Endocrine Pharmacology Summary

Hormone	Function	Regulation	Clinical Use
TSH	-Stimulates production of thyroid hormones	-Negative feedback inhibition by T3	-Used for diagnostic purposes to determine cause of hyperthyroidism (pituitary vs. thyroid gland failure) -Not used for treatment, deficiencies are treated by giving thyroxine itself
ACTH *(Acthar)*	-Regulates adrenal cortex and synthesis of adrenocorticosteroids (mainly glucocorticoids)	-Stimulated by stress (key regulator), CRH, ADH and hypoglycemia -Cortisol inhibits its release (negative feedback)	-Use is restricted for diagnosis; it's easier and less expensive to treat deficiency with glucocorticoid replacement
Somatostatin	-Inhibits secretion of: GH, TSH, Prolactin, ACTH, insulin, glucagon, pancreatic gastrin		-Not useful clinically
TRH (protirelin)	-Promotes secretion of TSH -Promotes release of Prolactin		-Used for tests to distinguish primary from secondary hypothyroidism
GH	-Stimulates lipolysis, elevates blood glucose -Enhances production of IGF-1		
Prolactin	-To develop lactation after birth -Inhibits release of GnRH (Increases during stress)	-Inhibited by dopamine -Release is stimulated by oxytocin -Synthesis is enhanced by Estradiol	-No therapeutic use, serum levels are measured to diagnose hyperprolactinemia
GnRH	-Stimulates secretion of LH & FSH (mainly LH)	-Feedback inhibition: testosterone & progesterone -Inhibited by: dopamine, endorphin & prolactin -Positive feedback: estradiol	
FSH	-Development of ovarian follicles (follicular phase of menstrual cycle) -Required for estrogen synthesis	-Inhibin controls its release	
Testosterone	-Negative feedback on GnRH production & downregulates GnRH receptors		
Progesterone	-Suppresses ovulation (Negative feedback on release of LH & FSH)		-Basis for oral contraceptives
Estradiol	-Enhances prolactin synthesis -Positive feedback on GnRH (triggers ovulation)		

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Oxytocin	-Stimulates myoepithelial contractions (in uterus during parturition & mammary gland during lactation) -Milk ejection from lactating mammary gland -Uterine contractions	-Suckling is major stimulus for release (milk ejection) by sensory receptors -Uterine contractions: reflexes in the cervical, vaginal and uterus stimulate its synthesis and release via neural input to hypothalamus	
PTH	-Maintenance of calcium, phosphate, magnesium homeostasis (bone, intestine, kidney) by: mobilization of calcium from bone, reabsorption of calcium from kidney and enhancing intestinal calcium absorption indirectly by activating release of vit D3	-Secretion stimulated by low concentration of free Ca+2 -Inhibited by Vitamin D3	
Calcitonin	-Maintenance of calcium, phosphate, magnesium homeostasis (bone, kidney) -**Antagonist of PTH** -Restore level of calcium to below a normal setpoint → which inhibits release of calcitonin	- Secretion stimulated by high concentration of free Ca+2	
Vitamin D_3	-Maintenance of calcium, phosphate, magnesium homeostasis (bone, intestine, kidney) by: Enhancing intestinal calcium absorption, mobilization of calcium from bone, reabsorption of calcium from kidney	-Synthesis of $1,25(OH)_2D_3$ is activated by PTH	
Thyroid Hromones	-Normalize growth and development, body temperature and energy levels -Enhances CNS excitability		
aldosterone	-the main electrolyte regulating steroid		

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Corticosteroids -Glucocorticoids -Mineralocorticoid -Sex steroids	1) Carbohydrate, Protein, and Fat Metabolism ▪ The glucocorticoids increase blood glucose and liver glycogen levels by stimulating gluconeogenesis. ▪ They, also inhibit protein synthesis 2) Electrolyte and Water Metabolism ▪ Mineralocorticoid can increase the rate of sodium reabsorption and potassium excretion several fold 3) Cardiovascular Function ▪ Glucocorticoids directly stimulate cardiac output and potentiate the responses of vascular smooth muscle to the pressor effects of catecholamines and other vasoconstrictor agents	-ACTH stimulates their release (primarily glucocorticoids)	- Glucocorticoids (e.g., prednisolone) are used to suppress inflammation, allergy, and immune responses. - Anti-inflammatory therapy is used in many illnesses (e.g., Rheumatoid arthritis, ulcerative colitis, BA, eye, and skin inflammations). - Glucocorticoids are used also in Tissue transplantation and lymphopoiesis (leukemias and lymphomas).

