THOMAS ADEWUMI UNIVERSITY, OKO, KWARA STATE
Science | Technology | Medicine

LECTURE NOTE

ON

BCH 422

ENDOCRINOLOGY

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COURSE OUTLINE

- Organization of the mammalian endocrine system
- Chemistry and functions of hormones
- Mechanism of hormone action
- Role of cyclic AMP as a second messenger
- Adenylate cyclase system
- Storage and secretion of hormones
- Hormone receptors: isolation and properties
- Diabetes mellitus and hypoglycemia
- Biochemistry and functions of insulin and other hormones controlling carbohydrate metabolism
- Biochemistry and functions of thyroid hormones

DID YOU KNOW?

- Diabetes mellitus is caused by insufficiency or inefficiency of a hormone called insulin.
- The low incidence of atherosclerosis and coronary heart disease in women during reproductive age is due to estrogens.
- Growth hormone deficiency causes dwarfism while its excessive production results in gigantism (in children) or acromegaly (in adults).
- Identification of hCG in urine is employed for the early detection of pregnancy.

THE ENDOCRINE SYSTEM

- The living system is remarkably **regulated** and **coordinated**.

- This is brought about by an excellent ***communication system***, which coordinates the various biological functions.

- This is achieved by two distinctly organized functional systems:

  1. **Nervous system:** It coordinates the body functions through the transmission of electrochemical impulses.

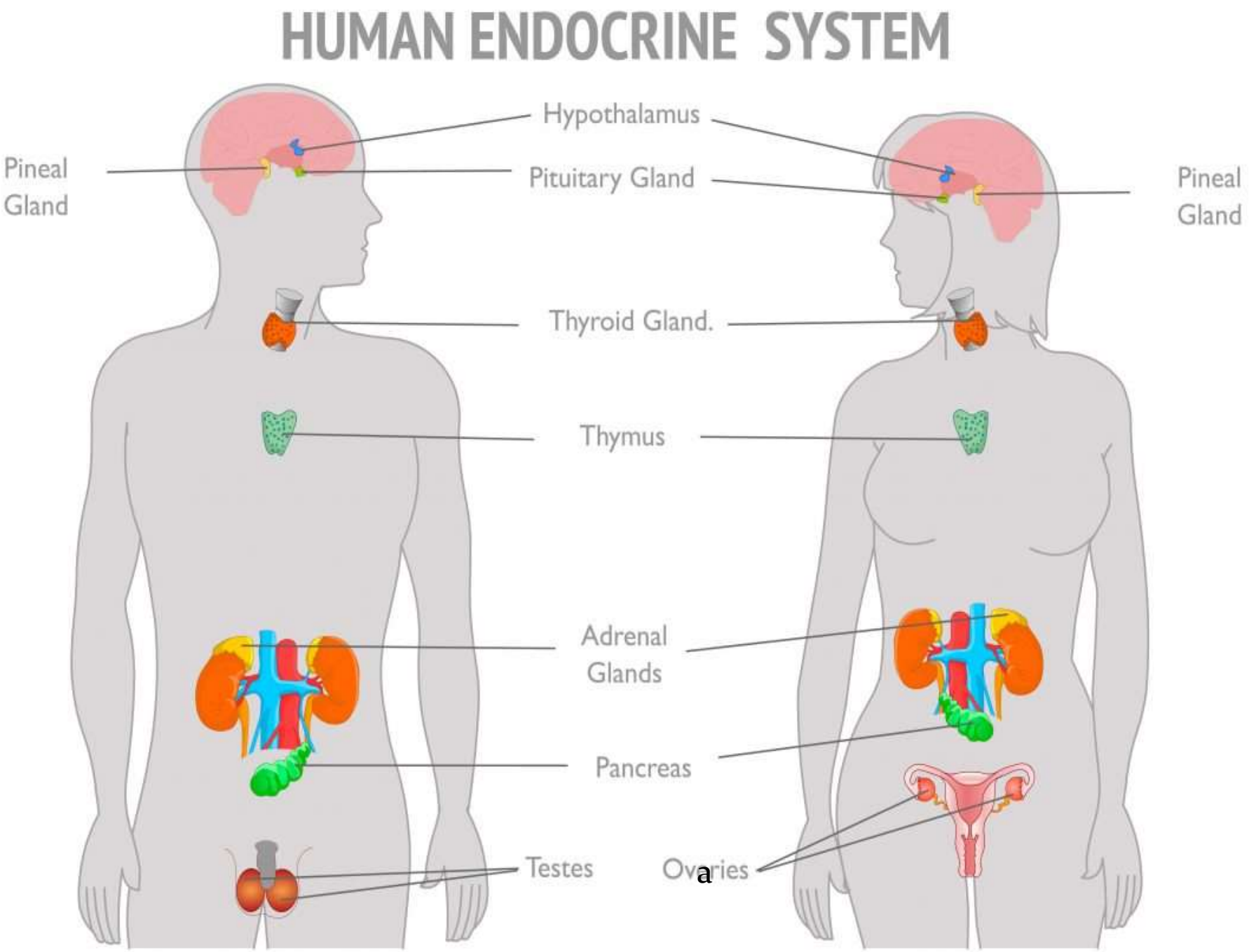
  2. **Endocrine system:** It acts through a wide range of chemical messengers known as **hormones**.

- The endocrine system is a control system comprising hormones that are released by ductless glands directly into the circulatory system to target and regulate specific organs.

- **Endocrine cells** are the cells that make up the endocrine system, and these cells typically make up larger tissues and organs that function within and outside of the endocrine system.

- On the other hand, **endocrine glands** are glands of the endocrine system that secrete hormones directly into interstitial spaces where they are absorbed into the blood rather than through a duct.

- The major glands of the endocrine system include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, thymus, hypothalamus and adrenal glands.



Source: napervilleintegratedwellness.com

HYPOTHALAMUS

- The hypothalamus is a small part of the brain below the thalamus, that contains a number of nuclei with a variety of functions.
- One of its most important functions is to link the nervous system to the endocrine system via the pituitary gland.
- All vertebrate brains contain a hypothalamus, and in humans, it is the size of an almond.
- Body temperature, hunger, thirst, fatigue, sleep, circadian rhythms, as well as certain social behaviors, such as maternal attachment, sexual and aggressive behaviors are all controlled by the hypothalamus.
- In vertebrates, the hypothalamus is the neural control center for all endocrine systems, and so regarded as the ***master coordinator of hormonal action***.

PITUITARY GLAND

- In humans, the pituitary gland (or hypophysis cerebri) is located at the base of the brain, protruding off the bottom of the hypothalamus.

- The human pituitary gland is oval-shaped, about the size of a chickpea, and weighs 0.5g on average.

- Hormones secreted from the pituitary gland help to control growth, blood pressure, energy management, all functions of the sex organs, thyroid glands, metabolism.

- Some aspects of pregnancy, childbirth, breastfeeding, water/salt concentration at the kidneys, temperature regulation, and pain relief are also controlled by the hormones of the pituitary gland.

PINEAL GLAND

- The pineal gland (also known as the pineal body or epiphysis cerebri) is a small endocrine gland located in the epithalamus, near the center of the brain.

- The shape of the gland resembles a pine cone, which gives it its name.

- It is one of the neuroendocrine organs in which capillaries are mostly permeable to solutes in the blood.

- In darkness, the pineal gland produces melatonin, a serotonin-derived hormone, which modulates sleep patterns following the diurnal cycles.

THYROID GLAND

- The thyroid (or thyroid gland) is a butterfly-shaped gland in vertebrates; located in the human neck below the Adam's apple, and consists of two connected lobes.

- The lower two thirds of the lobes are connected by a thin band of tissue called the isthmus (pl.: isthmi).

- The hormones of the thyroid gland influence metabolic rate, protein synthesis, calcium homeostasis, as well as growth and development in children.

THYMUS

- The thymus (pl.: thymuses or thymi) is a specialized primary lymphoid organ of the immune system and endocrine system located behind the sternum in the upper front part of the chest, stretching upwards towards the neck.

- It is made up of two lobes, each consisting of a central medulla and an outer cortex, surrounded by a capsule.

- Thymus cell lymphocytes or T-cells mature in the thymus.

- T-cells are critical to the adaptive immune system, where the body adapts to specific foreign invaders.

ADRENAL GLAND

- The adrenal glands (also known as suprarenal glands) are endocrine glands that produce a variety of hormones including adrenaline and the steroids aldosterone and cortisol.
- They are found above the kidneys.
- Each gland has an outer cortex which produces steroid hormones and an inner medulla.
- Adrenal hormones help in the regulation of blood pressure, electrolyte balance, metabolism and immune system suppression.
- They can also function to produce a rapid response throughout the body in stress situations.

PANCREAS

- The pancreas is an organ of the digestive system and endocrine system of vertebrates.
- In humans, it is located in the abdomen behind the stomach and functions as a mixed or heterocrine gland, i.e., it has both an endocrine and a digestive exocrine function.
- About 99% of the pancreas is exocrine and 1% is endocrine.
- As an endocrine gland, it functions mostly to regulate blood sugar levels.
- As a part of the digestive system, it functions as an exocrine gland secreting pancreatic juice containing bicarbonate that neutralizes acid entering the duodenum from the stomach.
- It also secretes digestive enzymes that catalyze the breakdown of carbohydrates, proteins and fats in food entering the duodenum from the stomach.

OVARIES

- The ovaries are ova-producing, whitish gonads in the female reproductive system located on either side of the uterus in the lower abdomen.
- There is an ovary found on the left and the right side of the body.
- When an ovum is released, it travels through the fallopian tube (or oviduct) into the uterus.
- The ovaries also secrete hormones that play a role in the menstrual cycle and fertility.
- The ovary progresses through many stages beginning in the prenatal period through menopause.
- It is also an endocrine gland because of the various hormones that it secretes

TESTES

- A testicle or testis (pl.: testes) is the male gonad in all bilaterians, including humans.
- Males have two testicles of similar size contained within the scrotum, which is an extension of the abdominal wall.
- Scrotal asymmetry, in which one testicle extends farther down into the scrotum than the other, is common.
- This is because of the differences in the vasculature's anatomy.
- For 85% of men, the right testis hangs lower than the left one.
- The functions of the testicles are to produce both sperm and androgens, primarily testosterone.

CHEMISTRY AND FUNCTIONS OF HORMONES

HORMONES

- Hormones maybe defined as chemical messengers produced in small amount by endocrine glands, secreted into the blood stream to control metabolism and biological activities in target cells or organs.
- They are regarded as the chemical messengers involved in the transmission of information from one tissue to another and from cell to cell.
- They affect distant cells by binding to specific receptor proteins in the target cell, resulting in a change in cell function.
- Hormones are required for the correct development of animals, plants and fungi.
- They may be classified in many ways based on their characteristics and functions.

CLASSIFICATION OF HORMONES BASED ON THEIR CHEMICAL NATURE

Hormones can be categorized into three groups based on their chemical nature:

1. Protein or peptide hormones e.g. insulin, glucagon, antidiuretic hormone, oxytocin.

2. Steroid hormones e.g. glucocorticoids, mineralocorticoids, sex hormones.

3. Amino acid derivatives e.g. epinephrine, norepinephrine, thyroxine (T_4), triiodothyronine (T_3).

CLASSIFICATION OF HORMONES BASED ON THEIR MECHANISM OF ACTION

Hormones are classified into two broad groups (I and II) based on the location of the receptors to which they bind and the signals used to mediate their action:

Group I hormones: These hormones bind to intracellular receptors to form receptor hormone complexes (the intracellular messengers) through which their biochemical functions are mediated.

