. Read the next section and tally your responses with the effects given herewith.

- *Insulin deficiency*

The central role of insulin in carbohydrate, lipid and protein metabolism can be best understood by examining the consequences of its deficiency in humans. The most prominent feature of diabetes mellitus is *hyperglycemia* (high blood sugar levels). This is due to :

- decreased entry of glucose into cells
- decreased urtilization of glucose by various tissues, and
- increased production of glucose (gluconeogenesis) by the liver.

Figure 11.10 depicts the pathophysiology of insulin deficiency. Thus polyuria, polydipsia and weight loss in spite of adequate caloric intake are the major symptoms of insulin deficiency. High levels of blood sugar lead to excretion of sugar in urine (glycosuria). The urine volume is increased due to osmotic diuresis leading to polyuria and polydipsia. Due to non-utilization of glucose as a source of energy, alternative sources of energy like fats are used leading to weight loss.

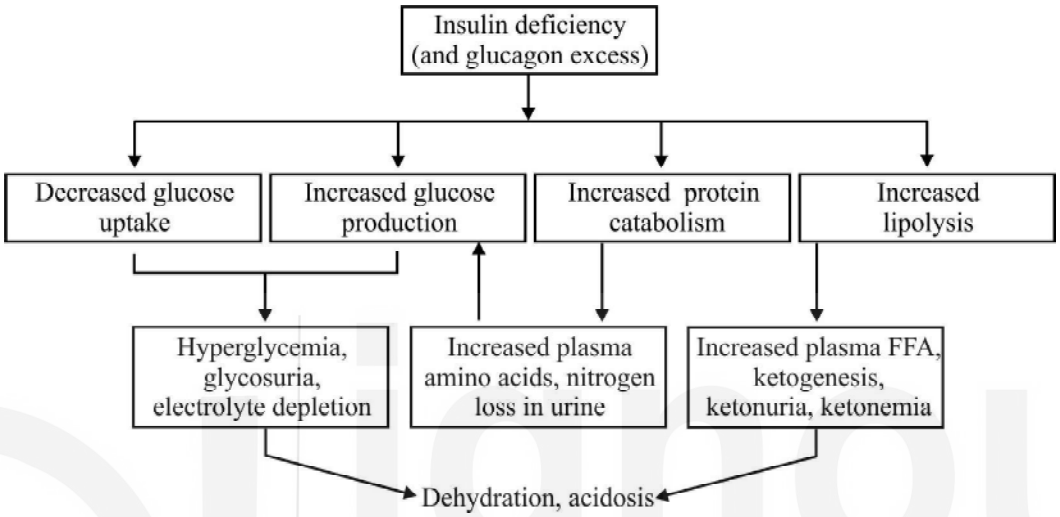

Figure 11.10: Pathophysiology of insulin deficiency

Next, let us get to know about *glucagon*, the other hormone produced by the pancreas.

B) **Glucagon**

You may already be aware that glucagon is the hormone secreted by the β-cells of the islets of Langerhans of the pancreas. Glucagon has several functions, but, diametrically opposed to those of insulin. Hence, one of the most important functions of glucagon would be to increase the blood glucose concentration. Secretion of glucagon is inhibited by glucose, emphasizing the fact that the actions of glucagon oppose those of insulin.

While insulin as we have just seen promotes energy storage by stimulating glycogenesis, lipogenesis and protein synthesis, glucagon causes the rapid mobilization of potential energy sources by various mechanisms. Let us study the effects of glucagon next.

- *Effects on glucose metabolism*

The major effect of glucagon on glucose metabolism is:

- breakdown of liver glycogen (glycogenolysis), and
- increased synthesis of glucose from non-carbohydrate sources (gluconeogenesis) in the liver.

Thus liver is the primary target of glucagon action. However, both of these effects of glucagon greatly enhance the availability of glucose to the other organs of the body. Let us now see how these effects are brought about.

As a result of glycogenolysis in the liver, the blood glucose concentration increases within minutes. Glucagon, being a Group II hormone, binds to specific receptors in the hepatic cell plasma membrane which results in the activation of the enzyme *adenylyl cyclase*. As discussed earlier, adenylyl cyclase forms cAMP, which activates a protein kinase and causes phosphorylation of several proteins including the enzyme glycogen phosphorylase. Being active in the phosphorylated form, phosphorylase enhances the rate of glycogen degradation, releasing glucose to blood. Simultaneously

glycogen synthase is also phosphorylated by the kinase. However, the synthase is inactive in this form and glycogen synthesis is inhibited. Thus while glucagon on one hand adds glucose to blood, on the other hand it prevents glucose from leaving blood for glycogenesis. The overall effect is a large increase in blood sugar concentration. In fact, this whole sequence of events has a cascading effect. Hence, only a few micrograms of glucagon can cause the blood glucose level to double or more within a few minutes. It should be noted here that glucagon has no effect on glycogenolysis in muscle tissue. You may recall reading about this earlier also in Unit 6, sub-section 6.7.5.

