

ENDOCRINE PHARMACOLOGY

FOR B.PHARMACY STUDENTS

(Paradise Valley University College)

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Introduction

- The metabolic effects of the different systems of the body:
 - controlled by autonomic nervous system and the secretions of the endocrine, or ductless glands.
- Hormones:
 - heterogeneous group of chemicals,
 - released into the blood stream and travel to all parts of the body.
- The pharmacology of the individual hormones is of importance,
 - under or over production of the hormones can have striking metabolic consequences.

- The hypothalamus and pituitary gland function cooperatively as master regulators of the endocrine system.
 - control reproduction, growth, lactation, thyroid and adrenal gland physiology, and water homeostasis.
- Deficiency or overproduction of these hormones disrupts this control.
- Clinical use of protein hormones in the past was limited;
 - Preparations had to come from glands or urine.
- Recombinant DNA techniques and the development of more stable analogues that can be injected in a depot form
 - permit increased and more effective use of these hormones.

Table: Hypothalamic Releasing and Inhibiting Hormones that regulate the anterior pituitary

Hormone	Principal Effects
TRH: Thyrotropin-releasing hormone	Promotes TSH and PRL secretion
CRH: Corticotropin-releasing hormone	Promotes ACTH secretion
GnRH: Gonadotropin-releasing hormone	Promotes FSH and LH secretion
PRH: Prolactin-releasing hormone	Promotes PRL secretion
PIH: Prolactin-inhibiting hormone	Inhibits PRL secretion
GHRH: Growth hormone-releasing hormone	Promotes GH secretion
Somatostatin	Inhibits GH and TSH secretion

Table: Pituitary Hormones

Hormone	Target Organ	Principal Effects
Anterior Pituitary		
FSH: Follicle-stimulating hormone	Ovaries, testes	Female: growth of ovarian follicles and secretion of estrogen Male: sperm production
LH: Luteinizing hormone	Ovaries, testes	Female: ovulation, maintenance of corpus luteum Male: testosterone secretion
TSH: Thyroid-stimulating hormone	Thyroid gland	Growth of thyroid, secretion of thyroid hormone
ACTH: Adrenocorticotrophic hormone	Adrenal cortex	Growth of adrenal cortex, secretion of corticosteroids
PRL: Prolactin	Mammary glands, testes	Female: milk synthesis Male: increased LH sensitivity and testosterone secretion
GH: Growth hormone (somatotropin)	Liver	Somatomedin secretion, widespread tissue growth
Posterior Pituitary		
ADH: Antidiuretic hormone	Kidneys	Water retention
OT: Oxytocin	Uterus, mammary glands	Labor contractions, milk release; possibly involved in ejaculation, sperm transport, and sexual affection

DRUGS FOR DIABETES MELITUS

- *Diabetes Mellitus*

- ▶ is a heterogeneous group of syndromes characterized by an elevation of blood glucose . Cause is
 - a relative or absolute deficiency of insulin or
 - resistance to insulin's action
- **Symptoms:** include hyperglycemia, glucosuria, polyuria, polydipsia, polyphagia

EFFECTS OF INSULIN

SITE	ACTIONS
Muscle	↑ glucose transport into cell ↑ glycogenesis ↑ protein and triglyceride synthesis
Liver	↑ glucose transport into cell ↑ glycogenesis ↑ glucose utilization in Krebs cycle ↑ protein synthesis
Adipose	↑ glucose transport into cell ↑ glycogenesis ↑ triglyceride synthesis

■ **Four clinical classifications of diabetes:**

✓ Type 1 diabetes (insulin-dependent diabetes mellitus IDDM) or juvenile-onset diabetes

» patient secretes no insulin

» Cause is felt to be autoimmune.

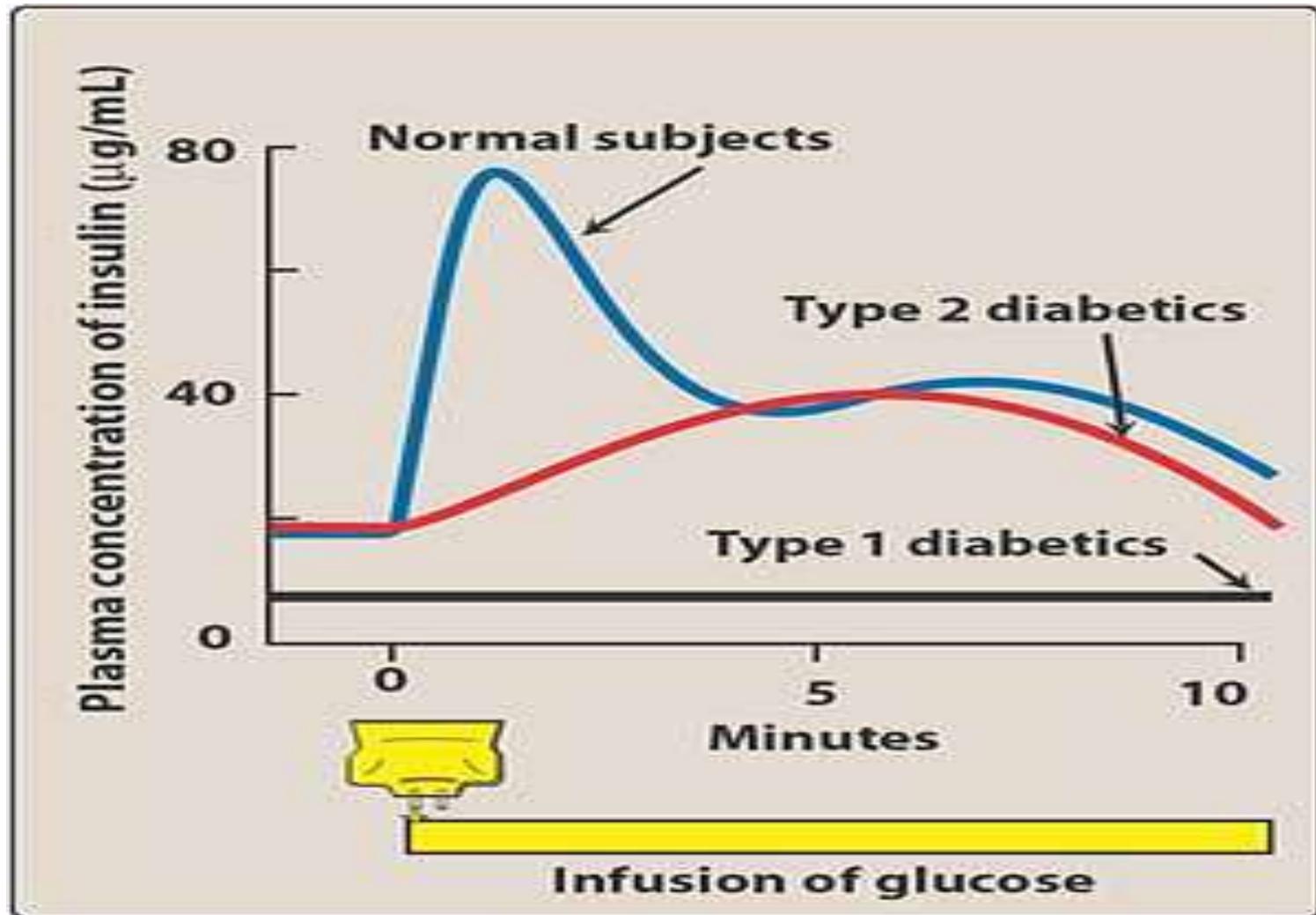
» 10% of those with diabetes are type I

✓ Type 2 diabetes (non insulin dependent diabetes mellitus NIDDM) or maturity-onset diabetes