Group I hormones are lipophilic in nature and are mostly derivatives of cholesterol (exception—T_3 and T_4). e.g. estrogens, androgens, glucocorticoids, calcitriol.

- **Group II hormones:** These hormones bind to cell surface (plasma membrane) receptors and stimulate the release of certain molecules called **second messengers**, which in turn, perform various biochemical functions.

- Thus, hormones themselves are the first messengers.

- Group II hormones are **subdivided into three** categories based on the chemical nature of the second messengers:

  (a) The second messenger is cAMP e.g. ACTH, FSH, LH, PTH, glucagon, calcitonin.

  (b) The second messenger is phosphatidylinositol/calcium e.g. TRH, GnRH, gastrin, CCK.

  (c) The second messenger is unknown e.g. growth hormone, insulin, oxytocin, prolactin.

PROPERTIES OF HORMONES

i. Hormones have low molecular weight.
ii. They are small organic molecules.
iii. They are transported in the blood stream.
iv. They are soluble in water, making it possible to be transported via blood.
v. They are non-antigenic.
vi. Their rate of diffusion is very high and are readily oxidized but their effect do not remain constant.
vii. They are effective in low concentration.
viii. They have their target sites different from where they are produced and are specific to a particular target.
ix. They are non-specific for organisms and may influence the body process of other individuals.
x. When their function is over, they are readily destroyed, excreted or inactivated.
xi. Their activities are not hereditary.

FUNCTIONS OF HORMONES

Hormones regulate and coordinate a wide range of physiological and behavioral activities such as:

i. Metabolism of food.
ii. Growth and development.
iii. Hunger and thirst.
iv. Preservation of body temperature.
v. Maintenance of homeostasis
vi. Sleep and wake cycle
vii. Mental and emotional functions.
viii. Establishing and sustaining sexual development and reproduction

Principal human hormones—classification (by mechanism of action), origin and major functions

Hormone(s)	Origin	Major Function(s)
Group I. HORMONES THAT BIND TO INTRACELLULAR RECEPTORS		
Estrogens	Ovaries and adrenal cortex	Female sexual characteristics, menstrual cycle.
Progestins	Ovaries and placenta	Involved in menstrual cycle and maintenance of pregnancy.
Androgens	Testes and adrenal cortex	Male sexual characteristics, spermatogenesis.
Glucocorticoids	Adrenal cortex	Affect metabolisms, suppress immune system.
Mineralocorticoids	Adrenal cortex	Maintenance of salt and water balance.
Calcitriol (1, 25–DHCC)	Kidney (final form)	Promotes absorption of Ca^{2+} from intestine, kidney and bone.
Thyroid hormones (T_3, T_4)	Thyroid	Promote general metabolic rate.

Source: Satyanarayana & Chakrapani, 2013

Group II. HORMONES THAT BIND TO CELL SURFACE RECEPTORS

A. The second messenger is cAMP

Adrenocorticotropic hormone (ACTH)	Anterior pituitary	Stimulates the release of adrenocorticosteroids.
Follicle stimulating hormone (FSH)	Anterior pituitary	In females, stimulates ovulation and estrogen synthesis. In males, promotes spermatogenesis.
Luteinizing hormone (LH)	Anterior pituitary	Stimulates synthesis of estrogens and progesterone and causes ovulation. Promotes androgen synthesis by testes.
Chorionic gonadotropin (hCG)	Anterior pituitary	Stimulates progesterone release from placenta.
Thyroid stimulating hormone (TSH)	Anterior pituitary	Promotes the release of thyroid hormones (T_3, T_4).
β-Endorphins and enkephalins	Anterior pituitary	Natural endogenous analgesics (pain relievers).
Antidiuretic hormone (ADH)	Posterior pituitary (stored)	Promotes water reabsorption by kidneys.
Glucagon	Pancreas	Increases blood glucose level, stimulates glycogenolysis and lipolysis.
Parathyroid hormone (PTH)	Parathyroid	Increases serum calcium, promotes Ca^{2+} release from bone.
Calcitonin	Thyroid	Lowers serum calcium. Decreases Ca^{2+} uptake by bone and kidney.
Epinephrine	Adrenal medulla	Increases heart rate and blood pressure. Promotes glycogenolysis in liver and muscle and lipolysis in adipose tissue.
Norepinephrine	Adrenal medulla	Stimulates lipolysis in adipose tissue.

B. The second messenger is phosphatidyl inositol/calcium

Thyrotropin-releasing hormone (TRH)	Hypothalamus	Promotes TSH release.
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	Stimulates release of FSH and LH.
Gastrin	Stomach	Stimulates gastric HCl and pepsinogen secretion.
Cholecystokinin (CCK)	Intestine	Stimulates contraction of gall bladder and secretion of pancreatic enzymes.

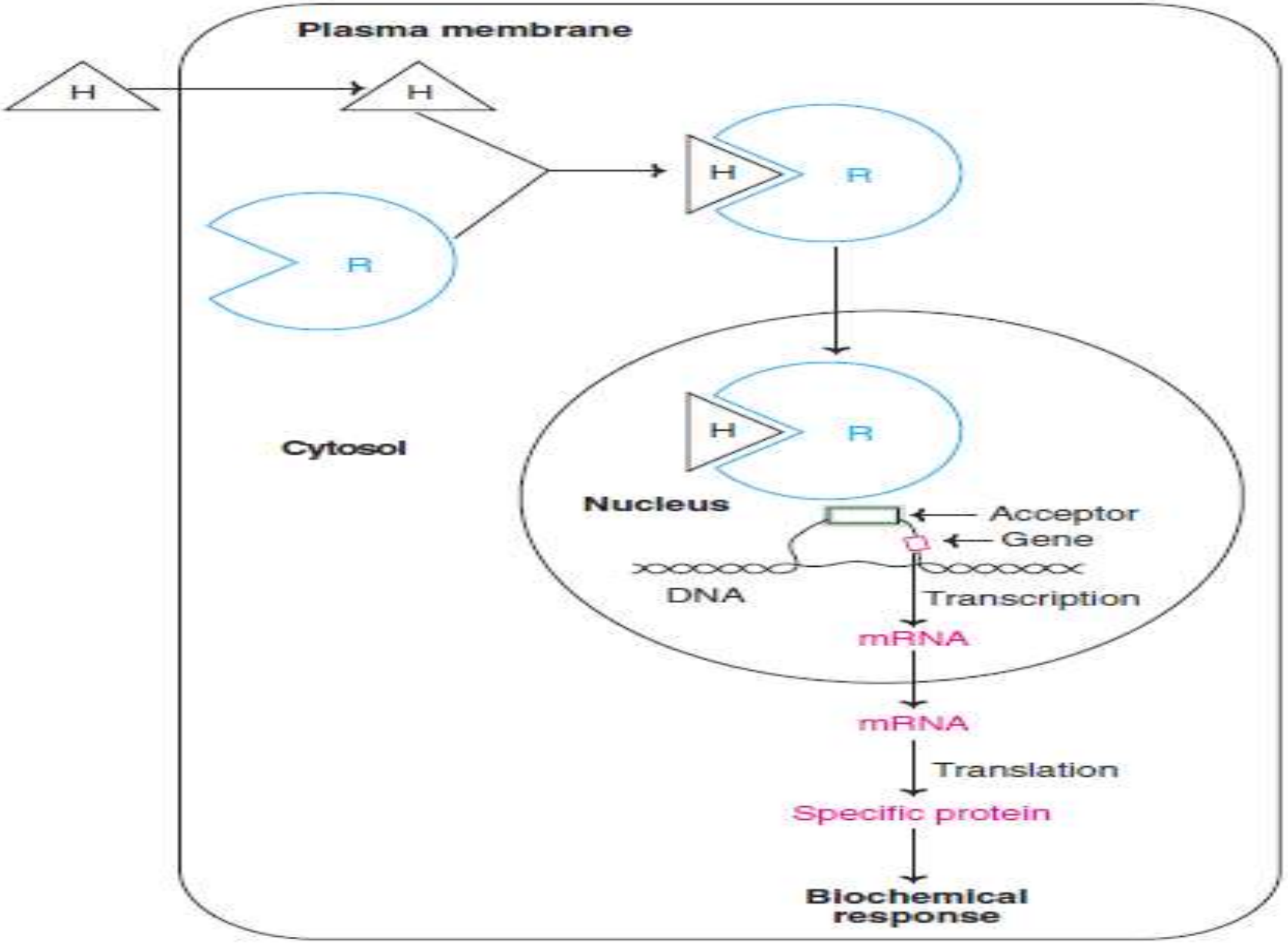
C. The second messenger is unknown/unsettled

Growth hormone (GH)	Anterior pituitary	Promotes growth of the body (bones and organs).
Prolactin (PRL)	Anterior pituitary	Growth of mammary glands and lactation.
Oxytocin	Posterior pituitary (stored)	Stimulates uterine contraction and milk ejection.
Insulin	Pancreas	Lowers blood glucose (hypoglycemic effect), promotes protein synthesis and lipogenesis.
Somatomedins (insulin-like growth factors, IGF-I, IGF-II)	Liver	Growth related functions of GH are mediated. Stimulates growth of cartilage.

MECHANISM OF HORMONE ACTION

MECHANISM OF ACTION OF GROUP I HORMONES

- GroupI hormones are lipophilic in nature and can easily pass across the plasma membrane.
- They act through the intracellular receptors located either in the cytosol or the nucleus.
- The hormone-receptor complex binds to specific regions on the DNA called hormone responsive element (HRE) and causes increased expression of specific genes as illustrated below.
- It is believed that the interaction of hormone-receptor complex with HRE promotes initiation and, to a lesser extent, elongation and termination of RNA synthesis (transcription).
- The ultimate outcome is the production of specific proteins (translation) in response to hormonal action.



Mechanism of action of group I hormones

(H–Hormone; R–Receptor; HR–Hormone-receptor complex)

MECHANISM OF ACTION OF GROUP II HORMONES

- These hormones are considered as the first messengers.
- They exert their action through mediatory molecules, collectively called second messengers.
- A typical example of a second messenger is cAMP.

ROLE OF CYCLIC AMP AS A SECOND MESSENGER AND THE ADENYLATE CYCLASE SYSTEM

Cyclic AMP (cAMP)

- Cyclic AMP (cyclic adenosine 3′,5′-monophosphate) is a ubiquitous nucleotide.
- It consists of adenine, ribose and a phosphate (linked by 3′,5′ linkage).
- cAMP acts as a second messenger for a majority of polypeptide hormones.
- The membrane-bound enzyme adenylate cyclase converts ATP to cyclic AMP, and cAMP is hydrolysed by phosphodiesterase to 5′-AMP.
- cAMP undergoes rapid hydrolysis, catalyzed by the enzyme phosphodiesterase (inhibited by caffeine and theophylline) to 5’ AMP which is inactive.
- Hence, the effect of cAMP will be short-lived if the hormone stimulating adenylate cyclase is removed.