The increased level of cAMP following release of glucagon, stimulates the conversion of amino acids to glucose by inducing a number of enzymes involved in the gluconeogenic pathway. This includes the key regulatory enzyme of gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK). Glucagon through cAMP increases the rate of transcription of mRNA from the PEPCK gene, and this stimulates the synthesis of more PEPCK. Additionally, glucagon also causes induction of fructose-1,6-bisphosphatase and glucose-6-phosphatase. In fact glucagon is considered to be the most potent gluconeogenic hormone.

Next, we shall read about the effect of glucagon on lipid metabolism.

- *Effect on lipid metabolism*

Glucagon is a potent lipolytic agent. It increases the cAMP levels in the adipose cell. This causes activation of a kinase that phosphorylates the hormone-sensitive enzyme lipase. The lipase hydrolyzes the stored fat into its components, glycerol and fat. Thus glucagon secretion results in mobilization of fat. The fatty acids released are transported by blood to be metabolized for energy by other body tissues. High levels of fatty acids in blood have a sparing action on the utilization of glucose, thus conserving low blood glucose for those tissues that are totally or in great part dependent on glucose as fuel. However, excessive breakdown of fatty acid in turn promotes *ketogenesis* (synthesis of ketone bodies-acetone, acetoacetate and 3-hydroxy butyrate). Invariably, it leads to the undesirable condition of ketosis.

With this, we end our study of the biochemical role of hormones of the pancreas. Next, we shall study about the role of hormones produced by the thyroid.

11.5.2 Thyroid

The thyroid gland produces two hormones – triiodothyronine (T_3) and tetraiodothyronine or thyroxine (T_4). Additionally, the thyroid has now been recognized to be involved in the secretion of the third hormone, calcitonin in human beings. Let us get to know about these hormones.

A) *T_3 and T_4*

Hormones, T_3 and T_4, are unique in that they require the element iodine for biological activity. Hence the biological role of these two thyroid hormones has already been discussed under the functions of iodine in the section on trace minerals in Unit 10, earlier. We suggest you look up the unit once again now to study their functions. We will move on to calcitonin.

B) *Calcitonin*

In human beings, calcitonin is secreted not by the parathyroid glands but by the thyroid gland. It has weak effects on blood calcium but opposite those of parathormone (PTH). Calcitonin reduces blood Ca^{2+} concentration by decreasing resorption of bone mineral. Hence it functions to increase deposition of Ca^{2+} and phosphate in the bone.

What about the parathyroid? What are the hormones produced in this gland? Read and find out.

11.5.3 Parathyroid

The parathyroid gland of the adult human being consists mainly of cells called chief cells which secrete the parathyroid hormone or parathormone (PTH). You may recall reading about the parathyroid in the Applied Physiology Course, Unit 11. Let us study about the role of the parathormone hormone here once again.

Parathormone

This hormone is intimately associated with the metabolism of calcium and phosphorus in the body. Much of the effect of PTH on its target organs is mediated by the second messenger, cAMP. This ultimately results in the activation of the intracellular enzymes or proteins that finally mediate the biologic actions of the hormone. These actions are concerned with calcium and phosphate metabolism, which are discussed next.

- *Effect on calcium homeostasis*

We have already seen that calcium ion regulates a number of important physiologic and biochemical processes. To ensure that these processes operate normally, the plasma Ca^{2+} concentration is maintained within very narrow limits. The physiologic maintenance of calcium balance depends on the long-term effects of PTH acting on intestinal absorption. This effect is brought about in an indirect manner by stimulating the synthesis of calcitriol (vitamin D hormone) in the intestine. Calcitriol then promotes the absorption of Ca^{2+} from the intestinal lumen. (The details of this have already been discussed in the section on vitamin D, in Unit 10). However, if there is a prolonged deficiency of calcium in the diet resulting in inadequate intestinal absorption of Ca^{2+}, then PTH acts directly on bone and kidney. PTH increases the rate of dissolution of bone, both organic and inorganic phases and the concentration of Ca^{2+} in the extracellular fluid (ECF) is increased. PTH also reduces the renal clearance or excretion of calcium. This again results in an increased concentration of Ca^{2+} in ECF. The most rapid changes occur through the action on the kidney. But because bone contains the maximum amount of Ca^{2+}, the largest effect is from the bone.