» patient secretes insufficient amounts of insulin and insulin receptors are resistant to existent circulating insulin

» The B2-cell mass may become gradually reduced necessitating exogenous insulin

- ✓ diabetes due to other causes (e.g. nonpancreatic diseases, genetic defects or medication induced)
- ✓ gestational diabetes (carbohydrate intolerance with onset or first recognition during pregnancy)



	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Frequently over age 35
Nutritional status at time of onset	Frequently undernourished	Obesity usually present
Prevalence	5 to 10 percent of diagnosed diabetics	90 to 95 percent of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

■ ***Drugs for the management of diabetes mellitus***

❖ ***Insulin***

➤ Short duration:

✓ Rapid acting eg insulin lispro

✓ Short acting eg regular insulin

➤ Intermediate duration eg NPH insulin

➤ Long duration eg insulin glargine

❖ ***Oral hypoglycemics***

✚ Insulin secretagogues

✚ Insulin sensitizers

✚ Alpha glucosidase inhibitors

■ Insulin

- Insulin preparations vary primarily in their times of onset of activity and in their durations of activity.
 - » due to differences in the amino acid sequences of the polypeptides and presence of extra molecule
- Currently human insulin is produced by recombinant DNA technology

Four principal types of injected insulin are available:

- ✓ rapid-acting
- ✓ short-acting
- ✓ intermediate-acting; and
- ✓ long-acting

- **Rapid-acting**
 - **insulin lispro, insulin aspart, and insulin *glulysine***
 - offer more flexible treatment regimens and may lower the risk of hypoglycemia
- **short-acting**
 - **Regular insulin (soluble, crystalline zinc insulin)**
 - usually given subcutaneously
 - intravenously in emergencies
- Rapid and short acting insulin preparations are usually not used alone but, rather, along with a longer-acting insulin to assure proper glucose control

- **Intermediate-acting insulin**
 - **lente insulin (insulin zinc suspension)**
 - **NPH insulin/insulin isophane**
 - NPH means neutral protamine Hagedorn
- Duration of action is intermediate due to delayed absorption of the insulin because of its conjugation with protamine, forming a less-soluble complex.

- **Long-acting insulin preparations**
 - Insulin glargine and Insulin detemir
- **Insulin combinations**
 - Various premixed combinations of human insulins
 - » 70-percent NPH insulin plus 30-percent regular insulin
 - » 50 percent each of NPH insulin and regular insulin

Types of insulin: time course of action after SC injection

Class	Generic name	Time course		
		Onset (min)	Peak (hr)	Duration (hr)
Short duration: Rapid acting	<ul style="list-style-type: none"> •Insulin lispro •Insulin aspart 	15-30	0.5-2.5	3-6.5
		10-20	1-3	3-5
Short duration: Slower acting	<ul style="list-style-type: none"> •Regular insulin 	30-60	1-5	6-10
Intermediate duration	<ul style="list-style-type: none"> •NPH insulin •Lente insulin 	60-120	6-14	16-24
Long duration	<ul style="list-style-type: none"> •Insulin glargine 	70	None	24

- ***Route of administration***

- ☛ Insulin is generally administered by subcutaneous injection.

- » In a hyperglycemic emergency, regular insulin is injected intravenously or IM.

- Insulin is inactivated by insulin degrading enzyme (also called insulin protease), which is found mainly in the liver and kidney.

- » Diabetics with renal insufficiency may require adjustment of the insulin dose.

■ ***Adverse Effects***

1. Hypoglycemia is the most serious and common adverse reactions to an overdose of insulin
2. Weight gain- during intensive (more frequent) insulin therapy
3. Hypertrophy of subcutaneous fatty tissue if injected repeatedly at the same site
4. allergic reactions, and local injection site reactions

■ Oral Hypoglycemic Agents

- are useful in the treatment of patients who have Type 2 diabetes
- Patients with long-standing disease may require a combination of hypoglycemic drugs with or without insulin to control their hyperglycemia.
 - » Insulin is added because of the progressive decline in B2 cells that occurs due to the disease or aging.
- Oral hypoglycemic agents should not be given to patients with Type 1 diabetes.

❖ *Oral hypoglycemics*

- ✚ Insulin secretagogues
 - The sulphonylureas
 - Meglitinides
- ✚ Insulin sensitizers
 - Biguanides
 - Thiazolidinediones
- ✚ Alpha glucosidase inhibitors

- ***Sulfonylureas***
 - ***first generation- eg tolbutamide***
 - ***second-generation – eg glyburide , glipizide , and glimepiride***
- **Mechanisms of action**
 - ✓ insulin release- by blocking the ATP-sensitive K⁺ channels
 - ✓ increase in peripheral insulin sensitivity
 - ✓ reduction in hepatic glucose production
- **Therapeutic Uses**
 - to control hyperglycemia in type 2 DM patients who cannot achieve appropriate control with changes in diet alone

- **Contraindications**

- type 1 DM, pregnancy, lactation, and for the older preparations, significant hepatic or renal insufficiency.

- **Pharmacokinetics**

- Given PO
- Because of its short half-life (6-12 hours), tolbutamide is the safest sulfonylurea for elderly diabetics

■ **Adverse effects**

- cause weight gain, hyperinsulinemia, and hypoglycemia.
- should be used with caution in patients with hepatic or renal insufficiency
- Glyburide has minimal transfer across the placenta and may be a reasonably safe alternative to insulin therapy for diabetes in pregnancy

- **Meglitinide analogs : eg repaglinide and nateglinide**
 - are not sulfonylureas but have common actions
 - ✓ blocking the ATP-sensitive K⁺ channels causes insulin release
 - in contrast to the sulfonylureas, the meglitinides have a rapid onset and a short duration of action.
- Used as monotherapy or combined therapy with metformin or the glitazones in improving glycemic control
 - » Meglitinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action.