ADENYLATE CYCLASE SYSTEM

- The adenylate cyclase system is a two-component enzyme system.
- Adenylate cyclase (EC 4.6.1.1, also known as adenyl cyclase and adenylyl cyclase) is an enzyme with systematic name **ATP diphosphate-lyase**.
- It catalyzes the cyclase reaction when associated with the hormone-bound receptor and a regulatory protein called **stimulatory G-protein** (so named due to their ability to bind to guanine nucleotides.).
- Adenylate cyclase is a member of the ADCY superfamily, which regulates intracellular signaling, and is related to cell sensitivity to chemotherapy and ionizing radiation.
- It has key regulatory roles in essentially all cells.
- It is part of the cAMP-dependent pathway, a G protein-coupled receptor-triggered signaling cascade used in cell communication.

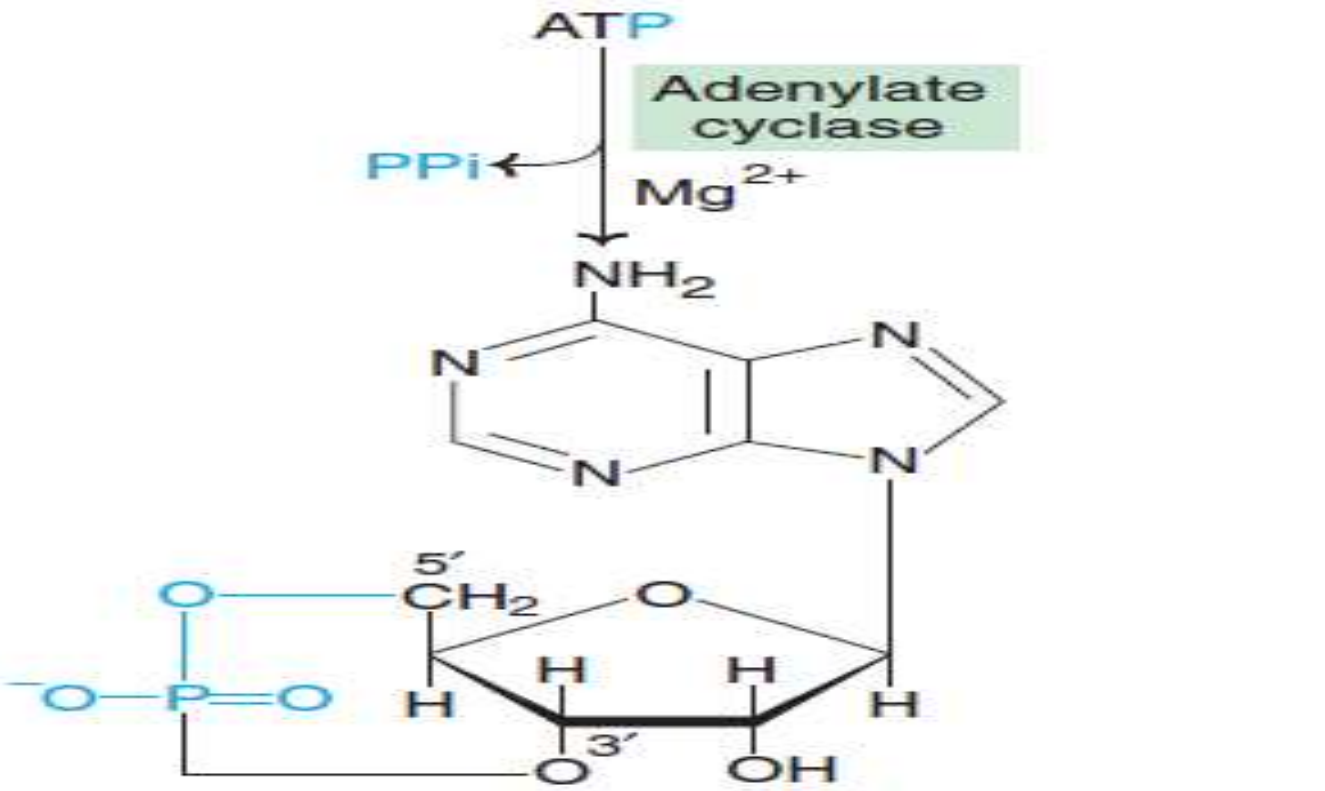
- The main function of adenylate cyclase enzymes is to transform ATP into cyclic AMP.

- Six distinct classes of adenylate cyclase have been described, and all catalyze the same reaction but representing unrelated gene families with no known sequence or structural homology.

- The best known class of adenylyl cyclases is class III or AC-III, which occurs widely in eukaryotes and has important roles in many human tissues.

- All classes of adenylyl cyclase catalyze the conversion of adenosine triphosphate (ATP) to 3',5'-cyclic AMP (cAMP) and pyrophosphate.

- Magnesium ions are generally required and appear to be closely involved in the enzymatic mechanism.



Synthesis and Degradation of cAMP

Action of cAMP

- The cAMP produced by adenylate cyclase serves as a regulatory signal via specific cAMP-binding proteins, either transcription factors, enzymes (e.g., cAMP-dependent kinases), or ion transporters.

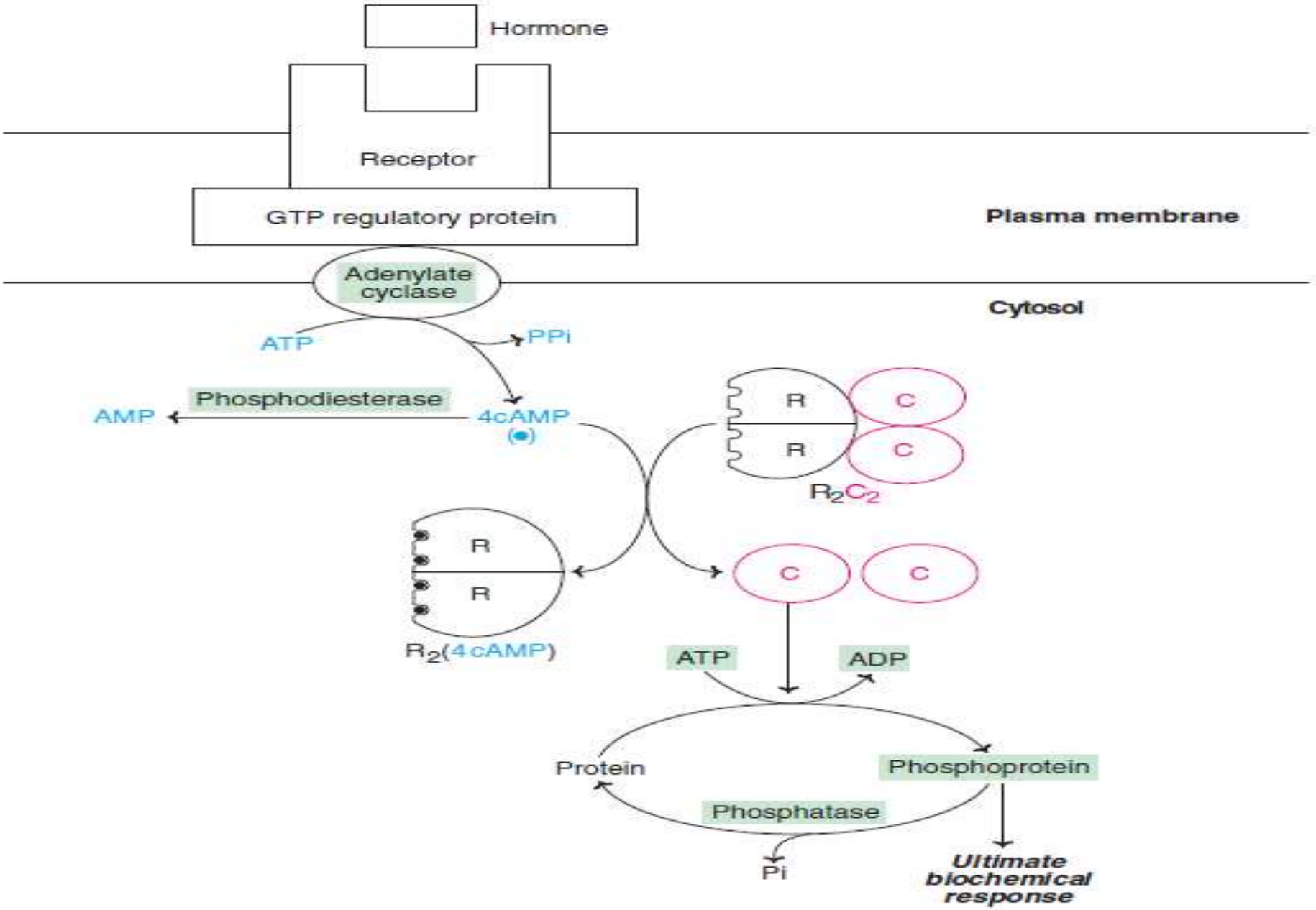
- cAMP performs its role as a second messenger in eliciting biochemical responses.

- It activates protein kinase A (A stands for cAMP), which is a heterotetramer enzyme consisting of 2 regulatory subunits (R) and 2 catalytic subunits (C).

- cAMP binds to inactive protein kinase and causes the dissociation of R and C subunits.

$$\underset{\text{(inactive)}}{4\text{cAMP} + R_2C_2} \longrightarrow \underset{\text{(inactive)}}{R_2(4\text{cAMP})} + \underset{\text{(active)}}{2C}$$

- The active subunit (C) catalyzes phosphorylation of proteins (transfer of phosphate group to serine and threonine residues).
- It is the phosphoprotein that ultimately causes the biochemical response.
- However, cAMP does not act on all protein kinases.
- For instance, on protein kinase C (the second messenger is diacylglycerol).
- A group of enzymes called protein **phosphatases** hydrolyze and remove the phosphate group added to proteins.



Overview of synthesis and action of cAMP

(R_2C_2–cAMP dependent protein kinase A; R_2–Regulatory subunits; C_2–Catalytic subunits; C–Active catalytic unit of R_2C_2

SECRETION OF HORMONES

- The rate of hormone synthesis and secretion is often regulated by a homeostatic negative feedback control mechanism.
- Such a mechanism depends on factors that influence the metabolism and excretion of hormones.
- Thus, higher hormone concentration alone cannot trigger the negative feedback mechanism.
- Negative feedback must be triggered by overproduction of an "effect" of the hormone.
- For instance, blood glucose levels are maintained at a constant level in the body by a negative feedback mechanism.

- When the blood glucose level is too high, the pancreas secretes insulin and when the level is too low, the pancreas then secretes glucagon.

- Hormone secretion can be stimulated and inhibited by:

1. Other hormones (stimulating- or releasing -hormones).
2. Plasma concentrations of ions or nutrients, as well as binding globulins.
3. Neurons and mental activity
4. Environmental changes, e.g., of light or temperature

- One special group of hormones is the tropic hormones that stimulate the hormone production of other endocrine glands.

- For example, thyroid-stimulating hormone (TSH) causes growth and increased activity of another endocrine gland, the thyroid, which increases output of thyroid hormones.

- To release active hormones quickly into the circulation, hormone biosynthetic cells may produce and store biologically inactive hormones in the form of pre- or pro-hormones.

- These can then be quickly converted into their active hormone form in response to a particular stimulus.

- **Eicosanoids** are considered to act as local hormones because they possess specific effects on target cells close to their site of formation.

- They also have a rapid degradation cycle, making sure they do not reach distant sites within the body.