- *Effect on phosphate homeostasis*

Calcium in the body is usually associated with phosphate. The hydroxyapatite crystal in bone consists mainly of calcium phosphate. Hence phosphate is released along with calcium from bone following the action of PTH on dissolution of bone mineral. But at the same time, PTH increases renal phosphate clearance by diminishing proximal tubular reabsorption of phosphate ions. So the net effect of PTH on bone and kidney is to increase the ECF calcium concentration and decrease the ECF phosphate concentration. This ensures that calcium and phosphate concentrations are maintained in an inverse proportion. This is essential to prevent the development of a supersaturated concentration of calcium and phosphate in the plasma and precipitation of the two mineral ions. PTH also increases the rate of tubular reabsorption of sodium, potassium and amino acids.

Having looked at the role of parathormone, next let us study about the hormones produced by the adrenal medulla and the cortex.

11.5.4 Adrenal Medulla

The adrenal medulla produces the catecholamine hormones dopamine, norepinephrine (noradrenaline) and epinephrine (adrenaline). The major product of the adrenal medulla is *epinephrine* which constitutes 80% of the catecholamines in the adrenal medulla. Tyrosine is the immediate precursor of catecholamines.

The effect of the catecholamine hormones depends on the kind of receptors they bind to. They act through 2 major classes of receptors called α-*adrenergic* and β-

adrenergic. Each is divided into 2 subclasses– α_1 and α_2 and β_1 and β_2. The classification is based on the relative order of binding of various *agonists* (molecules that mimic the action of the hormones) and *antagonists* (molecules that oppose the action of the hormones). Different catecholamine hormones have different binding affinities for the four types of the adrenergic receptors. In fact no hormone has exclusive affinity for any single receptor. A hormone could bind to more than one type of receptor. Further the degree of affinity for each receptor would be variable. Hence the effect a particular hormone can exert would depend upon the sum total of the effects of the individual receptor and the affinity with which the hormone binds to the receptors. Table 11.5 lists the actions elicited on binding to the receptors.

Table 11.5: Actions elicited through adrenergic receptors

α_1	α_2	β_1	β_2
Increased glycogenolysis Smooth muscle contraction • Blood vessels • Genitourinary tract	Smooth muscle relaxation • Genitourinary tract Smooth muscle contraction • Some vascular beds Inhibition of • Lipolysis • Renin release • Platelet aggregation • Insulin secretion	Stimulation of lipolysis Myocardial contraction • Increased rate • Increased force	Increased hepatic Gluconeogenesis Glycogenolysis Increased muscle Glycogenolysis Increased release of Insulin Glucagon Renin Smooth muscle relaxation Bronchi Blood vessels Genitourinary tract Gastrointestinal tract

Table 11.5 indicates that some of the functions of the α receptors are excitatory while others are inhibitory. Similarly β-receptors also have both, excitatory and inhibitory effects. Hence α and β receptors are not identified by excitation or inhibition but only with the affinity the hormone has for the receptors in a specific target organ. It is also generally believed that there is a less distinct division of a receptors into α_1 and α_2.

Catecholamines belong to Group II class of hormones. Hence their receptors are located on the cell surface. However the second messenger is different. α_2 and β adrenergic receptors function through cAMP while the α_1 adrenergic receptor utilizes Ca^{2+} or phosphatidyl inositols as indicated in Table 11.1 earlier.

What is the role of the hormones epinephrine and norepinephrine? Let us find out next.

Epinephrine and Norepinephrine

Both these hormones have somewhat different effects in exciting the α and β receptors. Norepinephrine binds to and activates mainly the α receptors, while the β receptors are activated to a lesser extent. On the other hand, epinephrine binds to and activates both α and β receptors to an equal extent. Therefore, the relative effects of norepinephrine and epinephrine on different target organs will be determined by the type of receptors in the organs. If they are all β receptors, then epinephrine will have greater effect on that target organ.

Stimulation of adrenal medulla causes release of both the hormones into circulation. The circulating norepinephrine causes constriction of essentially all the blood vessels of the body. Some of the effects include increased activity of the heart, inhibition of the gastrointestinal tract, dilation of the pupils of the eye etc.

Epinephrine causes almost the same effects but with some differences since it activates α and β receptors to the same extent. It has greater effect on cardiac stimulation than norepinephrine. It also causes only weak constriction of the blood vessels in the muscles. A further difference relates to their effects on tissue metabolism. Epinephrine has 5 to 10 times as great a metabolic effect as norepinephrine. It can increase the metabolic rate of the whole body to as much as 100% above normal.