Drug	MOA	Uses	Side Effects	Notes
Parodel (bromocriptine)	Doapminergic agonist	Treatment of hyperprolactinemia (amenorrhea)		Hyperprolactinemia can be caused by overproduction of prolactin by a pituitary tumor which shuts off GnRH
Hydration + Saline + Diuretics	-Increases urinary excretion of calcium along with sodium and prevents its reabsorption by the kidney	Main treatment of hypercalcemia in acute sever forms		
Glucocostiroids		Treatment of hypercalcemia associated with hematological malignant neoplasms		
Mythramycin	-Inhibits bone resorption	Treatment of hypercalcemia caused by hematological and solid neoplasms		-Toxic antibiotic
Calcitonin	-Inhibits osteoclast activity and prevent bone resorption	-Treatment of hypercalcemia -Treatment of Paget's Disease		
Bisphosphonates	-Prevent bone resorption	-Treatment of hypercalcemia -Treatment of Paget's Disease	-In Paget's Disease, long term continuous use may be associated with induction of osteomalacia through direct impairment of new bone formation; therefore they are given in a cyclic pattern.	-Givens IV or Orally -In treating Paget's Disease, they are given in a cyclic pattern.
Oral Phosphate	-Antihypercalcemic agent	-Treatment of hypercalcemia -Commonly used as a temporary measure during diagnostic workup		

Drug	MOA	Uses	Side Effects	Notes
Estrogen	-Decreases bone resorption	-Treatment of hypercalcemia -Given to post-menopausal women with primary hyperparathyroidism		
Oral Calcium + Vitamin D (or a potent analogue)		-Main treatment of hypoparathyroidism		-Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level
Estrogen Replacement Therapy	-Increases bone density	-Prophylactic regimen of osteoporosis at the onset of menopause -Decreases risk of colon cancer -Decreased vaginal atrophy	-Slight increased risk of breast cancer, endometrial cancer, stroke and deep vein thrombosis (combination with a progestin negate such risk)	-Calcium supplementation and Vit D3 is also taken prophylactically
Calcitriol + Oral phosphate-binding agents + Ca^{+2} supplementation		-Treatment of renal osteodystrophy (Chronic renal failure leads to hyperphosphatemia + hypocalcemia)		-Calcitriol is the active form of vitamin D3 (1,25(OH)2D3) -Renal osteodystrophy: Chronic renal failure leads to hyperphosphatemia + hypocalcemia. Secondary cause of hyperparathyroidisim include hyperphosphatemia and decreased 1,25(OH)D2
Liothryonine Sodium (Cytomel): *Sodium salt of T3*		-Treatment of hypothyroidism -The use of T3 alone is recommended only in special situations as in the initial therapy of myxedema and myxedema coma and the short-term suppression of TSH in patients undergoing surgery for thyroid cancer.		-It is the sodium salt of the naturally occurring levorotatory isomer of T3. -Generally not used for maintenance thyroid hormone replacement therapy because of its short plasma half-life and duration of action.

Drug	MOA	Uses	Side Effects	Notes
Levothyroxine Sodium: ***Sodium salt of T4***		- It is the preparation of choice for maintenance of plasma T4 and T3 concentrations for thyroid hormone replacement therapy in hypothyroid patients.		-It is the sodium salt of the naturally occurring levorotatory isomer of T4.
Liotrix (Euthroid, Thyrolar): ***A mixture***	-The idea of combining T4 and T3 in replacement therapy so as to mimic the normal ratio secreted by the thyroid	-Treatment of hypothyroidism		-A 4:1 mixture of levothyroxine sodium and liothyronine sodium
Thionamides (Propylthiouracil, methylthiouracil)	-Inhibit production of thyroid hormones	-The management of hyperthyroidism and thyrotoxic crisis (thyroid storm) and in the preparation of patients for surgical subtotal thyroidectomy	-If given in excessive amounts over a long period: -Agranulocytosis severe and dangerous leukopenia (lowered white blood cell count) causing a neutropenia in the circulating blood -Rash, cholestatic jaundice, drug fever, psychosis	-They do not inhibit secretion of stored hormones → when they are used alone, their effects are not apparent until the preexisting store of hormones is depleted -Propylthiouracil and methylthiouracil (methimazole; Tapazole) are the most commonly used preparations in the United States
Iodides (NaI, KI)	-Inhibition of T3 & T4 release and synthesis -Decrease of size & vascularity of the hyperplastic gland	-Treatment of hyperthyroid: 1. Operation preparation 2. Thyroid crisis.	-Rash -Swollen salivary glands, mucous membrane ulcerations	
Radioactive iodine (^{131}I)		-Treatment of thyrotoxicosis	-Its therapeutic effect depends on emission of β rays with an effective half-life of 5 days & a penetration range of 0.4-2 mm → woman in pregnancy or lactation is forbidden!	-The only isotope for treatment of thyrotoxicosis.