STORAGE OF HORMONES

- Hormones are synthesized and stored in endocrine cells.
- They are stored in large dense-core vesicles packed with protein, commonly known as **secretory granules**.
- Cells retain the granules until stimulated, when they release the contents through exocytosis.
- This is so that large amounts of hormones may be rapidly available when needed.
- Purified hormones that have been lyophilized and sealed under vacuum or with dry nitrogen are very stable when stored at or below -15°C.

HORMONE RECEPTORS:

ISOLATION AND PROPERTIES

HORMONE RECEPTORS

- Receptors are chemical structures, composed of protein, that receive and transduce signals that may be integrated into biological systems.

- The action of receptors can be classified in three main ways: **relay of signal, amplification, or integration**.

- Relaying sends the signal onward, amplification increases the effect of a signal ligand, and integration allows the signal to be incorporated into another biochemical pathway.

- A molecule that binds to a receptor is called a ligand and can be a protein, peptide (short protein), or another small molecule, such as a neurotransmitter, hormone, pharmaceutical drug, toxin, calcium ion or parts of the outside of a virus or microbe.

- Most hormones initiate a cellular response by initially binding to receptors.

CLASSIFICATION OF RECEPTORS

- Receptor proteins can be classified by their location as:

- **Cell surface receptors** (transmembrane receptors): They are receptors that are embedded in the plasma membrane of cells and act in cell signaling by receiving extracellular molecules, e.g. ligand-gated ion channels, G protein-coupled receptors, and enzyme-linked hormone receptors.

- **Intracellular receptors:** They are globular protein receptors located inside the cell rather than on its cell membrane, e.g. cytoplasmic receptors and nuclear receptors

PROPERTIES OF HORMONE RECEPTORS

- The interaction of hormone and receptor typically triggers a cascade of secondary effects within the cytoplasm of the cell.
- This is described as signal transduction, often involving phosphorylation or dephosphorylation of various other cytoplasmic proteins, changes in ion channel permeability, or increased concentrations of intracellular molecules that may act as secondary messengers (e.g., cyclic AMP).
- A cell may have several different receptors that recognize the same hormone but activate different signal transduction pathways, and a cell may also have several different receptors that recognize different hormones and activate the same biochemical pathway.
- Receptors for most peptide as well as many eicosanoid hormones are embedded in the cell membrane as cell surface receptors.
- The majority of these receptors belong to the G protein-coupled receptor (GPCR) class of seven alpha helix transmembrane proteins.

- Some protein hormones also interact with intracellular receptors located in the cytoplasm or nucleus by an intracrine mechanism.

- For steroid or thyroid hormones, their receptors are located inside the cell within the cytoplasm of the target cell.

- These receptors belong to the nuclear receptor family of ligand-activated transcription factors.

- To bind their receptors, these hormones must first cross the cell membrane, and they can do so because they are lipid-soluble.

- The combined hormone-receptor complex then moves across the nuclear membrane into the nucleus of the cell, where it binds to specific DNA sequences, regulating the expression of certain genes, and thereby increasing the levels of the proteins encoded by these genes.

- However, it has been shown that not all steroid receptors are located inside the cell, as some are associated with the plasma membrane.

ISOLATION OF RECEPTORS

- Membrane receptors may be isolated from cell membranes by complex extraction procedures.
- These extraction procedures use solvents, detergents, and/or affinity purification.
- The structures and actions of receptors may be studied by using biophysical methods such as X-ray crystallography, NMR, circular dichroism, and dual polarisation interferometry.
- Computer simulations of the dynamic behavior of receptors have been used to gain understanding of their mechanisms of action.

DIABETES MELLITUS & HYPOGLYCEMIA

DIABETES MELLITUS

- Diabetes mellitus (Greek: *diabetes*—a siphon or running through; *mellitus*—sweet) is a metabolic disorder characterized by increased blood glucose level (hyperglycemia) due to insufficient or inefficient insulin.

- Consequently, the blood glucose level is elevated which spills over into urine.

- Diabetes mellitus is the third leading cause of death (after heart disease and cancer) in many developed countries, and it affects about 6 to 8% of the general population.

- The complications of diabetes affect the eye, kidney, nervous system, and it is a major cause of blindness, renal failure, amputation, heart attacks and stroke.

- The term diabetes, whenever used, refers to diabetes mellitus, however, **diabetes insipidus** is another disorder characterized by large volumes of urine excretion due to antidiuretic hormone deficiency.

- An important feature of diabetes is that the body cells are starved of glucose despite its very high concentration around i.e. scarcity in plenty.

- Insulin is required for the uptake of glucose by muscle (skeletal, cardiac and smooth), adipose tissue, leukocytes and mammary glands.

- Surprisingly, about 80% of glucose uptake in the body is not dependent on insulin.

- Tissues into which glucose can freely enter include brain, kidney, erythrocytes, retina, nerve, blood vessels and intestinal mucosa.

- As regards liver, glucose entry into hepatocytes does not require insulin.

- However, insulin stimulates glucose utilization in liver and, thus, indirectly promotes its uptake.

CLASSIFICATION OF DIABETES MELLITUS

- Diabetes mellitus is broadly divided into 2 groups:
- **Insulin-dependent diabetes mellitus (IDDM):** This type of diabetes is also known as type I diabetes or (less frequently) juvenile onset diabetes.
- It mainly occurs in childhood (particularly between ages 12-15), and it accounts for about 10 to 20% of the known diabetics.
- It is characterized by almost total deficiency of insulin due to destruction of β-cells of the pancreas.
- The β-cell destruction may be caused by drugs, viruses, or autoimmunity.
- Usually, the symptoms of diabetes appear when 80-90% of the β-cells have been destroyed, and the pancreas ultimately fails to secrete insulin in response to glucose ingestion.
- The patients of IDDM require insulin therapy.

- **Non-insulin dependent diabetes mellitus (NIDDM):** This type is also called type II diabetes or (less frequently) adult-onset diabetes.

- It is the most common, accounting for 80 to 90% of the diabetic population, and it occurs in adults (usually above 35 years) and is less severe than IDDM.

- The causative factors of NIDDM include genetic and environmental factors, and it more commonly occurs in obese individuals.

- Overeating coupled with underactivity leading to obesity is associated with the development of NIDDM.

- Obesity acts as a diabetogenic factor and leads to a decrease in insulin receptors on the insulin responsive (target) cells, but the patients have either normal or even increased insulin levels.

- Many a times, weight reduction by diet control alone is often sufficient to correct NIDDM.

Comparison of two types of diabetes mellitus

Character	Insulin-dependent diabetes mellitus (IDDM)	Non-insulin dependent diabetes mellitus (NIDDM)
General		
Prevalence	10-20% of diabetic population	80-90% of diabetic population
Age at onset	Usually childhood (<20 yrs)	Predominantly in adults (>30yrs)
Body weight	Normal or low	Obese
Genetic predisposition	Mild or moderate	Very strong
Biochemical		
Defect	Insulin deficiency due to destruction of β-cells	Impairment in the production of insulin by β-cells and/or resistance of target cells to insulin
Plasma insulin	Decreased or absent	Normal or increased
Auto antibodies	Frequently found	Rare
Ketosis	Very common	Rare
Acute complications	Ketoacidosis	Hyperosmolar coma
Clinical		
Duration of symptoms	Weeks	Months to years
Diabetic complications at diagnosis	Rare	Found in 10-20% cases
Oral hypoglycemic drugs	Not useful for treatment	Suitable for treatment
Administration of insulin	Always required	Usually not necessary

Source: Satyanarayana and Chakrapani, 2013

METABOLIC CHANGES IN DIABETES

- Diabetes mellitus is associated with several metabolic alterations.

- Most important among them are hyperglycemia, ketoacidosis and hypertriglyceridemia.

1. **Hyperglycemia:** Elevation of blood glucose concentration is the hallmark of uncontrolled diabetes.

Hyperglycemia is primarily due to reduced glucose uptake by tissues and its increased production via gluconeogenesis and glycogenolysis.

When the blood glucose level goes beyond the renal threshold, glucose is excreted into urine (glycosuria).

2. **Glucose toxicity:** High concentrations of glucose can be harmful causing osmotic effects/hypertonic effects (water drawn from cells into extracellular fluid and excreted into urine, resulting in dehydration), β-cell damage by free radicals (due to enhanced oxidative phosphorylation, oxidative stress, and increased free radicals) and glycation of proteins (associated with diabetic complications like neuropathy, nephropathy, retinopathy etc.).

3. **Ketoacidosis:** Increased mobilization of fatty acids results in overproduction of ketone bodies, which often leads to ketoacidosis.

4. **Hypertriglyceridemia:** Conversion of fatty acids to triacylglycerols and the secretion of VLDL and chylomicrons is comparatively higher in diabetics.

   Also, the activity of the enzyme lipoprotein lipase is low in diabetic patients, so the plasma levels of VLDL, chylomicrons and triacylglycerols are increased.

   Hypercholesterolemia is also frequently seen in diabetics.

LONG TERM EFFECTS OF DIABETES

- Hyperglycemia is directly or indirectly associated with several complications.
- These include atherosclerosis, retinopathy, nephropathy and neuropathy.
- The biochemical basis of these complications is not clearly understood.
- However, it is believed that at least some of them are related to microvascular changes caused by glycation of proteins.

MANAGEMENT OF DIABETES

- The diagnosis of diabetes can be made on the basis of individual's response to oral glucose load, through the oral glucose tolerance test (OGTT).

- Diet, exercise, drug and, insulin administration are the management options in diabetics.

- Approximately, 50% of the new cases of diabetes can be adequately controlled by diet alone, 20-30% need oral hypoglycemic drugs while the remaining 20-30% require insulin.

- **Dietary management:** Diabetic patients are advised to consume low calories (i.e. low carbohydrate and fat), high protein and fiber rich diet.

- Carbohydrates should be taken in the form of starches and complex sugars, and as far as possible, refined sugars (sucrose, glucose) should be avoided.

- Fat intake should be drastically reduced so as to meet the nutritional requirements of unsaturated fatty acids.

- Diet control and exercise will help, to a large extent, obesed NIDDM patients.

- **Hypoglycemic drugs:** Oral hypoglycemic drugs are broadly of two categories: sulfonylureas and biguanides.

- The latter are less commonly used these days due to side effects, but sulfonylureas such as acetohexamide, tolbutamide and glibenclamide are frequently used.

- They promote the secretion of endogenous insulin and thus help in reducing blood glucose level.

- **Management with insulin:** Two types of insulin preparations are commercially available: short acting and long acting.

- The short acting insulins are unmodified and their action lasts for about 6 hours, while the long acting insulins are modified ones (such as adsorption to protamine) and act for several hours, which depends on the type of preparation.

- The advent of genetic engineering is a boon to diabetic patients since bulk quantities of insulin can be produced in the laboratory.

HYPOGLYCEMIA

- Hypoglycemia is a condition of low blood glucose level.
- When the concentration of blood glucose falls below 45 mg/dl, the symptoms of hypoglycemia appear, and the manifestations include headache, anxiety, confusion, sweating, slurred speech, seizures and coma, and, if not corrected, death.
- All these symptoms are directly and indirectly related to the deprivation of glucose supply to the central nervous system (particularly the brain) due to a fall in blood glucose level.
- The mammalian body has developed a well regulated system for an efficient maintenance of blood glucose concentration, so hypoglycemia is not commonly observed.
- However, there are three types of hypoglycemia encountered by physicians.