- There is no sulfur in its structure, so repaglinide may be used in type 2 diabetic individuals with sulfur or sulfonylurea allergy.
- well absorbed orally after being taken 1 to 30 minutes before meals
 - » must be used with caution in patients with hepatic impairment. And also for renal impairment
- Cause hypoglycemia and weight gain (lower than that with the sulfonylureas)

- **Biguanides; eg Metformin**
- **Mechanism of action:**
 - ✓ The main mechanism of action of metformin is reduction of hepatic gluconeogenesis.
 - ✓ also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization.
 - can be administered in combination with sulfonylureas, thiazolidinediones, and/or insulin.
 - Given PO
 - The patient often loses weight because of loss of appetite.
 - Hypoglycemia has occurred when metformin was taken in combination

- Acute side effects are largely gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, metallic taste and diarrhea)
- should be temporarily discontinued in patients undergoing diagnosis requiring intravenous radiographic contrast agents.
- Rarely, potentially fatal lactic acidosis has occurred
- are contraindicated in patients with renal disease, alcoholism, hepatic disease, or conditions predisposing to tissue anoxia (eg, chronic cardiopulmonary dysfunction)

- **Thiazolidinediones or glitazones**
 - **pioglitazone** and **rosiglitazone**
- **MOA**
 - Tzds are ligands of peroxisome proliferator-activated receptor-gamma (PPAR-g)
 - » resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle
 - Well absorbed orally
 - can be used as monotherapy or in combination with other hypoglycemics or with insulin
 - ✓ The glitazones are recommended as a second-line alternative for patients who fail or have contraindications to metformin therapy.

- It is recommended that these agents should not be used in nursing mothers.
- Very few cases of liver toxicity have been reported with rosiglitazone or pioglitazone.
 - » it is recommended that liver enzyme levels of patients on these medications be measured initially and periodically thereafter.
- Weight increase can occur, possibly through the ability of TZDs to increase subcutaneous fat or due to fluid retention. Edema is more likely to occur when these agents are combined with insulin

- **Alpha glucosidase Inhibitors**
 - **Acarbose, miglitol**
- **MOA**
 - by reversibly inhibiting membrane-bound alpha glucosidase in the intestinal brush border
 - » hydrolysis of oligosaccharides to glucose and other sugars is inhibited thereby resulting in lower postprandial glucose levels.
 - Acarbose also inhibits pancreatic amylase, thus interfering with the breakdown of starch to oligosaccharides.
- are taken at the beginning of meals.

- Unlike the other oral hypoglycemic agents, these drugs do not stimulate insulin release, nor do they increase insulin action in target tissues.
 - » Thus, as monotherapy, they do not cause hypoglycemia
- NB: the hypoglycemic patient should be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs
 - Alpha-glucosidase inhibitors have a relatively weak antidiabetic effect and significant adverse effects, and they are used primarily as adjunctive therapy in individuals who cannot achieve their glycemic goals with other medications.

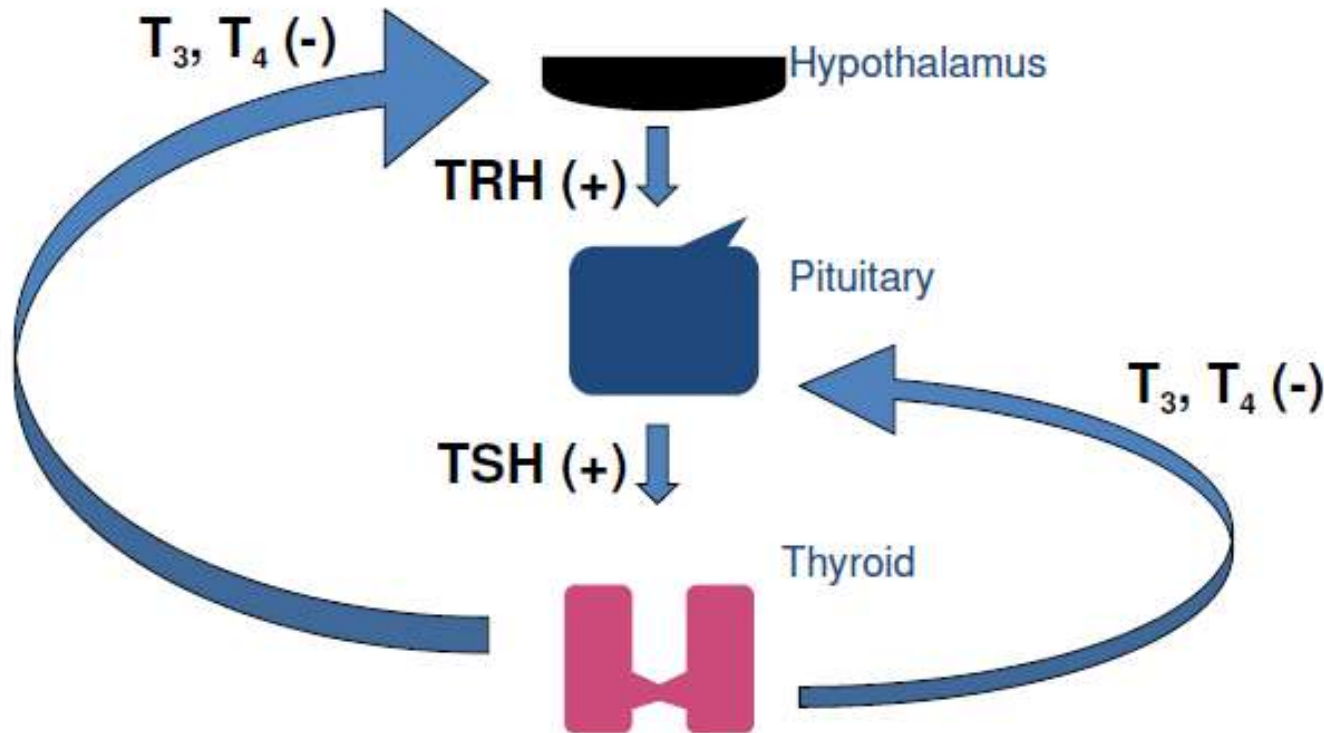
- major side effects are flatulence, diarrhea, and abdominal cramping.
- Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.
- * **Diabetic ketoacidosis- is managed with**
 - ✓ IV insulin
 - ✓ IV fluids to rehydrate
 - ✓ Potassium supplementation
 - ✓ sodium bicarbonate

THYROID AND ANTITHYROID DRUGS

- ❑ The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for their normal function.
- ❑ The two major thyroid hormones are triiodothyronine (T₃; the most active form) and thyroxine (T₄).
- ❑ Thyroid function is controlled by thyroid-stimulating hormone (TSH; thyrotropin), which is synthesized by the anterior pituitary where the generation of TSH is governed by the hypothalamic thyrotropin-releasing hormone (TRH).