Drug	MOA	Uses	Side Effects	Notes
Propranolol (β-blocker)		-βblockers are effective in treatment of thyrotoxicosis.		-Propranolol is the most widely studied and used.
Glucose insulin potassium (GIK) infusion		-improves mortality in patients with acute myocardial infarction		-widely applicable -low cost therapy
Insulin	1) Stimulates glucose uptake by tissues 2) Decrease hepatic glycogenolysis by inhibiting glycogen phosphorylase 3) Inhibit hepatic gluconeogenesis 4) Promote hepatic glucose storage into glycogen by stimulating glycogen synthetase 5) Inhibit lipolysis inhibiting hormone-sensitive lipase activity, thereby decreasing plasma free fatty acid and glycerol levels 6) promote the active transport of amino acids into cells for incorporation into protein	1- Diabetes mellitus ❖ The only effective drug for type 1 diabetes ❖ Also used in the following situations of type 2 diabetes: 1. Not effectively controlled by food limitation and oral antidiabetic drugs 2. Nonketotic hyperosmolar hyperglycemia coma 3. Accompanies serious infection 2- Hyperkalemia 3- component of GIK solution (for limiting myocardial infarction and arrhythmias).	• Insulin allergy: itching, redness, swelling, anaphylaxis shock • Insulin resistance (especially in high dose) • Hypoglycemia: nausea, hungry, tachycardia, sweating, and tremulousness. (First aids needed while convulsions and coma happen) • Lipodystrophy at injection sites: atrophy (we can change the place of injection) • Complications in the kidney for patients who use exogenous insulin for a long time.	-Chemistry: 51 AA arranged in two chains (A & B) linked by disulfide bridges. -Secretion: By β cells in pancreatic islet. -Degradation: Liver & kidney => Endogenous insulin: Liver (60 %) & kidney (35 %-40 %) =>Exogenous insulin: Liver (35 %-40 %) & kidney (60 %), -Sources of exogenous insulin: •Bovine & porcine insulin • Human insulin by replacement of porcine insulin 30-alanine in B chain by threonine. Recombinant human insulin by Escherichia coli -T1/2 in plasma: 3-5 min -Commercially available insulins differ in their onset of action, maximal activity, and duration of action (rapid onset of action→ short duration of action. -**intermediate acting insulin** is the most common type.

Drug	MOA	Uses	Side Effects	Notes
Sulfonylureas **-1st generation:** Tolbutamide, Chlorpropamide **and** Tolazamide **-2nd generation:** Glybenclamide, Glyburide, **Glipizide and Glymepride** **-3rd generation: Glyclazide**	**Rapid mechanism**: The **primary** mechanism of action of the sulfonylureas is direct stimulation of insulin release from the pancreatic B-cells. **Long term profit involved mechanism:** **1)** Inhibition of glucagon secretion by pancreas α cells **2)** Ameliorating insulin resistance **3)** Increase insulin receptors number & their affinity to insulin	1- **Type 2 diabetes mellitus** 2- **Diabetes insipidus**: *chlorpropamide* is used.	• Gastrointestinal disorders • Allergy • Hypoglycemia (Chlorpropamide is forbidden for old patients and those with functional disorder in liver or kidney. • Hepatic injury	-Once Sulfonylurea receptor in β-cell membrane is activated →ATP-sensitive K+-channel is inhibited →Cellular membrane is depolarized →Ca2+ entry via voltage-dependent Ca2+ channel →Insulin is released **Pharmacological effects** 1. Hypoglycemic effect 2. Antidiuretic effect: *chlorpropamide* & *glybenclamide* 3. Antiplatelet-aggregation effect: *glyclazide*.
Thiazolidinediones (Tzds) **-Rosiglitazone** **-Troglitazone** **-Pioglitazone** **-Ciglitazone**	They all act to **decrease** insulin resistance and **enhance** insulin action in target tissues, so they **increase** the sensitivity of insulin. Once Peroxisome proliferator-activated receptor-γ(PPAR-γ) is activated →Nuclear genes involved in glucose & lipid metabolism and adipocyte differentiation are activated	Insulin resistance & type 2 diabetes mellitus.	• Troglitazone occasionally induces hepatic injury	- Sometimes termed ***glitazones***. They are a novel class of drugs that were initially identified for their insulin-sensitizing properties. **Pharmacological effects** - Improving function of pancreas β cells - Ameliorating insulin resistance - Ameliorating fat metabolic disorder - Preventing and treating type 2 diabetes mellitus and their cardiovascular complications