TYPES OF HYPOGLYCEMIA

1. **Post-prandial hypoglycemia:** This is also called reactive hypoglycemia, and is observed in subjects with an elevated insulin secretion following a meal.

   This causes transient hypoglycemia and is associated with mild symptoms.

   The patient is advised to eat frequently rather than the 3 usual meals.

2. **Fasting hypoglycemia:** Low blood glucose concentration in fasting is not very common.

However, fasting hypoglycemia is observed in patients with pancreatic β-cell tumor and hepatocellular damage.

3. **Hypoglycemia due to alcohol intake:** Alcohol consumption may cause hypoglycemia in some individuals who are starved or engaged in prolonged exercise,.

   This is due to the accumulation of NADH (during the course of alcohol metabolism by alcohol dehydrogenase), which diverts the pyruvate and oxaloacetate (substrates of gluconeogenesis) to form lactate and malate respectively.

   The net effect is that gluconeogenesis is reduced due to alcohol consumption.

4. **Hypoglycemia due to insulin overdose:** The most common complication of insulin therapy in diabetic patients is hypoglycemia.

   This is particularly observed in patients who are on intensive treatment regime.

5. **Hypoglycemia in premature infants:** Premature and underweight infants have smaller stores of liver glycogen, and are susceptible to hypoglycemia.

BIOCHEMISTRY AND FUNCTIONS OF INSULIN AND OTHER HORMONES CONTROLLING CARBOHYDRATE METABOLISM

INSULIN

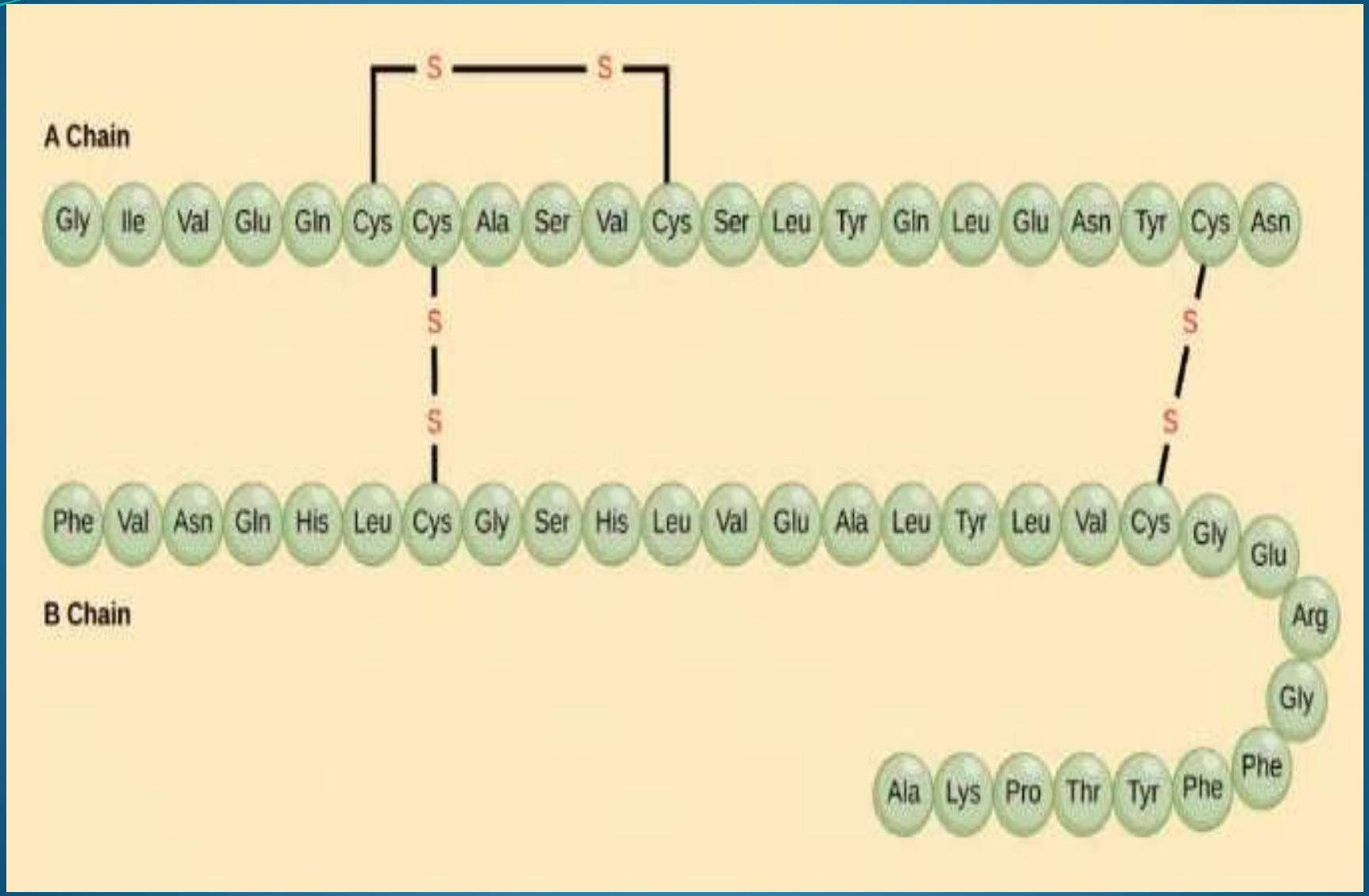
- Insulin is a peptide hormone produced by β-cells of the islets of Langerhans of the pancreas.
- It has a profound influence on the metabolism of carbohydrate, fat and protein, and is often considered as an anabolic hormone because it promotes the synthesis of glycogen, triacylglycerols and proteins.
- It was discovered by Frederick Banting and Charles Best in 1921.
- Insulin occupies a special place in the history of biochemistry and medicine, as it was the first hormone to be isolated, purified and synthesized.
- It was also the first hormone to be sequenced, and first hormone to be produced by recombinant DNA technology.

- Comprising 51 amino acids, insulin has a molecular weight of 5.7 kdt and consists of two polypeptide chains: an α chain, which contains 21 amino acids and a β chain, which has 30 amino acids.

- Both chains are covalently linked by two inter-chain disulfide bridges.

- It also has a third intra-chain disulfide bridge.

- The molecular formula of human insulin is $C_{257}H_{383}N_{65}O_{77}S_6$.



Structure of Insulin

Source: CNX OpenStax

BIOSYNTHESIS OF INSULIN

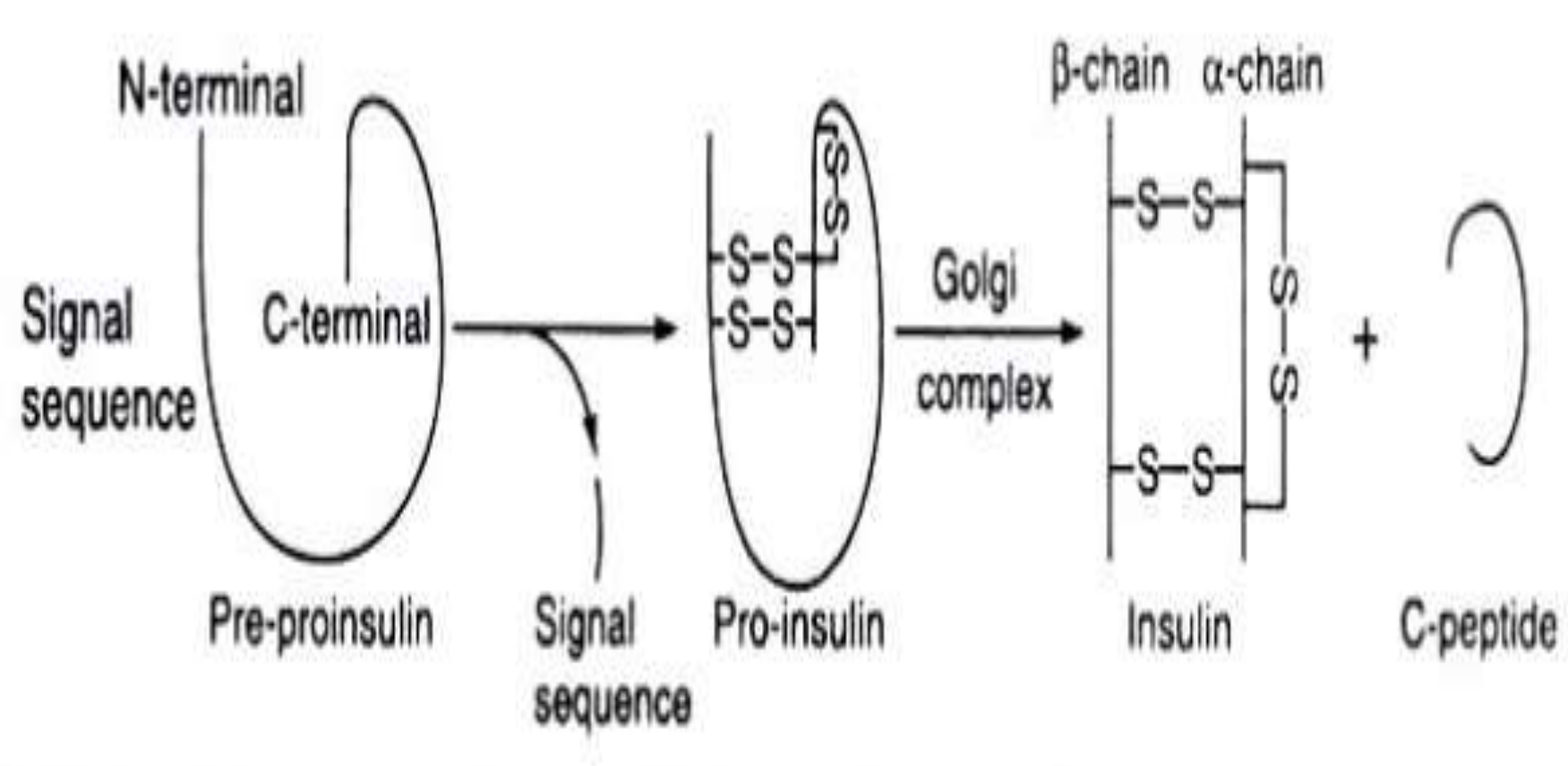
- Insulin is synthesized by the β-cells of islets of Langerhans of the pancreas in response to high level of glucose.
- Firstly, genes on chromosome 11 coding for insulin are transcribed to mRNA in the nucleus.
- After moving to the cytoplasm, insulin mRNA is then translated as a single chain precursor called **preproinsulin**, which consists of 109 amino acid residues, and has a molecular weight of 11.5 kdt.
- There is then removal of its signal peptide at the N-terminus during insertion at the endoplasmic reticulum by signal peptidase to generate **proinsulin**, which consists of 86 amino acid residues along with disulphide bonds, and has a molecular weight of about 9 kdt.

- Proinsulin is transported to the Golgi complex where it is hydrolyzed by a trypsin-like peptidase to yield a 53 amino acid insulin precursor and pro-c-peptide has 33 amino acids.

- The enzyme carboxypeptidase hydrolyses c-terminal peptide bonds in the pro-c-peptide and the insulin precursor to release 2-c-terminal basic amino acids from each.

- Two molecules of Arginine are driven out from the insulin precursor and lead to the formation of active **insulin** (consisting of 51 amino acids).