Epinephrine increases glycogen breakdown in liver and muscle tissue. β-adrenergic stimulation activates glycogen phosphorylase and inhibits glycogen synthase through cAMP-dependent mechanism. You are already familiar with the effect of epinephrine on glycogenolysis in liver and muscle and release of glucose into the blood (carbohydrate metabolism) and a revision of that portion would be merited. Catecholamines also stimulate hepatic gluconeogenesis through α-adrenergic mechanisms. They increase delivery of gluconeogenic precursors to the liver – lipolytic (glycerol) and glycogenolytic (lactate and pyruvate). In addition, there is also increased hepatic uptake of amino acids. The net effect is increased availability of glucose in circulation.

Both epinephrine and norepinephrine activate hormone-sensitive lipase in adipose tissue, liver, heart and skeletal muscle. Any kind of physical or mental stress (or alarm) results in the secretion of these hormones into blood. Accordingly these hormones are also referred to as *fight* or *flight* hormones since they help the person through their actions to fight the stress condition. In the case of animals, they decide to either stand and/or fight the alarm condition or to run away from the situation. Hence the alternative name given is *flight*.

11.5.5 Adrenal cortex

The hormones secreted by the adrenal cortex are called *corticosteroids*. They all have a steroid structure and in fact are synthesized from *cholesterol*. There are three types of adrenocortical hormones – glucocorticoids, mineralocorticoids and androgens. *Qunatitatively* the first two hormones are more important. Only small amounts of androgens are secreted. We will be discussing the two major classes of the hormones, next.

A) **Glucocorticoids**

The glucocorticoids are 21-carbon steroids with many actions. One of their most important functions is to increase the blood glucose concentration and hence get their name. Cortisol, also known as hydrocortisone, is the predominant glucocorticoid in humans. Corticosterone is less abundant in humans, but is the main glucocorticosteroid in rodents. Glucocorticoid hormones affect basal metabolism, host defense mechanisms, blood pressure and response to stress. Let us learn about these effects and the effects of this hormone on carbohydrate, protein and lipid metabolism, next.

- *Effect on carbohydrate metabolism*

One of the most important functions of glucocorticoids is stimulation of gluconeogenesis in the liver, which could be as much as 6- to 10-fold. They increase all the enzymes required to convert amino acids into glucose in the liver cells. This is brought about by activating DNA transcription in the nucleus, with the formation of messenger RNAs that in turn lead to the synthesis of all the enzymes required for gluconeogenesis. Additionally, the hormones cause mobilization of amino acids from the extrahepatic tissues, mainly from the muscles. Hence, there is an increased delivery of amino

acids (the gluconeogenic substrate) to the liver from the peripheral tissues, thereby promoting gluconeogenesis. Thus glucocorticoids counteract the effects of insulin at numerous steps in glucose homeostasis. Glucocorticoids also increase hepatic glycogen deposition by promoting activation of the enzyme glycogen synthase. In this regard, they resemble insulin.

Glucocorticoids also cause a moderate decrease in the rate of glucose utilization in the body. Though the exact mechanism is not known, glucocorticoids may depress the reoxidation of NADH to NAD^+ resulting generally in decreased glycolysis. Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilization by the cells result in increased blood glucose concentration. This increase could even be 50% or more above the normal.

- *Effect on protein metabolism*

One of the principal effects of cortisol is reduction of protein stores in essentially all body cells except those of the liver. This is brought about by decreased protein synthesis, as well as, by increased catabolism of protein already present in the cell. There is decreased amino acid transport into extrahepatic tissues, as well as, decreased synthesis of RNA especially in muscle and lymphoid tissue. Great excess of glucocorticoids can result in extreme wasting of muscle tissue. The opposite effect is seen in the liver where there is increased synthesis of protein.

- *Effect on fat metabolism*

Glucocorticoids promote mobilization of fat from the adipose tissue. This increases the concentration of free fatty acids in the plasma, consequently increasing their utilization as energy sources. Cortisol may also have a direct effect on promoting oxidation of fatty acids in the cells. This helps in conserving glucose in the condition of low blood glucose concentration.

Excess of cortisol secretion or administration can cause obesity, with excess deposition of fat in the chest and head regions of the body giving a buffalo-like torso and a rounded 'moon face'.

- *Effect in stress and inflammation*

All types of stress, physical and neurogenic, cause an immediate and marked increase in secretion of cortisol. When large amounts of cortisol are secreted or administered, it has anti-inflammatory effects. It can, not only prevent inflammation from occurring, but once the inflammation has started, it can also cause rapid resolution of inflammation. It affects several stages in the inflammation process to bring about these effects. Cortisol also blocks the inflammatory response to allergic reactions.