Drug	MOA	Uses	Side Effects	Notes
Biguanides **- phenformin** **- metformin**	Hypoglycemic mechanism remains unclear	1) Used for obese diabetes and type 2 diabetes. 2) Metformin is also used to treat atherosclerosis for down-regulation of LDL& VLDL	• lactic acidosis is a major adverse reaction.	- insulin secretion and appetite are unchanged. - Used alone or co-administered with insulin or Sulfonylureas -Arteriosclerosis occurs when the blood vessels that carry oxygen and nutrients from your heart to the rest of body (arteries) become thick and stiff
α-glucosidase inhibitors **-acarbose** **-voglibose** **-miglitol**	inhibit digestion of starch & disaccharides via competitively inhibiting intestinal α-glucosidase (sucrase, maltase, glycoamylase, dextranase)	Used in type 2 diabetes	• flatulence • diarrhea • bellyache (because they inhibit the absorption process)	-Used alone or together with sulfonylureas -Patients with inflammatory bowel disease and kidney impaired are not treated with these drugs (forbidden)
Meglitinides **-Repaglinide**	increase insulin release by inhibiting ATP-sensitive K+-channel.	Used In type 2 diabetes.		-Carefully used for patients with kidney or liver impaired. -Used alone or together with biguanides . -Unlike sulfonylureas, they have no direct effect on insulin release
hydrocortisone (cortisol)		1) Orally for replacement therapy 2) IV for shock and asthma 3) topically for eczema (ointment) 4) enemas for treating ulcerative colitis.		-the main carbohydrate regulating steroid
Prednisolone		Given orally in inflammation and allergic diseases		- the most widely used drug
Betamethasone & dexamethasone		Very useful for high-dose therapies (e.g., cerebral edemas)		- very potent, w/o salt-retaining properties

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Beclometasone, diproprionate & budesonide		1) Topically: severe eczema for local anti-inflammatory effects 2) used in asthma (aerosol)		- pass membranes poorly; more active when applied topically than orally
Triamcinolone		1) used for severe asthma 2) used for local joint inflammation (intra-articular inj.)		
Steroid Hormones	1) Steroids transported by transcortin enter the target cell by diffusion and then form a complex with its cytosolic receptor protein 2) Glucocorticoids bind to cytoplasmic glucocorticoid receptors. As a result, the heat shock protein dissociates. 3) receptor– steroid complex is rapidly translocated to the nucleus. 4) Within the nucleus, the glucocorticoid receptor induces gene transcription by binding to glucocorticoid response elements. 5) Translation takes place and a protein (for example lipocortin) Is formed 6) Lipocortin suppresses the activation of phospholipase A2. It also inhibits PG endoperoxide H synthase.	**1- Replacement Therapy in Adrenal insufficiency** ✓ in treating primary adrenal insufficiency, one should administer sufficient cortisol to diminish hyperpigmentation and abolish postural hypotension 2- **Inflammatory States** ✓ Rheumatoid arthritis	1) Euphoria 2) Buffalo Hump 3) Moon face with red cheeks 4) Hypertension 5) Thinning of skin 6) Thin arms and legs (muscle wasting) 7) Poor wound healing 8) Easy bruising 9) Increased abdominal fat 10) Cataracts 11) Benign intracranial hypertension. 12) Osteoporosis 13) Obesity 14) Negative nitrogen balance 15) Increased appetite 16) Increased susceptibility to infections 17) Tendency to hyperglycemia	-Adrenal insufficiency may result from: a) hypofunction of the adrenal cortex (primary adrenal insufficiency, Addison's disease, ACTH levels are **high** -due to feedback- so we might have hyperpigmentation) b) malfunctioning of the hypothalamic–pituitary system (secondary adrenal insufficiency, ACTH levels are **low**) - Rheumatoid arthritis is the original condition for which anti-inflammatory steroids were used. - intraarticular glucocorticoid injections have proven to be efficacious, particularly in children

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