- About 95% of the proinsulin is converted to active insulin in the Golgi complex.



Synthesis of Insulin

Source: CNX OpenStax

REGULATION OF INSULIN SECRETION

- About 40-50 units of insulin is secreted daily by the human pancreas.
- The normal insulin concentration in plasma is 20-30 μU/ml.
- The important factors that influence the release of insulin from the β-cells of the pancreas include the following:

1. Factors stimulating insulin secretion: These include glucose, amino acids and gastrointestinal hormones.

Glucose is the most important stimulus for insulin release, and the effect is more predominant when glucose is administered orally (either directly or through a carbohydrate-rich meal).

A rise in blood glucose level is a signal for insulin secretion.

Amino acids induce the secretion of insulin.

This is particularly observed after the ingestion of a protein-rich meal that causes transient rise in plasma amino acid concentration.

Among the amino acids, arginine and leucine are potent stimulators of insulin release.

Gastrointestinal hormones (secretin, gastrin, pancreozymin) enhance the secretion of insulin.

The GIT hormones are released after the ingestion of food.

2. Factors inhibiting insulin secretion: Epinephrine is the most potent inhibitor of insulin release.

In emergency situations like stress, extreme exercise and trauma, the nervous system stimulates adrenal medulla to release epinephrine.

Epinephrine suppresses insulin release and promotes energy metabolism by mobilizing energy-yielding compounds—glucose—from the liver and fatty acids from adipose tissue.

Insulin degradation: Insulin is degraded by a protease enzyme called **insulinase**, which is mainly found in liver and kidney.

In the plasma, insulin has a normal half-life of 4-5 minutes.

This short half-life permits rapid metabolic changes in accordance to alterations in the circulating levels of insulin.

FUNCTIONS OF INSULIN

- Insulin is responsible for regulating the movement of glucose from the blood into cells.
- It regulates the metabolism of carbohydrates, fats and protein.
- It is considered an “anabolic” or building hormone, as it assists processes that build compounds for storage and decrease processes that break down those storage reserves.
- Insulin increases glycogenesis and decreases glycogenolysis.
- It decreases gluconeogenesis in the liver, and increases glycolysis in liver and adipose tissue.
- It decreases the breakdown of amino acids in the liver, and increases amino acid uptake and protein synthesis in muscle, liver, and adipose tissue.
- It decreases lipolysis, and increases lipogenesis and esterification of fatty acids in the liver and adipose tissue.

Metabolic effects of insulin—a summary

Metabolism	*Net effect*	*Effect on important enzyme(s)*
Carbohydrate metabolism		
1. Glycolysis	Increased	Glucokinase ↑ Phosphofructokinase ↑ Pyruvate kinase ↑
2. Gluconeogenesis	Decreased	Pyruvate carboxylase ↓ Phosphoenol pyruvate carboxykinase ↓ Glucose 6-phosphatase ↓
3. Glycogenesis	Increased	Glycogen synthetase ↑
4. Glycogenolysis	Decreased	Glycogen phosphorylase ↓
5. HMP shunt	Increased	Glucose 6- phosphate dehydrogenase ↑
Lipid metabolism		
6. Lipogenesis	Increased	Acetyl CoA carboxylase ↑
7. Lipolysis	Decreased	Hormone sensitive lipase ↓
8. Ketogenesis	Decreased	HMG CoA synthetase ↓
Protein metabolism		
9. Protein synthesis	Increased	RNA polymerase ↑
10. Protein degradation	Decreased	Transaminases ↓ Deaminases ↓

Source: Satyanarayana and Chakrapani, 2013

MECHANISM OF INSULIN ACTION

- Insulin binds to specific plasma membrane receptors present on the target tissues, such as muscle and adipose.

- This results in a series of reactions ultimately leading to the biological action.

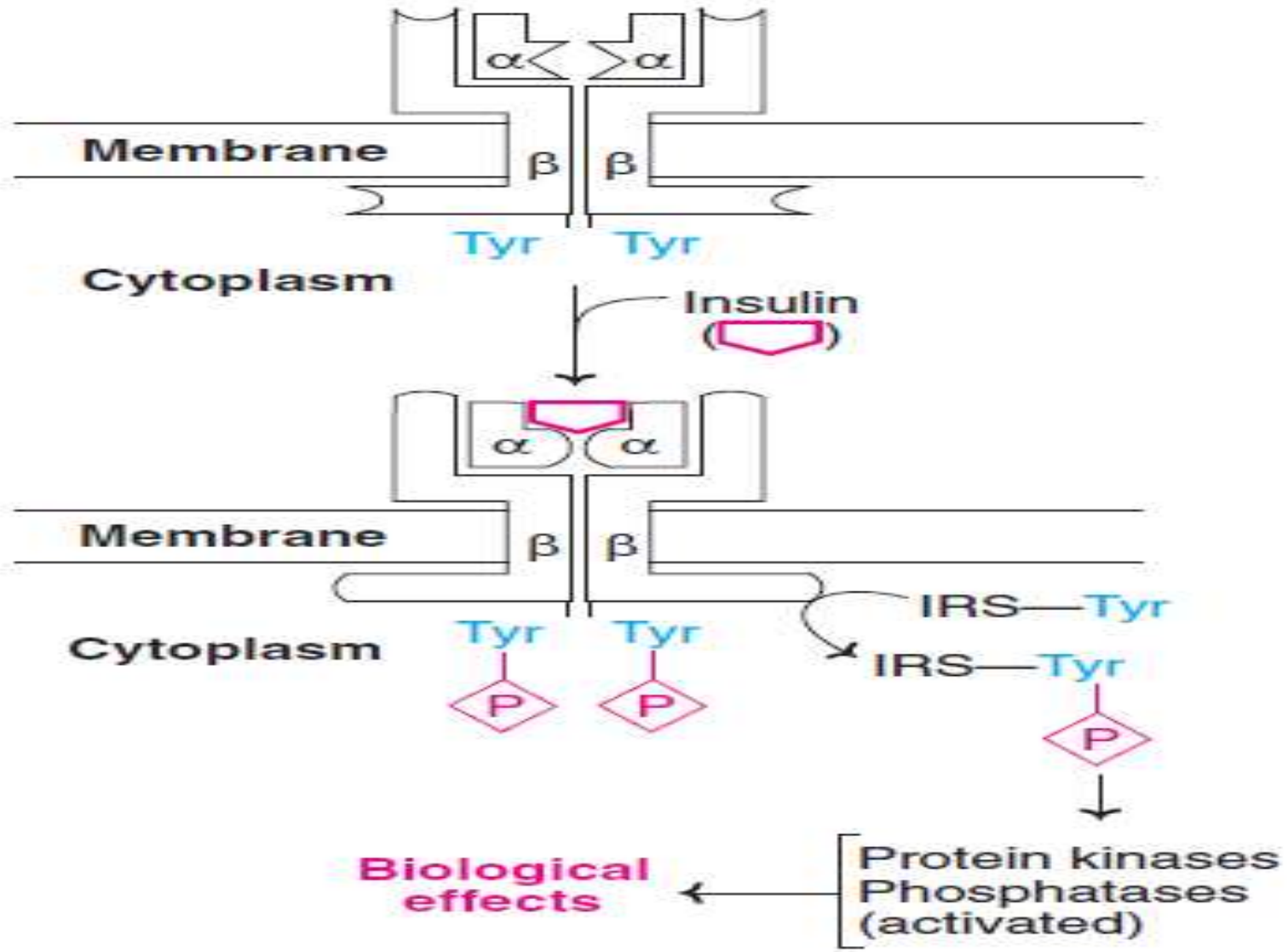
- Three distinct mechanisms of insulin action are known:

1. **Insulin receptor mediated signal transduction:** The insulin receptor is a tetramer consisting of 4 subunits of two types and is designated as $\alpha_2\beta_2$.

The subunits are in the glycosylated form, and are held together by disulfide linkages.

- The β-subunit (mol. wt. 135,000) is extracellular, and it contains the insulin binding site.
- The β-subunit (mol. wt. 95,000) is a transmembrane protein, which is activated by insulin.
- The cytoplasmic domain of β-subunit has tyrosine kinase activity.
- The insulin receptor is synthesized as a single polypeptide and cleaved to α and β subunits which are then assembled.
- The insulin receptor has a half-life of 6-12 hours, and there are about 20,000 receptors per cell in mammals.

- **Signal transduction:** As the hormone insulin binds to the receptor, a conformational change is induced in the α-subunits of insulin receptor.
- This results in the generation of signals which are transduced to β-subunits.
- The net effect is that insulin binding activates tyrosine kinase activity of intracellular β-subunit of insulin receptor.
- This causes the autophosphorylation of tyrosine residues on β-subunit.
- It is believed that receptor tyrosine kinase also phosphorylates insulin receptor substrate (IRS).
- The phosphorylated IRS, in turn, promotes activation of other protein kinases and phosphatases, finally leading to biological action



Insulin receptor mediated signal transduction

(IRS—Insulin receptor substrate)

2. **Insulin-mediated glucose transport:** The binding of insulin to insulin receptors signals the translocation of vesicles containing glucose transporters from intracellular pool to the plasma membrane.

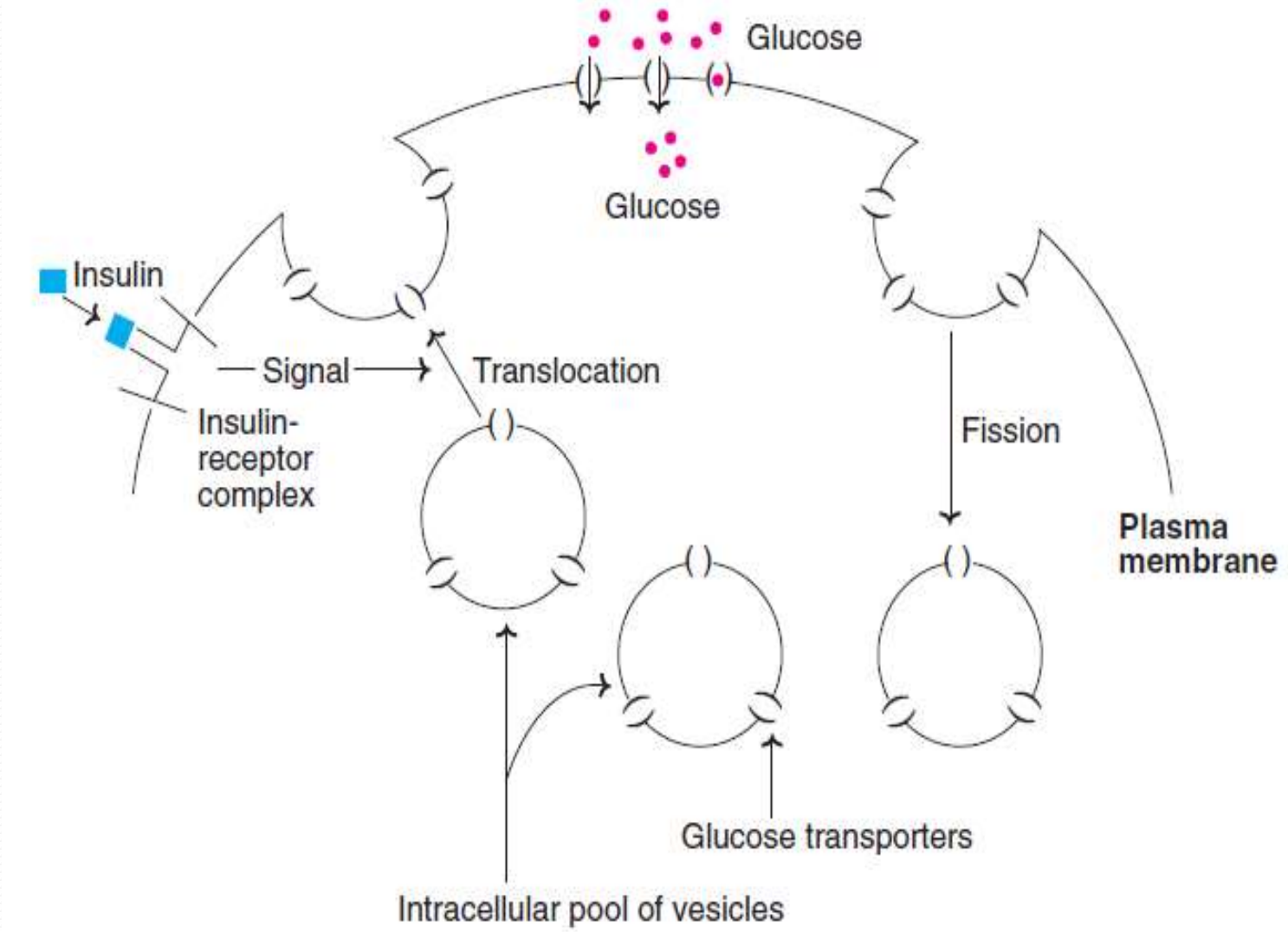
The vesicles fuse with the membrane recruiting the glucose transporters.