□ When the concentration of T3 and T4 increased TSH and TRH will be inhibited by feedback mechanism

Thyroid Axis



In general thyroid hormone (T3 & T4) have the following three principal actions:

1. Stimulation of energy use

–↑ O_2 consumption &

–↑ Heat production

2. Stimulation of the heart

–↑ Heart rate

–↑ force of contraction ↑ Co

3. Promotion of growth & development

–Brain & other components of the NS

–Maturation of skeletal muscle

Synthesis of thyroid hormones:

– Major steps:

- Uptake of iodide ion by the gland
- Oxidation of iodide
- Iodination of tyrosyl groups of thyroglobulin
- Coupling of iodothyrosine residue by ether linkage to generate iodothyronines
- Proteolysis of thyroglobulin
- Release of T4 and T3 into the blood
- Conversion of T4 to T3 in the peripheral tissues

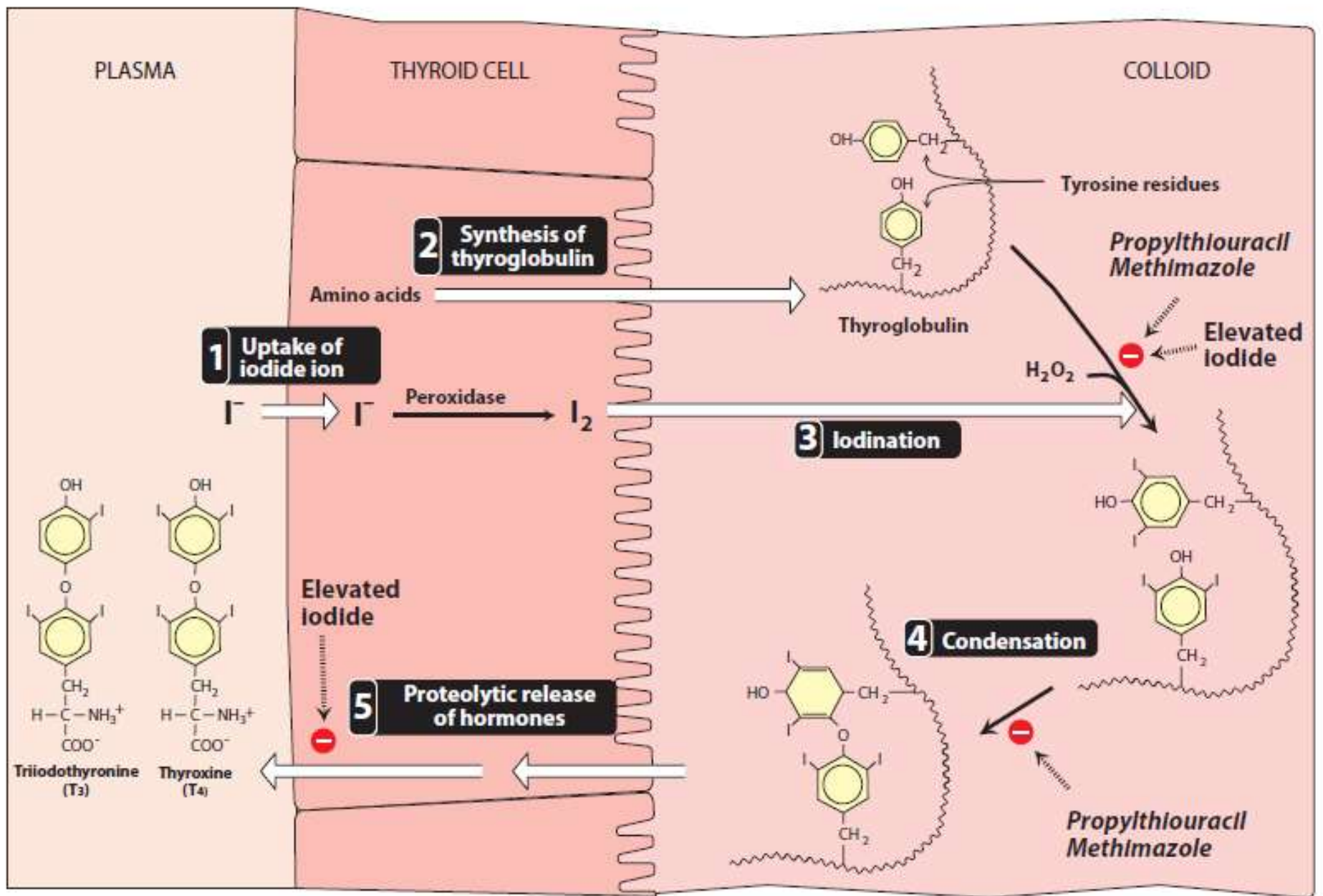


Figure 24.7

- ***Thyroid pathophysiology***
 - Hypothyroidism : can be mild or severe
 - ☛ Adults: Severe → myxedema
 - ☛ Infants → Cretinism
 - Hyperthyroidism
 - Eg Grave's diseases

Thyroid hormone excess and deficit

Hyperthyroidism

- Palpitations
- Heat intolerance
- Tachycardia
- Diaphoresis
- Nervousness
- Weight loss
 - ✓ *Increased appetite*
- Scanty menses
- Exophthalmos
- TSH decreased

Hypothyroidism

- Fatigue
- Cold Intolerance
- Dry skin, coarse hair
- Lethargy
- Weight gain
 - ✓ *Anorexia*
- Heavy menses
- Hoarse voice
- TSH increased

■ **Thyroid Hormones**

– **Levothroxine (T_4)**

– Is a synthetic preparation of thyroxin (T_4)

– Drug of choice for thyroid hormone replacement

■ **Pharmacokinetics**

– Absorption of oral T_4 is variable

– Much of T_4 is converted to T_3 → for most pts no need to give T_3 along with T_4

– $T_{1/2}$ of T_4 7 days

- **Therapeutic uses**

- 1) For the Rx of hypothyroidism

- a) ordinary hypothyroidism

- b) cretinism

- c) myxedema coma

- d) simple goiter

- 2) Hypothyroidism resulting from insufficient TSH or TRH

- **Adverse Effects**

- If dosage is excessive:

- Thyrotoxicosis

- Tachycardia, angina, tremor, nervousness, hypethermia

■ Liothyronine (T_3)

– Qualitatively similar to those of T_4 (thyroxine)

➤ Contrasts with T_4

– T_3 has a more rapid onset of action

– Has shorter $t_{1/2}$ & shorter duration of action

– T_3 is more expensive

» B/C of its high price & relatively short duration of action, T_3 is less desirable than T_4 for long-term use

» Superior than T_4 in a situation that requires speedy results (e.g. myxedema coma)

Drugs used to treat hyperthyroidism

- Three major categories:

1) Thioamides

- » Propylthiouracil
- » Methimazole
- » Carbimazole

2) Iodides

- » Lugol's solution
- » KI tablets
- » Sodium iodide inj.

3) Radioactive iodine

4) Adrenoreceptor blocking agents eg propranolol

■ Propylthiouracil (PTU)

■ MOA

- ☛ both PTU and methimazole inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form T3 and T4
- ☛ PTU can also block the conversion of T4 to T3
- Less potent than methimazole
- Since the synthesis rather than the release of hormones is affected, the onset of these agents is slow, often requiring 3-4 weeks before stores of T₄ are depleted.
- propylthiouracil is preferable in pregnancy because it is more strongly protein-bound and, therefore, crosses the placenta less readily.