- *Effect on blood cells and on host defense mechanisms*

Cortisol decreases the number of eosinophils and lymphocytes in the blood. Administration of large doses of cortisol also causes significant atrophy of all the lymphoid tissue throughout the body, which in turn decreases the output of both T cells and antibodies from the lymphoid tissue. The level of immunity is greatly decreased. At the same time, the ability of glucocorticoids in suppressing immunity makes them among the most useful of all drugs to prevent immunological rejection of transplanted organs like kidneys, heart etc.

Excess of glucocorticoid leads to bone dissolution by decreasing bone formation and increasing bone resorption. This can ultimately lead to osteoporosis. Hence using corticosteroids as therapeutic agents should be done only under expert medical supervision.

- *Permissive effects*

Small amounts of glucocrticoids must be present for a number of metabolic reactions to occur, although the glucocorticoids do not produce the reactions by themselves. This effect is called *permissive action*. Permissive effects include the requirement for glucocorticoids to be present for glucagon and catecholamines to exert their calorigenic effects, for catecholamines to exert their lipolytic effects and for catecholamines to produce pressor responses and bronchodilation.

Having studied about the glucocorticoids, next let us get to know more about other hormone produced by the adrenal cortex i.e. the mineralocorticoids.

B) ***Mineralocorticoids***

Mineralocorticoids, like glucocorticoids are also 21-carbon steroids. *Aldosterone* is the most potent hormone and accounts for about 90% of all mineralocorticoid activity. *Deoxycorticosterone* is secreted in about the same amount as aldosterone, but has only 3% of the mineralocorticoid activity of aldosterone. Even cortisol which is the major glucocorticoid secreted by the adrenal cortex has significant amount of mineralocorticoid activity. Let us get to know about the role of these hormones in our body.

- *Effects on transport of ions*

The major actions of aldosterone and other steroids with mineralocorticoid activity are on ion transport. They increase the reabsorption of Na^+ from the urine, sweat, saliva and gastric juice. Na^+ diffuse out of the urine (or sweat, saliva and gastric juice) into the surrounding epithelial cells and are actively transported from these cells into the interstitial fluid. The amount of Na^+ removed from these fluids is proportionate to the rate of active transport of Na^+. Thus mineralocorticoids cause retention of Na^+ in the extra cellular fluid (ECF). They also function in the transport of K^+ and to a lesser extent, the transport of H^+. In fact the increased amounts of Na^+ are exchanged for K^+ and H^+ in the renal tubules, resulting in excretion of K^+ causing K^+ diuresis. Therefore, the net effect of excess aldosterone in the plasma is to increase the total quantity of Na^+ in the ECF while decreasing the K^+ concentration. In the kidneys, they act primarily on the epithelium of the cortical collecting ducts.

The transport of these ions involves an active transport mechanism through the Na^+/K^+ pump. Energy for the functioning of this pump is provided by hydrolysis of ATP. Aldosterone increases the activity of several mitochondrial enzymes, and this could result in the generation of the ATP required to drive Na^+/K^+ pump. The proteins synthesized also include the Na^+-K^+ ATPase molecules. The NADH/NAD^+ ratio increases and when the NADH is oxidized in the mitochondrial respiratory chain, ATP will be formed. One of the mitochondrial enzymes which increases in concentration is *citrate synthase*. This is brought about by the action of aldosterone in directly inducing the transcription of the enzyme gene. Aldosterone also increases the number of membrane Na^+ channels, and this presumably increases intracellular Na^+. Additionally, aldosterone binds to the cell membrane and by a rapid nongenomic (not involving the gene) action increases the activity of membrane Na^+-K^+ exchangers. This produces an increased intracellular Na^+ and the second messenger involved is inositol triphosphate.

- *Effect on extracellular fluid volume*

When Na^+ is reabsorbed by the kidney tubules, there is simultaneous osmotic absorption of almost equivalent amounts of water. Therefore, the extracellular volume increases almost as much as the retained sodium. Hence the net effect is that there is not much change in the ECF concentration of sodium.

Finally, let us study about the role of hormones produced by the pituitary gland.

11.5.6 Hypophysis (The Pituitary Gland)

The newer name for the pituitary gland is *hypophysis*. Physiologically (you may recall reading in the Applied Physiology Course, Unit 11) it is divisible into two distinct portions – the anterior pituitary also known as the *adenohypophysis* and the posterior pituitary also known as the *neurohypophysis*.