- The glucose transporters are responsible for the insulin–mediated uptake of glucose by the cells.

- As the insulin level falls, the glucose transporters move away from the membrane to the intracellular pool for storage and recycle.

3. **Insulin mediated enzyme synthesis:** Insulin promotes the synthesis of enzymes such as glucokinase, phosphofructokinase and pyruvate kinase.

- This is brought about by increased transcription (mRNA synthesis), followed by translation (protein synthesis).



Insulin-mediated Glucose Transport

GLUCAGON

- Glucagon is a peptide hormone composed of 29 amino acids (mol. wt. 3,500) in a single chain.
- It is secreted by α-cells of the pancreas, and it opposes the actions of insulin.
- Glucagon is synthesized as proglucagon (mol. wt. 9,000), which on sequential degradation releases active glucagon.
- Unlike insulin, the amino acid sequence of glucagon is the same in all studied mammalian species.
- Glucagon has a short half-life in plasma (i.e. about 5 minutes).

- The secretion of glucagon is stimulated by low blood glucose concentration, amino acids derived from dietary protein and low levels of epinephrine.

- Increased blood glucose level inhibits glucagon secretion.

- Glucagon binds to the specific receptors on the plasma membrane and acts through the mediation of cyclic AMP, the second messenger.

FUNCTIONS OF GLUCAGON

Glucagon influences carbohydrate, lipid and protein metabolisms, and its effects oppose that of insulin.

1. Effects on carbohydrate metabolism: Glucagon is the most potent hormone that enhances blood glucose level (hyperglycemic).

Primarily, glucagon acts on liver to cause increased synthesis of glucose (gluconeogenesis) and enhanced degradation of glycogen (glycogenolysis).

The actions of glucagon are mediated through cyclic AMP.

2. Effects on lipid metabolism: Glucagon promotes fatty acid oxidation, resulting in energy production and ketone body synthesis (ketogenesis).

3. Effects on protein metabolism: Glucagon increases amino acid uptake by liver which, in turn, promotes gluconeogenesis, and thus, glucagon lowers plasma amino acids.

OTHER HORMONES REGULATING CARBOHYDRATES METABOLISM

- **Epinephrine:** This hormone is secreted by adrenal medulla, and it acts both on muscle and liver to bring about glycogenolysis by increasing phosphorylase activity.

  The end product is glucose in liver and lactate in muscle, so the net outcome is that epinephrine **increases blood glucose level**.

- **Thyroxine:** It is a hormone of thyroid gland, and it **elevates blood glucose level** by stimulating hepatic glycogenolysis and gluconeogenesis.

- **Glucocorticoids:** These hormones are produced by adrenal cortex, and they stimulate protein metabolism and increase gluconeogenesis (increase the activities of the enzymes—glucose 6-phosphatase and fructose 1,6-bisphosphatase).

Glucose utilization by extrahepatic tissues is inhibited by glucocorticoids, so the overall effect of glucocorticoids is to **elevate blood glucose concentration**.

- **Growth hormone and adrenocorticotropic hormone (ACTH):** The anterior pituitary gland secretes growth hormone and ACTH.

The uptake of glucose by certain tissues (muscle, adipose tissue etc.) is decreased by growth hormone.

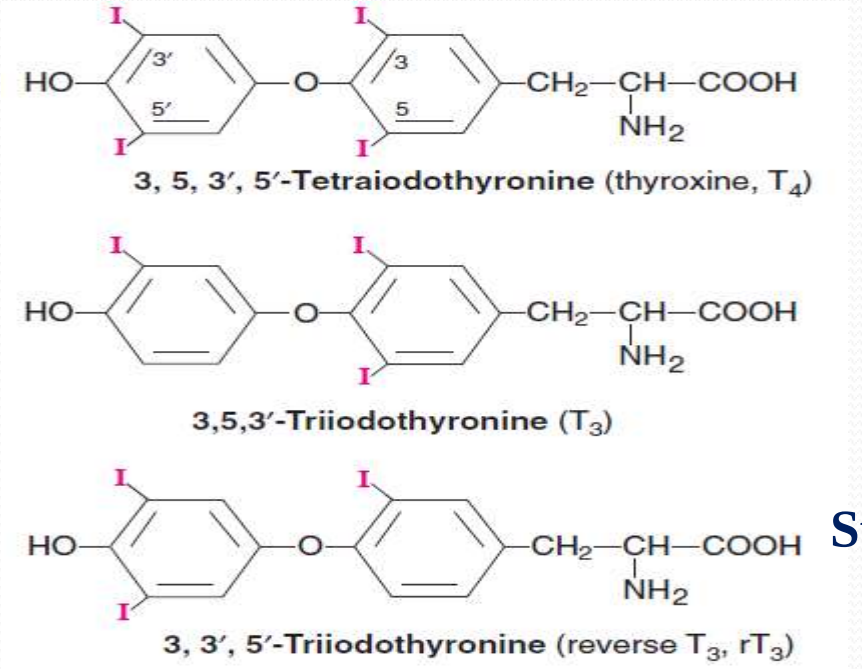
ACTH **decreases glucose utilization**.

The net effect of both these hormones is hyperglycemic.

BIOCHEMISTRY AND FUNCTIONS OF THYROID HORMONES

THYROID HORMONES

- Thyroid hormones are hormones produced by the thyroid gland.
- The thyroid gland produces two principal hormones—thyroxine (T_4; 3,5,3’,5’-tetraiodothyronine) and 3,5,3’-triiodothyronine (T_3)—which regulate the metabolic rate of the body.
- It also secretes calcitonin, a hormone concerned with calcium homeostasis.



Structures of thyroid hormones

BIOSYNTHESIS OF THYROID HORMONES

- Iodine is essential for the synthesis of thyroid hormones, and more than half of the body's total iodine content is found in the thyroid gland.

- The uptake of iodide by the thyroid gland occurs against a concentration gradient (about 20:1).

- It is an energy-requiring process and is linked to the ATPase-dependent Na^+-K^+ pump.

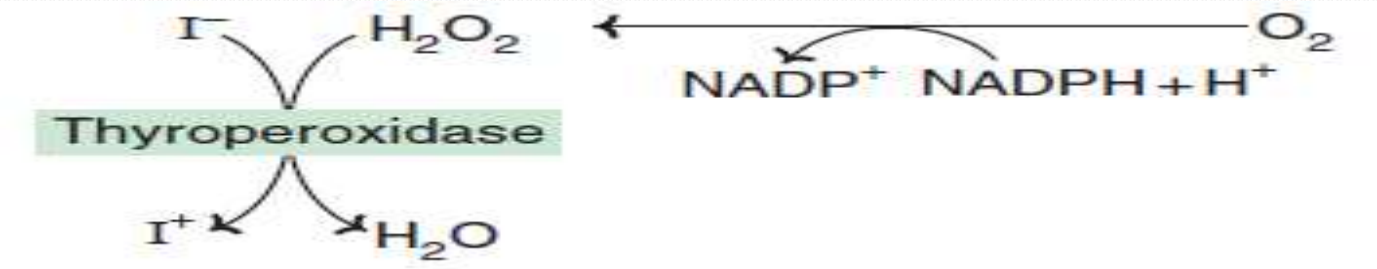
- Iodide uptake is primarily controlled by TSH, and antithyroid agents such as thiocyanate and perchlorate inhibit iodide transport.

- The conversion of iodide (I^-) to active iodine (I^+) is an essential step for its incorporation into thyroid hormones.

- Thyroid is the only tissue that can oxidize I^- to a higher valence state I^+.

- This reaction requires H_2O_2 and is catalyzed by the enzyme thyroperoxidase (mol. wt. 60,000).

- An NADPH-dependent system supplies H_2O_2.



- TSH promotes the oxidation of iodide to active iodine while the antithyroid drugs (thiourea, thiouracil, methinazole) inhibit.

- **Thyroglobulin and synthesis of T_3 and T_4:** Thyroglobulin (mol. wt. 660,000) is a glycoprotein and precursor for the synthesis of T_3 and T_4.

- Thyroglobulin contains about 140 tyrosine residues, which can serve as substrates for iodine for the formation of thyroid hormones.