- thioamides are well absorbed from the gastrointestinal tract, but they have short half-lives
- Several doses of PTU are required per day, whereas a single dose of methimazole suffices due to the duration of its antithyroid effect

■ **Therapeutic uses**

1. For therapy of Graves's disease
2. As adjunct to radiation therapy (to control hyperthyroidism until radiation effects manifest)
3. To suppress hormone synthesis in preparation for subtotal thyroidectomy, and
4. For patients experiencing thyrotoxic crisis

■ **Adverse effects**

- nausea and gastrointestinal distress, pruritic rash
- Hypothyroidism (excessive dosing)
- Agranulocytosis (rarely) . Since there is cross sensitivity with methimazole, do not replace each other during agranulocytosis

- **Iodide products**
- **MOA** – when present in high concentration:
 - a) ↓ Iodide uptake
 - b) Inhibits thyroid hormone synthesis (iodination of tyrosines). This effect lasts only a few days
 - c) Inhibits release of thyroid hormones (from thyroglobulin) into the blood stream
 - » A more important effect of iodides
 - d) Inhibits the conversion of T_4 to T_3
 - » With long-term iodide administration suppressant effects become weaker → rarely used alone

■ Therapeutic uses

- ✓ Preoperatively to control hyperthyroidism in Graves disease → ↓ size of gland & makes the gland firmer.
- ✓ to treat potentially fatal thyrotoxic crisis (thyroid storm)
- Iodide is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks
 - » Today, iodide is rarely used as the sole therapy

■ Preparation

1. Lugols solution – contains
Iodine ---- 5%
Potassium Iodide 10%
2. potassium iodide – Tablet, Solution
3. Sodium iodide (IV)

■ Adverse Effects

- ✓ Chronic administration → iodism
- ✓ metallic taste in the mouth
- ✓ sore mouth and throat
- ✓ swelling of the tongue or larynx
- ✓ Rashes, ulcerations of mucous membranes
- ✓ Frontal headache

■ Radioactive Iodine (^{131}I)

- ^{131}I , a radioactive isotope of stable iodine, emits a combination of beta- particles & gamma rays
- Is concentrated in the thyroid gland. Destruction of the thyroid tissue is produced primarily by emission of gama-rays

■ **Therapeutic uses**

- ✓ Rx of hyperthyroidism, especially in older pts with heart disease
- ✓ In the Rx of thyroid cancer
- ✓ Diagnostic use- to diagnose a variety of thyroid disorders (hypothyroidism & Hyperthyroidism)
 - The amt & location of ^{131}I uptake reveals the extent of thyroid activity

■ **Adverse effects**

- Delayed hypothyroidism
- Contraindicated in pregnancy & nursing mothers

■ **Thyroid storm**

- β -Blockers that lack sympathomimetic activity, such as propranolol are used to block the sympathetic effects

 - » Intravenous administration is effective

- In the presence of severe heart failure or asthma , calciumchannel blocker, diltiazem can be alternatively used

- PTU is used since it inhibits the peripheral conversion of T4 to T3

 - » But not methimazole

- Iodides

AGENTS THAT AFFECT BONE MINERAL HOMEOSTASIS

- Calcium and phosphate: major mineral constituent of bone
- Parathyroid and vitamin D
- Calcitonin, prolactin, growth hormone, insulin, thyroid hormone, glucocorticoids, and sex hormone.

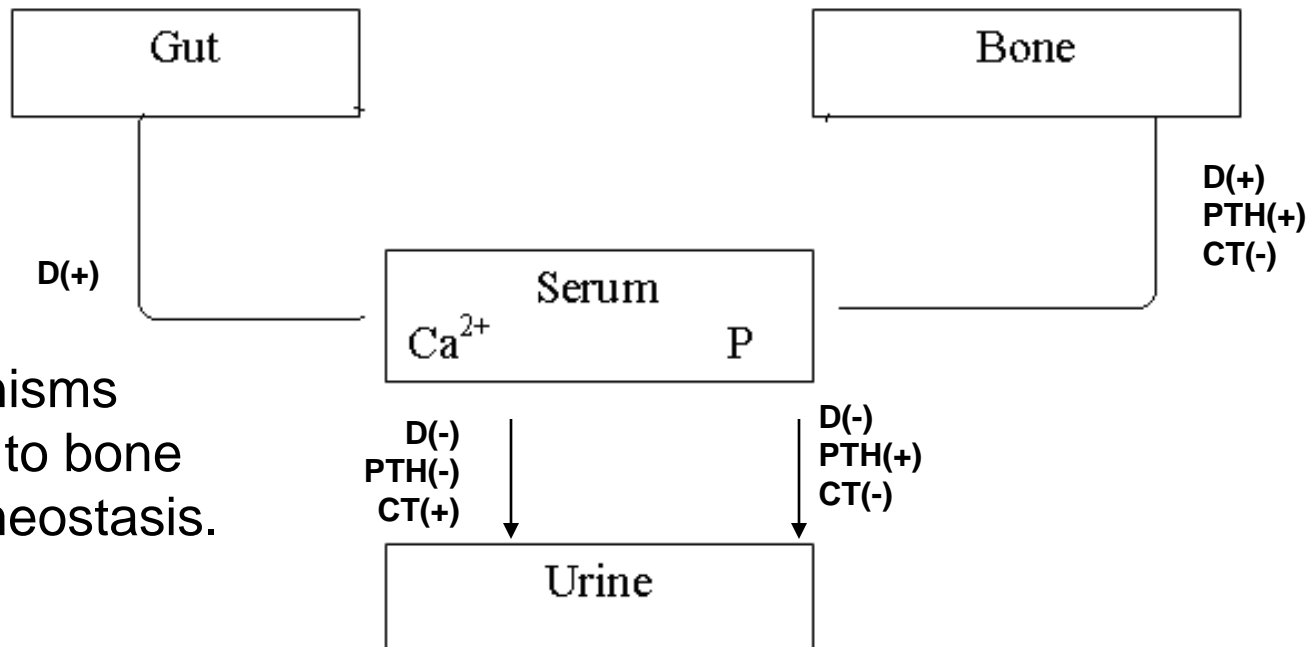


Fig. Mechanisms contributing to bone mineral homeostasis.

PARATHYROID GLANDS

- Tiny masses on the posterior of the thyroid gland
- Secrete parathyroid hormone
 - Raise calcium levels in the blood
 - Stimulate osteoclasts to remove calcium from bone
 - Stimulate the kidneys and intestine to absorb more calcium

CALCITONIN

- Produced by C cells(parafollicular) in the thyroid gland
- Decreases blood calcium levels by causing its deposition on bone
- Antagonistic to parathyroid hormone

Parathyroid disorders ;

- ✓ **Hyperparathyroidism:** an excess production of parathyroid hormone which may be due to tumours, hereditary factors or secondary to renal disease.
- Causes bone decalcification and renal calculi due to an hypercalcemia.
- Treatment:
 - Calcitonin SC or IMI
 - Surgery
 - ✓ **Hypoparathyroidism:** leads to a hypocalcaemia causing neuromuscular excitability, cardiac irregularities, and digital paraesthesia