The anterior pituitary secretes six important hormones and several less important hormones. Two of the six important hormones, namely *the thyroid stimulating hormone* and the *growth hormone*, are already discussed above. The posterior pituitary secretes two hormones–*vasopressin* and *oxytocin*. Let us get to know about the role of these hormones, starting with the hormones of the anterior pituitary i.e. the adenohypophysis.

A) **Adenohypophysis (Anterior Pituitary)**

Thyroid stimulating hormone (TSH)

TSH is also referred to as *thyrotropin* or *thyrotropic hormone*. The target gland of TSH is specifically the *thyroid gland*. TSH regulates the functions of the thyroid gland. TSH has several acute effects on thyroid function. These occur in minutes and involve increases of all phases of the biosynthesis of the two hormones of the thyroid gland – triiodothyronine (T_3) and tetraiodothyronine or thyroxine (T_4). These include iodide concentration, organification, coupling and thyroglobulin hydrolysis. You have already come across these two hormones in the section on iodine in Unit 10. TSH also has several chronic effects on the thyroid gland. These require several days and include increases in the synthesis of proteins, phospholipids and nucleic acids in the thyroid gland as well as increase in size and number of thyroid cells. All this leads to increased production of T_3 and T_4 that will in turn exert their effects in the body. Thus long-term metabolic effects of TSH are due to the production and action of the thyroid hormones.

Growth hormone (GH)

GH exerts its effects on all or almost on all tissues of the body. It is required for postnatal growth and is also called *somatotropic hormone* or *somatotropin*. Thus it is required for normal carbohydrate, lipid, protein and mineral metabolism as discussed herewith.

- *Effect on growth*

GH causes growth of almost all tissues of the body that are capable of growing. The effects of GH on growth are mediated by growth factors called *somatomedins*. They are secreted by liver and other tissues in response to stimulation by GH. The first of these factors isolated was also called 'sulfation factor' because it stimulated the incorporation of sulfate into cartilage. However, since it also stimulated collagen formation, its name was changed to somatomedin. In human beings, the growth related effects are primarily mediated by somatomedin C or insulin-like growth factor I (IGF-I) and to a much lesser extent by insulin-like growth factor II (IGF-II).

- *Effect on protein metabolism*

GH increases the transport of amino acids into muscle cells resulting in an increased protein synthesis. There is increased positive nitrogen balance. At the same time, there is a decrease in the breakdown of cell protein resulting in a decrease in plasma and urinary levels of amino acids and urea. The net effect is a generalized increase in protein content of the body.

Thus GH is a protein anabolic hormone. Increase in protein synthesis is accompanied by increased transcription of DNA to form RNA and increased translation of RNA to form proteins. In these respects GH actions resemble some of the actions of insulin.

- *Effect on carbohydrate metabolism*

GH generally antagonizes the effects of insulin. GH decreases peripheral utilization of glucose and simultaneously increases hepatic production by stepping up gluconeogenesis. Both these effects lead to increased blood glucose levels. GH increases liver glycogen, probably from activation of gluconeogenesis from amino acids. Impairement of glycolysis may occur at several steps. There is mobilization of fatty acids from triacylglycerol stores in adipose tissue which may also contribute to the inhibition of glycolysis in muscle. Hence prolonged administration of GH may cause diabetes mellitus.

- *Effect on lipid metabolism*

As already mentioned above, GH promotes the release of free fatty acids and glycerol from adipose tissue, increasing the level of circulating free fatty acids. This results in increased oxidation of fatty acids in the liver. This could also lead to increased ketogenesis, particularly in diabetes. The increased mobilization of fat has a protein-sparing action that promotes protein deposition and growth.

- *Effect on mineral metabolism*

GH, probably through IGF-I promotes a positive calcium, magnesium and phosphate balance and causes the retention of Na^+, K^+ and Cl^-. A positive calcium, magnesium and phosphate balance is a result of action of GH in bone where it promotes growth of long bones at the epiphyseal plates in growing children. GH also increases formation of cartilage.

Having learnt about the role of the hormones produced by the anterior pituitary, we move on to the hormones produced by the neurohypophysis i.e. the posterior pituitary. What role do they play? Let's find out.

B) **Neurohypophysis (Posterior Pituitary)**

Within this, we shall study the role of oxytocin and vasopressin.

Oxytocin

Oxytocin, as you may already know, acts primarily on the uterus and breasts. Let us get to know what effect it has on these organs.

- *Effect on the uterus*

Oxytocin causes contraction of the smooth muscle of the uterus. In late pregnancy, the uterus becomes very sensitive to oxytocin which is accompanied by a marked increase in the number of oxytocin receptors and the mRNA of the oxytocin receptors. Secretion of oxytocin is increased during labour leading to high plasma levels. Oxytocin may also act on the non-pregnant uterus to facilitate sperm transport.