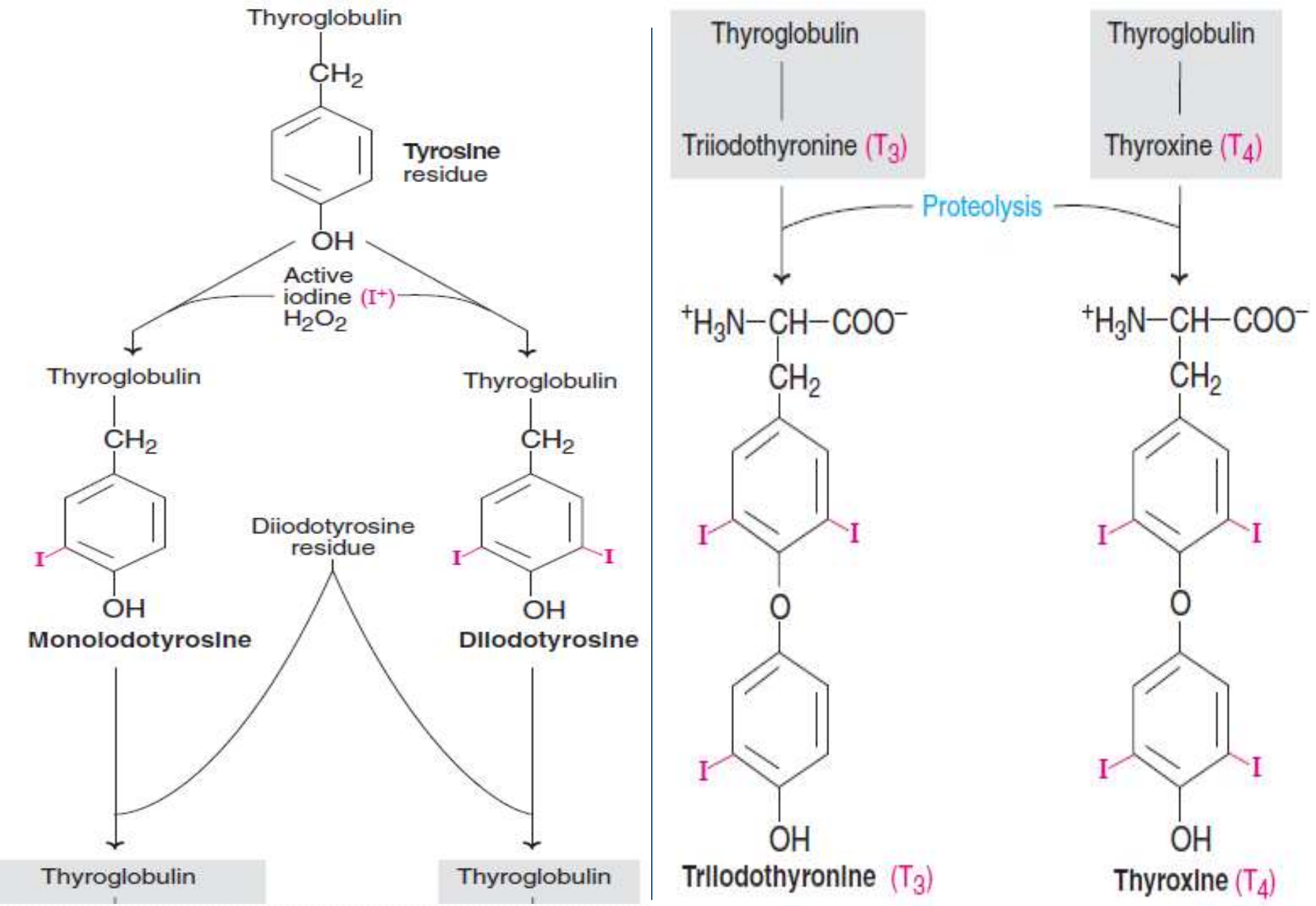
- Tyrosine (of thyroglobulin) is first iodinated at position 3 to form monoiodotyrosine (MIT) and then at position 5 to form diiodotyrosine (DIT).

- Two molecules of DIT couple to form thyroxine (T_4), and one molecule of MIT, when coupled with one molecule of DIT, triiodothyronine (T_3) is produced.

- The mechanism of coupling is not well understood.

- As the process of iodination is completed, each molecule of thyroglobulin contains about 6-8 molecules of thyroxine (T_4).

- The ratio of T_3 to T_4 in thyroglobulin is usually around 1:10.



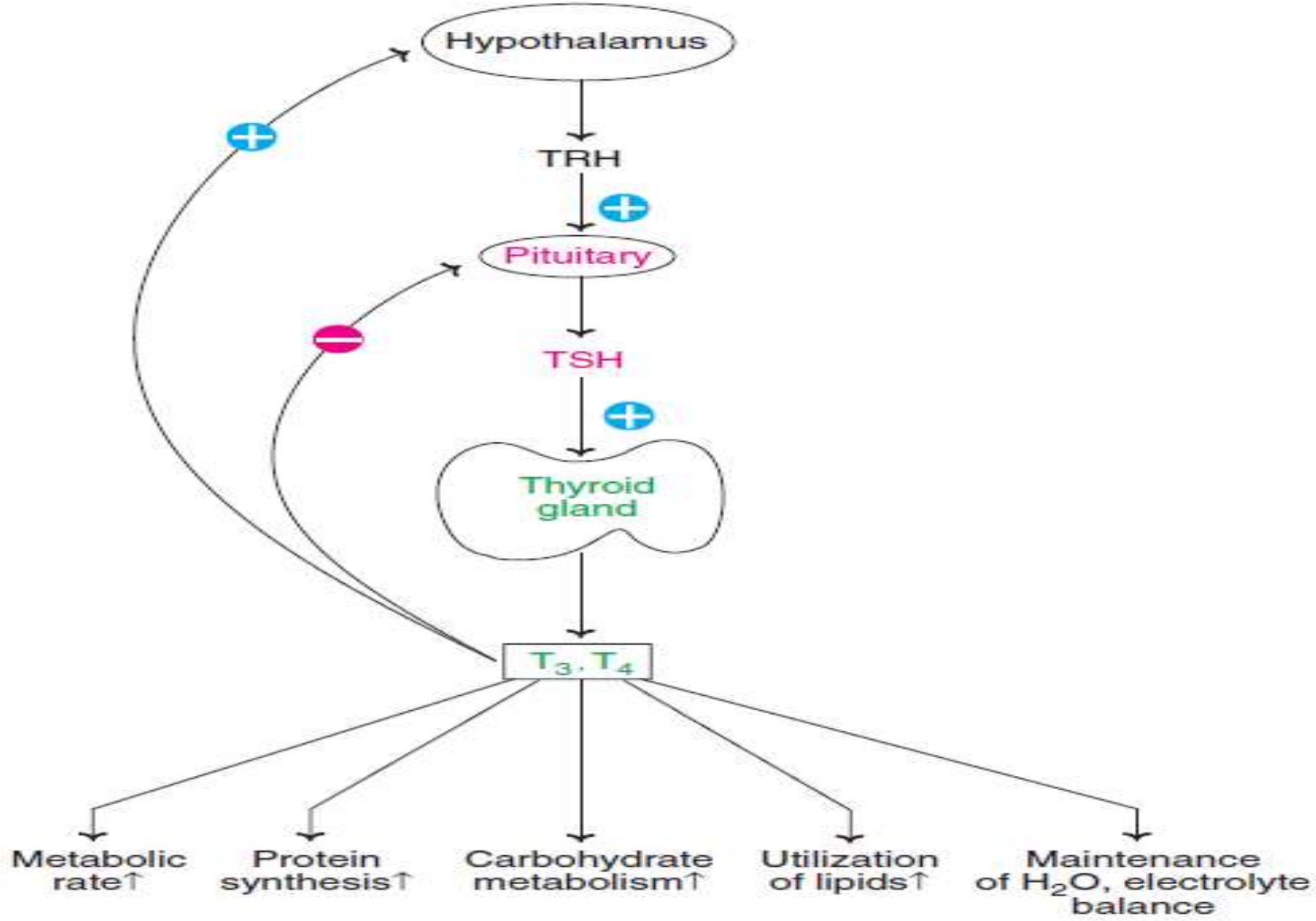
Biosynthesis of thyroid hormones

Regulation of T_3 and T_4 synthesis

- The synthesis of thyroid hormones is controlled by feedback regulation.
- T_3 appears to be more actively involved than T_4 in the regulation process.
- The production of thyroid stimulating hormone (TSH) by pituitary, and thyrotropin releasing hormone (TRH) by hypothalamus are inhibited by T_3, and to a lesser degree, by T_4.
- The increased synthesis of TSH and TRH occurs in response to decreased circulatory levels of T_3 and T_4.
- The body has sufficient stores of hormones to last for several weeks.
- Hence, it takes some months to observe thyroid functional deficiency.

Metabolic fate of T_3 and T_4

- Thyroid hormones undergo deiodination in the peripheral tissues.
- The iodine liberated may be reutilized by the thyroid.
- T_3 and T_4 may get conjugated with glucuronic acid or sulfate in the liver and excreted through bile.
- Thyroid hormones are also subjected to deamination to produce tetraiodothyroacetic acid (from T_4) and triiodothyroacetic acid (from T_3).
- These may then undergo conjugation and excretion.



Regulation of synthesis and functions of thyroid hormones

ABNORMALITIES OF THYROID FUNCTION

- The thyroid gland is the most susceptible endocrine gland for hypo- or hyperfunction.

- There are three known abnormalities associated with thyroid functions:

1. Goiter: It refers to any abnormal increase in the size of the thyroid gland.

Enlargement of the thyroid gland is mostly to compensate the decreased synthesis of thyroid hormones and is associated with elevated TSH.

Goiter is primarily due to a failure in the autoregulation of T_3 and T_4 synthesis, which may be caused by deficiency or excess of iodide.

- **Goitrogenic substances (goitrogens):** These are the substances that interfere with the production of thyroid hormones.
- These include thiocyanates, nitrates and perchlorates and the drugs such as thiourea, thiouracil, thiocarbamide etc.
- Certain plant foods—cabbage, cauliflower and turnip—contain goitrogenic factors (mostly thiocyanates).
- **Simple endemic goiter:** This is due to iodine deficiency in the diet.
- It is mostly found in the geographical regions away from sea coast where the water and soil are low in iodine content.
- Consumption of iodized salt is advocated to overcome the problem of endemic goiter.
- In certain cases, administration of thyroid hormone is also employed.

2. Hyperthyroidism: This is also known as thyrotoxicosis and is associated with overproduction of thyroid hormones.

Hyperthyroidism is characterized by increased metabolic rate (higher BMR), nervousness, irritability, anxiety, rapid heart rate, loss of weight despite increased appetite, weakness, diarrhea, sweating, sensitivity to heat and often protrusion of eyeballs (exopthalmos).

Hyperthyroidism is caused by **Grave's disease** (particularly in the developed countries) or due to increased intake of thyroid hormones.

Grave's disease is due to elevated thyroid stimulating IgG also known as long acting thyroid stimulator (LATS) which activates TSH and, thereby, increases thyroid hormonal production.

Thyrotoxicosis is diagnosed by scanning and/or estimation of T_3, T_4 (both elevated) and TSH (decreased) in plasma.

The treatment includes administration of antithyroid drugs, and in severe cases, thyroid gland is surgically removed.

3. Hypothyroidism: This is due to an impairment in the function of thyroid gland that often causes decreased circulatory levels of T_3 and T_4.

Disorders of pituitary or hypothalamus also contribute to hypothyroidism, and women are more susceptible than men.

Hypothyroidism is characterized by reduced BMR, slow heart rate, weight gain, sluggish behaviour, constipation, sensitivity to cold, dry skin etc.

Hypothyroidism in children is associated with physical and mental retardation, collectively known as cretinism.

Hypothyroidism in adult causes myxoedema, characterized by bagginess under the eyes, puffiness of face, slowness in physical and mental activities.

Thyroid hormonal administration is employed to treat hypothyroidism.

LABORATORY DIAGNOSIS OF THYROID FUNCTION

- Serum cholesterol level is increased in hypothyroidism and decreased in hyperthyroidism, but cholesterol estimation will be of no value in the assessment of thyroid function.

- This is because serum cholesterol level is elevated in other disorders (diabetes, obstructive jaundice, nephrotic syndrome etc.), however, cholesterol estimation may be utilized for monitoring thyroid therapy.

- The measurement of basal metabolic rate (BMR), as well as the estimation of serum protein bound iodine (PBI), which represent the circulating thyroid hormones, were once respectively used to reflect thyroid activity.

- More sensitive and reliable tests have been developed to assess thyroid activity such as measurement of the concentration of free T_3 and T_4, and TSH (by RIA or ELISA), radioactive iodine uptake (RAIU) and scanning of thyroid gland.

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