Treatment=

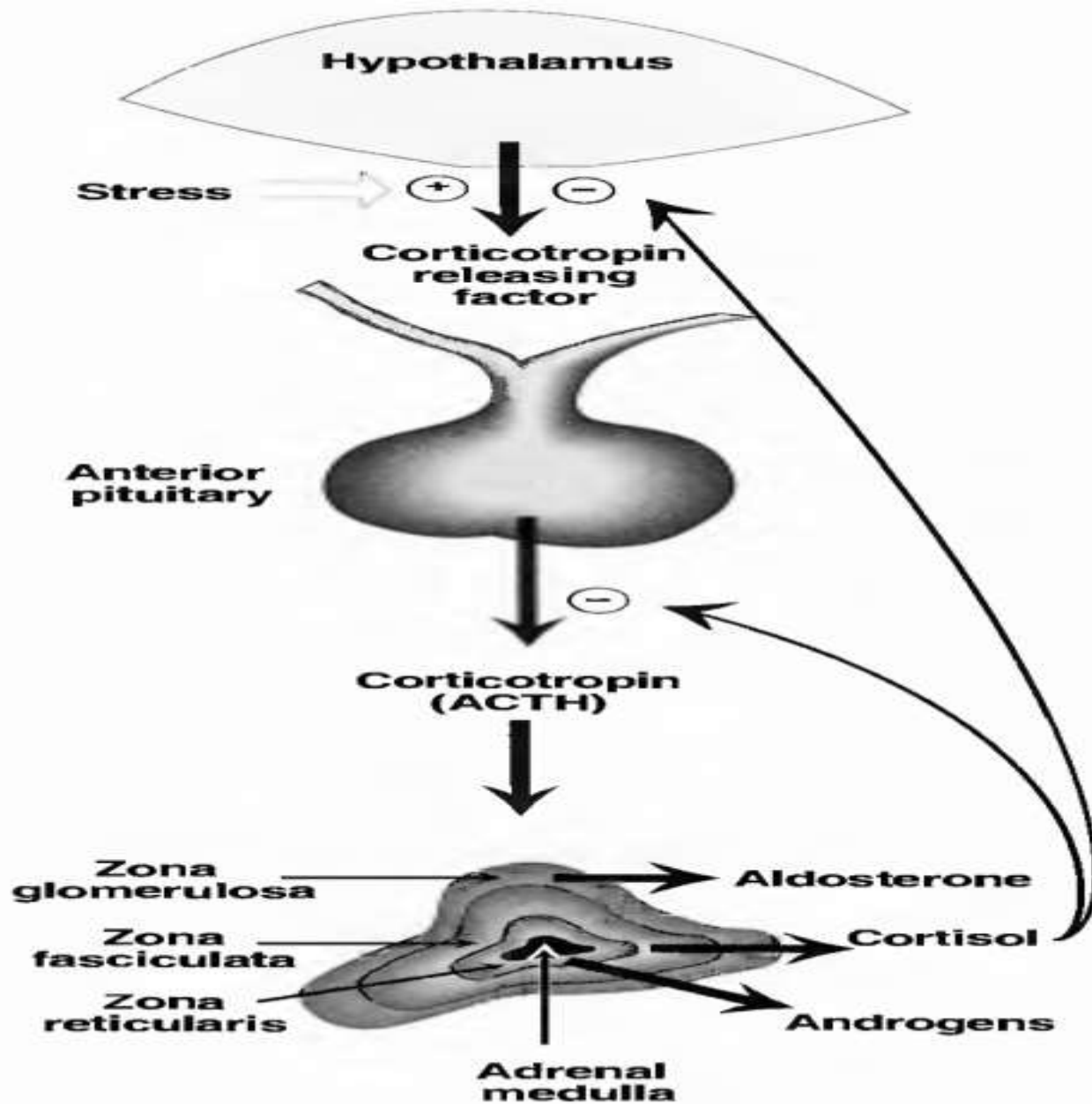
- Acute ; IV calcium
- Replacement: Calcium Supplements, Vit D

Corticosteroids

■ Introduction

- The adrenal gland consists of the cortex and the medulla (secretes epinephrine)
- the cortex synthesizes and secretes two major classes of steroid hormones
 1. The adrenocorticosteroids (glucocorticoids and mineralocorticoids)
 2. the adrenal androgens
- adrenal cortex is divided into three zones
 - I. The outer zona glomerulosa - produces mineralocorticoids (regulate salt and water metabolism)

- II. The middle zona fasciculata - synthesizes glucocorticoids (involved with normal metabolism and resistance to stress)
- III. The inner zona reticularis - secretes adrenal androgens



❖ **Glucocorticoids**

» Eg Cortisol

■ **Effects of all glucocorticoids:**

➤ **Promote normal intermediary metabolism**

✓ favor gluconeogenesis

✓ stimulate protein catabolism and lipolysis

- Glucocorticoid insufficiency may result in hypoglycemia

➤ Increase resistance to stress

- ✓ raising plasma glucose level
 - » provide the body with the energy it requires to combat stress caused, for example, by trauma, fright, infection, bleeding, or debilitating disease
- ✓ can cause a modest rise in blood pressure by enhancing the vasoconstrictor action of adrenergic stimuli on small vessels

➤ **Alter blood cell levels in plasma**

- ✓ decrease in eosinophils, basophils, monocytes, and lymphocytes (by redistributing them from the circulation to lymphoid tissue)
 - compromises the body's ability to fight infections
 - important in the treatment of leukemia
- ✓ Increase the blood levels of hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes

➤ **Have anti-inflammatory action:**

- dramatically reduce the inflammatory response and suppress immunity
- This is the most important therapeutic property
- This effect is due to
 - ☛ lowering and inhibition of peripheral lymphocytes and macrophages
 - ☛ inhibition of phospholipase A2
 - ☛ Reduced cyclooxygenase-2 synthesis in inflammatory cells
 - ☛ interference in mast cell degranulation



Corticosteroids



Lipocortin



Phospholipase A2



Phospholipids



Arachidonic acids



lipoxygenase

Cyclooxygenase



Leukotriene

Prostaglandins,
Thromboxane
Prostacyclins

↓ PAF by lipocortin

➤ **Affect other components of the endocrine system**

- Feedback inhibition of corticotropin production
 - » Inhibit further synthesis of glucocorticoid as well as thyroid-stimulating hormone
- decreased production of growth hormone

➤ **Can have effects on other systems**

- Adequate cortisol levels are essential for normal glomerular filtration

- But the effects of corticosteroids on other systems are mostly associated with the adverse effects of the hormones
 - » High doses of glucocorticoids stimulate gastric acid and pepsin production and may exacerbate ulcers.
 - » Chronic glucocorticoid therapy can cause severe bone loss
 - » Myopathy leads to weakness

❖ Mineralocorticoids

- control the body's water volume and concentration of electrolytes, especially sodium and potassium
- Aldosterone
 - acts on kidney tubules and collecting ducts, causing a reabsorption of sodium, bicarbonate, and water.
 - decreases reabsorption of potassium, which, with H⁺, is then lost in the urine
- Elevated aldosterone levels may cause alkalosis, hypokalemia, and blood pressure

■ Pharmacokinetics

- administered orally, intravenously, intramuscularly, intra-articularly, topically, or as an aerosol for inhalation
- Highly protein bound

- IM
 - Cortisone, Triamcinolone
- IV, IM
 - Dexamethasone, Hydrocortisone, Methyl prednisolone, Prednisolone
- Aerosol
 - Beclomethasone, Fluticasone, triamcinolone
- Topical
 - Beclomethasone, dexamethasone, hydrocortisone, triamcinolone
- All corticosteroids can be administered orally