- *Effect on the breasts*

Oxytocin plays a very important role in lactation. It causes milk to be expressed from the alveoli into the ducts so that the baby can obtain it by suckling. This mechanism is called *milk letdown* or *milk ejection*.

Finally, let us review the biochemical role of vasopressin, the other hormone produced by the posterior pituitary.

Vasopressin

This hormone is also called *antidiuretic hormone (ADH)*. Its principal physiologic effect is the retention of water by the kidney. Extremely minute quantities of ADH, even as little as 2 nanograms when injected into a person can cause *antidiuresis*, that is, decreased excretion of water by the kidneys and hence the name ADH. In the

presence of ADH, the permeability of the collecting tubules and ducts to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts. This results in conserving water in the body and producing very concentrated urine. In the absence of ADH, the urine is not concentrated and may be excreted in amounts exceeding 2L/day. ADH receptor is linked to adenylyl cyclase system which causes synthesis of cAMP. The cAMP is thought to mediate the effects of ADH in the renal tubule.

Higher concentrations of ADH have an effect of constricting the arterioles everywhere in the body and therefore of increasing the arterial pressure. Hence this hormone is also called *vasopressin*.

With our discussion on vasopressin, we end our study on the biochemical role of few of the hormones in our body.

Check Your Progress Exercise 4

1) Where are the various hormones synthesized? Indicate the organ and the hormone secreted.

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2) Explain the effect of insulin on carbohydrate metabolism.

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3) Explain the role of parathormone in calcium homeostasis.

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4) What are the hormones of the adenohypophysis and the neurohypophysis? Explain the role of any one of these hormone in our body.

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11.6 LET US SUM UP

This unit focused on the study of hormones. Initially the unit presented an overview on the endocrine system highlighting the hormones produced by the endocrine glands. The classification of hormones and the various components involved in the mechanism of hormonal action was discussed subsequently.

Finally, the biochemical role of some important hormones, namely, the insulin, glucagon secreted from the pancreas, the T3 and the T4 secreted from the thyroid, parathormone of the parathyroid gland, epinephrine / norepinephrine and glucocorticoid,

minerocorticoid, produced by the adrenal medulla and adrenal cortex and thyrotropin, growth hormone, oxytocin and vasopressin from the pituitary, were discussed.

11.7 GLOSSARY

Homeostatic responses : body's internal self-correcting mechanism that helps it maintain systemic balance following disruption.

Hormone : any substance in an organism that carries a signal to generate some sort of alteration at cellular level.

Receptor : cell-associated recognition molecules.

Signal Transduction : the biochemical events that conduct the signal of a hormone or growth factor from the cell exterior, through the cell membrane, and into the cytoplasm. This involves a number of molecules, including receptors, proteins, and messengers.

Transcription : the synthesis of an RNA copy from a sequence of DNA (a gene); the first step in gene expression.

11.8 ANSWERS TO CHECK YOUR POGRESS EXERCISES

Check Your Progress Exercise 1

1) a) Endocrine system is a system composed of the endocrine glands or ductless glands whose secretions pass directly into the blood stream.

   b) Hormone is any substance in an organism that carries a signal to generate some alteration at the cellular level.

2) i) messengers

   ii) tropic

   iii) hypothalamus

3) The hormonal cascade mechanism is a system which amplifies a specific signal. It means that small amounts of an extracellular compound can affect large number of intracellular enzymes without crossing the plasma membrane or binding to each target protein. The general sequence of events in the hormonal cascade system can be described as follows: A stimulus originates in the external environment or within the organism which are sensed. This signal is transmitted as an electrical pulse or as a chemical signal or both and is forwarded to the hypothalamus situated at the base of the brain. The hypothalamus secretes the appropriate hormone called the releasing hormone which is carried by blood to the anterior pituitary. The anterior pituitary then secretes the hormone called trophic hormone or tropin which is carried by blood to its appropriate endocrine gland which gets stimulated. The endocrine gland then synthesizes its specific hormone. Through blood, this specific hormone travels to specific tissue(s) and brings about the characteristic effects. Thus this signal pathway originates in the brain and culminates in the ultimate target cell.

Check Your Progress Exercise 2

1) Receptors are the cell-associated recognition molecules. These bind to the hormones and help them in initiating their biologic effects.

2) The hormones can be classified as follows based on their mechanism of action:

   Group I-Hormones that bind to intracellular receptors (Example thyroid hormones (T3 and T4), glucocorticoids etc.)