Examples of Corticosteroids available

- Hydrocortisone
- Prednisolone
- Dexamethasone
- Beclomethasone
- **Betamethasone**
- Budesonide
- Fluticasone
- **Prednisone**
- **Prednisolone**
- **Methylpredni- solone**
- **Triamcinolone**
- **Paramethasone**
- **Fluprednisolone**

Naturally occurring and synthetic steroids

Short-to medium acting	Antiinflammatory glucocort.	Salt retaining mineralocort	Equivalent oral dose
Hydrocortisone (cortisol)	1	1	20 _{oral} i.v. topical
Cortisone	0.8	0.8	25 _{oral}
Prednisone	4	0.3	5 _{oral,inj}
Prednisolone	5	0.3	5 _{oral,inj}
Intermediate-acting			
Triamcinolone	5	0	4 _{oral,inj,top}
Long-acting			
Betamethasone	25-40	0	0.6 _{oral,inj,top}
Dexamethasone	30	0	0.75 _{oral,inj,top}

- **Therapeutic uses of the adrenal corticosteroids**
- **Replacement therapy for primary adrenocortical insufficiency (Addison's disease)**
 - Hydrocortisone is given
 - Failure to do so results in death
 - two-thirds of the normal daily dose is given in the morning and one-third is given in the afternoon
- **Replacement therapy for secondary or tertiary adrenocortical insufficiency**
 - » Hydrocortisone is also used for these deficiencies

➤ **Diagnosis of Cushing's syndrome**

- Cushing's syndrome is caused by a hypersecretion of glucocorticoids (due to excessive release of ACTH by the anterior pituitary or an adrenal tumor)
- **Dexamethasone suppression test is used to diagnose the cause**
 - Dexamethasone is synthetic glucocorticoid
 - ☛ does not suppress glucocorticoid release from adrenal tumors
 - ☛ suppresses cortisol release in individuals with pituitary dependent Cushing's syndrome
 - ☛ NB: Chronic treatment with high doses of glucocorticoid is a frequent cause of iatrogenic Cushing's syndrome

➤ Replacement therapy for congenital adrenal hyperplasia

- » Due to an enzyme defect in the synthesis of one or more of the adrenal steroid hormones
- The choice of replacement hormone depends on the specific enzyme defect
 - » This replacement suppresses release of CRH and ACTH (so reduces adrenal androgen production)

➤ Relief of inflammatory symptoms

- Glucocorticoids dramatically reduce the manifestations of inflammations
 - » Eg: rheumatoid and osteoarthritic inflammations
 - » inflammatory conditions of the skin
- » Multiple action for anti-inflammatory effects
 - ✓ decreased production of prostaglandins and leukotrienes is believed to be central to the anti-inflammatory action
 - ✓ Also reduce the amount of histamine that is released from basophils and mast cells

➤ **Treatment of allergies**

- treatment of the symptoms of bronchial asthma, allergic rhinitis, and drug, serum, and transfusion allergic reactions
- Eg Beclomethasone dipropionate , triamcinolone

➤ **Acceleration of lung maturation**

- Respiratory distress syndrome is a problem in premature infants
 - » beclomethasone is administered intramuscularly to the mother 48 hours prior to birth, followed by a second dose 24 hours before delivery.

Indications (examples for moderate and high doses)

Allergic reactions	Drug reactions, bee stings, allergic rhinitis....
Collagen-vascular disorders	Rheumatoid arthritis, lupus erythematosus....
GIT diseases	Inflammatory bowel disease.....
Hematological disorders	Leukemia, acquired hemolytic anemia....
Organ transplants	Prevention and treatment of rejection (immunosuppression)
Severe infections	Sepsis...
Pulmonary diseases	Bronchial asthma, ARDS, IRDS (see below)....
Neurological disorders	Cerebral edema (dexamethasone)....

- **Adverse effects**

- Osteoporosis

- due to the ability of glucocorticoids to suppress intestinal Ca^{2+} absorption, inhibit bone formation, etc
 - Patients are advised to take calcium and vitamin D supplements.

- The classic Cushing-like syndrome redistribution of body fat, puffy face, increased body hair growth, acne, insomnia, and increased appetite are observed when excess corticosteroids are present
- Increased frequency of cataracts also occurs with long-term corticosteroid therapy.
- Hyperglycemia may develop and lead to diabetes mellitus
- Hypokalemia caused by corticosteroid therapy can be counteracted by potassium supplementation.

■ **Withdrawal**

- if the patient has experienced HPA suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal
- the dose must be tapered according to the individual₇₈

Inhibitors of adrenocorticoid biosynthesis

- inhibitors of the synthesis of adrenal steroids
 - » metyrapone, aminoglutethimide, ketoconazole, trilostane, spironolactone
- Mifepristone competes with glucocorticoids for the receptor
- **Aminoglutethimide:**
 - ☛ Inhibits the conversion of cholesterol to pregnenolone
 - ☛ synthesis of all hormonally active steroids is reduced
 - » Tamoxifen has largely replaced aminoglutethimide in the treatment of breast cancer
 - may also be useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids

■ **Spirolactone:**

- ☛ competes for the mineralocorticoid receptor
 - » Inhibits sodium reabsorption in the kidney
- ☛ also inhibits aldosterone and testosterone synthesis
- Effective against hyperaldosteronism
- Side effects are hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes

■ **Ketoconazole**

- ☛ is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis
- is used in the treatment of patients with Cushing's syndrome

Uterine Stimulants and Relaxants

- Drugs used to stimulate uterine contraction are known as oxytocics
- drugs that suppress uterine contraction are known as tocolytics

❖ Uterine Relaxants (Tocolytics)

- Suppress preterm labor

A. Magnesium sulfate (IV) — for Control of seizures and suppression of preterm labor; better for patients with B2 agonist contraindication such as hyperthyroidism or diabetes.

- It affects the action of calcium

B. Beta₂-Adrenergic Agonists

1. *Ritodrine*

- Relaxes uterine smooth muscle, so decreases frequency and intensity of contraction.

- **Therapeutic use**

- suppression of preterm labor for fetal development or for short-term while glucocorticoids promote maturation of fetal lungs

- begin with IV and then oral

- **Adverse effects** — includes maternal and fetal tachycardia, hyperglycemia, pulmonary edema

- Precautions and contraindications— eclampsia, severe preeclampsia, hemorrhage, maternal heart disease

2. Terbutaline — used “off-label” to suppress preterm labour.

- **Nifedipine** — Calcium channel blocker that has been used to suppress preterm labor.
- **Indomethacin** — is an inhibitor of prostaglandin synthesis. It is used as third-line drug for suppressing preterm labor.
- **Atosiban** (oxytocin antagonist) - delays preterm labour.
 - given IV
 - Adverse effects include symptoms of vasodilation, nausea, vomiting, and hyperglycaemia

❖ Uterine Stimulants (Oxytocics)

Three applications:

1. induction or augmentation of labor,
2. control of postpartum bleeding, and
3. induction of abortion
 - Three groups of uterine stimulants
 - A. oxytocin,
 - B. prostaglandins, and
 - C. ergot alkaloids

A. Oxytocin

- Oxytocin is endogenous hormone produced by the posterior pituitary gland
- **Physiologic and pharmacologic effects**
 - a. Uterine stimulation —Increased force, frequency, and duration of uterine contractions. Most pronounced effect in near term uterus.
 - b. Milk ejection —through contraction of the myo-epithelial cells around the alveoli of the mammary gland.
 - c. Water retention —Similar to ADH, so promotes renal retention
- Activation of the oxytocin receptor also stimulates prostaglandin synthesis

- **Pharmacokinetics**

- Given IV, IM, nasal
- Short half life (3-5 minutes)

- **Therapeutic uses**

- a) induction of labor (given through IV)
- b) augmentation of labor (IV)
- c) postpartum use to control bleeding(IM)
 - » postpartum and postabortal hemorrhage caused by uterine atony (marked relaxation of the uterine muscle).
- d) milk ejection (given as a nasal spray)
- e) abortion

- **Adverse effects** -- Although toxicities are uncommon when the drug is used properly; hypertensive crises, uterine rupture, water retention, and fetal death have been reported
 - When used as a nasal spray, adverse reactions are rare.
- **contraindications**—Improper use can be hazardous (uterine rupture), contraindicated in abnormal fetal presentation, fetal distress, and premature births.

B. Prostaglandins

- Carboprost, Misoprostol, Dinoprostone
- ***Therapeutic uses***
 - Aborting pregnancy
 - Control of postpartum hemorrhage
- ***Adverse effects***
 - a. GI disturbances—Extremely common
 - b. Cervical or uterine laceration
 - c. Other adverse effects—Include fever, headache, shivering/chills

C. Ergot alkaloids

- **ergometrine , ergonovine and Methylergonovine**
 - » both increase the strength, duration, and frequency of uterine contractions
 - » decrease the incidence of uterine bleeding

FAMILY PLANNING METHODS

I. Traditional

- Withdrawal
- Calendar
- Rhythm

II. Modern

- **Permanent**
 - **Female sterilization (tubectomy/tubal ligation)**
 - **Male sterilization (vasectomy)**
- **Nonpermanent**
 - **Condoms, pills, injectables, implants, mucus, IUD**

ORAL CONTRACEPTIVES

The main hormones used are synthetic analogues.

❑ Oestrogens:

- natural oestrogen is *oestradiol, estrone, estradiol*
- semisynthetic oestrogen is *ethinyloestradiol*
- *Synthetic : diethylstilbestrol*

❑ ESTRADIOL:

- Potent, produced in ovary,
- Oxidized into estrone by liver, estrone hydrated to estriol

□ ETHYLESTRADIOL:

– Highly potent, effective orally

Absorption & fate: absorbed from GI skin and rapidly metabolized in the liver

PHYSIOLOGIC ACTIONS OF ESTROGENS:

- ❖ **Ovary:** Indirect: by influencing secretion of gonadotrophin
- ❖ **Uterus:** Affects the proliferative phase of endometrium and increase the growth and sensitivity of myometrium for oxytocin
- ❖ **Cervix:** Cervical mucus will be thin and alkaline
- ❖ **Breast:** Growth of gland and duct

* **Anterior pituitary:** Inhibit the release of FSH and LH

* **Metabolic action**

- ✓ Retention of salt and water
- ✓ Increase level of HDL & TG
- ✓ Increases Ca^{2+} bone deposition
- ✓ It has a mild anabolic action

* **Blood coagulation:** Enhances level of factor II, VII, IX, X so increase the coagulability of blood and may predispose to **thromboembolic** condition

Therapeutic use of estrogens

contraceptive, functional uterine bleeding, dysmenorrhea, alleviation of menopausal disorder, osteoporosis, replacement therapy in ovarian failure, prevents atrophic vaginitis

Side effect:

- Thromboembolism, sodium and water retention, withdrawal bleeding, nausea, endometrial carcinoma

Contraindication:

- History of thromboembolism, in diagnosed uterine bleeding, endometrial carcinoma, liver disease

* **Progestogens:**

- The natural progestogen is *progesterone*
- The synthetic progestogen is ***norethisterone***

* Progesterone is less effective orally due to complete metabolism by liver so it is given through intramuscular route

* **Actions on genital organs:**

- Ovary: inhibition of ovulation
- Uterus: converts the endometrium for secretory phase and makes the myometrium less sensitive to oxytocin

* **Metabolic actions:**

- Thermogenic action
- Competes with aldosterone at renal tubule so inhibits sodium reabsorption

* **Synthetic/ semisynthetic progesterone:**

- Derivative of progesterone:
hydroxypregesterone
caproit/medroxyprogesterone
- Derivative of testosterone: dimethisterone
- Derivative of nortestosterone: norethisterone

Therapeutic uses:

➤ Hormonal contraception, functional uterine bleeding, dysmenorrhea, amenorrhea, endometrial carcinoma, premenstrual tension

- There are 3 types of oral contraceptive pills
 1. Combination preparations
 - oestrogens and progestogens in fixed ratio of doses
 - If you take the drugs, you will stop bleeding
 - You should stop taking them at the end of 21 days.
 2. Sequential preparations
 - Biphasic (2 different types of pills with varying concentrations of oestrogens and progestogens in 21 days)
 - Triphasic (3 different pills in 21 days)
 3. Progestogen only preparations (mini pill)
 - Used if the women cannot take oestrogens
 - Used in lactating mothers

* **Single entity preparations:**

– Oral progesterone:

✓ norethindrone(norgestril)

– Depot

✓ Im injection of long acting progestogen

E.g. medroxyprogesterone acetate
(depoprovera)

– Subcutaneous implant

–E.g. L-norgestril (norplant)

– **Mechanism of action:** progesterone makes cervical mucus thick, tough and hostile and also alter endometrial wall

- Post coital morning after pill
 - ✓ Oestrogen like diethyl stilbesterol

*** Beneficial effects of estrogen/progestrone oral contraceptive:**

- Reduced risk of endometrial carcinoma,
- Regular menses, no excessive blood loss
- Less premenstrual tension and dysmenorrhea
- Relief of endometriosis

- Oral contraceptive pills must not be taken in conjunction with some antibiotics (e.g. Rifampicin: inducer)
 - Oestrogens enter the enterohepatic circulation.
 - Normal flora of the gut separates the oestrogens from its conjugate, allowing it to be reabsorbed. If antibiotics are taken and disrupt the normal flora, the oestrogens cannot be “un-conjugated” and so are excreted.

- The morning after pill: oestrogen like diethyl stilbesterol
 - Needs to be taken within 72 hours of sex
 - combined oral contraceptives with 50µg estrogen
 - 2 pills and then another 2 after 12 hours

Ovulation inducing drug:

These are drugs used in the treatment of infertility due to ovulatory failure

Clomiphen is antiestrogenic drug which interferes with estrogen feedback inhibition at hypothalamus so enhance secretion of FSH and LH causing ovarian stimulation which finally leads to ovulation

- **Clomiphene citrate, 50 mg/day for five days**
- Ovulation should occur 5 to 10 days after final dose