   Group II- Hormones that bind to cell surface receptors which includes

   A - The second messenger is CAMP (e.g. glucagon, calcitonin etc.)

   B-The second messenger is cGMP (atrial natriuretic factor)

   C-The second messenger is calcium or phosphatidyl inositols or both (acetylcholine, α_1-Adrenergic catecholamines etc.)

   D - The second messenger is a kinase or phosphatase cascade (e.g. insulin, growth hormone, prolactin.)

3) (i) - (c)
   (ii) - (d)
   (iii) - (b)
   (iv) - (e)
   (v) - (f)
   (vi) - (a)

4) The hormonal response to a stimulus can be explained as such – the first step involves recognition of the stimulus. The stimulus is a challenge or a threat to the organism, an organ, or to the integrity of a single cell within that organism. Accordingly, one or more of hormones is secreted which brings about the desired adaptive responses or effect such as gene transcription, protein translocation or protein modification.

Check Your Progress Exercise 3

1) Receptors of Group II hormones work in collaboration with a specific protein called G Protein. Hence these receptors are also called G protein-coupled receptors or GPCR.

2) Signal transduction, is the biochemical events that conduct the signal of a hormone from the cell exterior, through the cell membrane, and into the cytoplasm. This involves a number of molecules, including receptors, proteins, and messengers. The mechanism involved is that after the hormone binds to its specific receptor on the surface of the target cell, the signal is passed through the membrane located G protein transducer to a membrane-bound effector. The action of the effector molecule generates an intracellular second messenger, which is usually a small molecule or ion like cAMP, cGMP, Ca^{2+} and phosphatidylinositides. The diffusible second messenger carries the signal to its ultimate destination, which may be in the nucleus, an intracellular compartment or the cell cytosol resulting in specific cell response.

3) cAMP, cGMP, calcium or phosphatidyl inositol, kinase or phosphatase cascade are the second messengers.

Check Your Progress Exercise 4

1) Hormones are synthesized in a variety of cellular arrangements. The various hormones synthesized by the respective organs are given below:

   - thyroid gland produces triiodothyronine
   - adrenal cortex produces glucocorticoid and mineralocorticoid
   - pituitary gland produces TSH, growth hormone, ACTH etc
   - ovaries produce estradiol and progesterone
   - small intestine produces glucagon-like peptide
   - kidney produces angiotensin II, and
   - the skin, liver, kidney produce 1,25 dihydroxy D_3 or calcitriol.

2) After a high-carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin. The insulin in turn causes rapid uptake, storage and utilization of glucose. In the liver glucose induces hexokinase and this increases the phosphorylation of glucose. As a result the intracellular concentration of free (unphosphorylated) glucose remains low, facilitating the entry of glucose into the cell. Further, insulin influences the intracellular utilization of glucose through the glycolytic pathway and glycogenesis and lipogenesis. In liver and muscle, insulin stimulates the conversion of glucose to glucose-6-phosphate, which is incorporated into glycogen by the enzyme glycogen synthase. Additionally insulin also activates a phosphatase that dephosphorylates glycogen synthase and maintains it in the active form. Insulin stimulates lipogenesis from glucose. The net action of all these effects of insulin is to decrease the blood glucose level. Thus this is the effect of insulin on carbohydrate metabolism.

3) PTH acts in an indirect manner by stimulating the synthesis of calcitriol in the intestine. Calcitriol then promotes the absorption of Ca^{2+} from the intestinal lumen. In case of prolonged deficiency of calcium in the diet, inadequate intestinal absorption of Ca^{2+} occurs. In such cases, PTH acts directly on bone and kidney and increases the rate of dissolution of bone and increases the concentration of Ca^{2+} in the extracellular fluid. PTH also reduces the renal clearance or excretion of calcium and increases concentration of Ca^{2+} in ECF.

4) The hormones of Adenohypophysis are Thyroid stimulating hormone (TSH) and Growth hormone (GH) and Neurohypophysis are Oxytocin and Vasopressin. The role of TSH is discussed as follows:

   The target gland of TSH is thyroid gland. TSH regulates the functions of thyroid gland and has several acute effects on the thyroid functioning. These occur in minutes and involve increases of all phases of the biosynthesis of the two hormones of the thyroid gland- triiodothyronine (T_3) and tetraiodothyronine or thyroxine (T_4). TSH also has several chronic effects on the thyroid gland which include increases in the synthesis of proteins, phospholipids and nucleic acids in the thyroid gland as well as increase in size and number of thyroid cells. All this leads to increased production of T_3 and T_4 that will in turn exert their effects in the body. Thus long-term metabolic effects of TSH are due to the production and action of the thyroid hormones.