Drugs Acting on The Endocrine System
The Endocrine system

- Maintenance of internal homeostasis through the secretion of hormones
- Endocrine glands make and release these endogenous substances to regulate
  - Reproduction
  - Growth and development
  - Energy metabolism
  - Fluid and electrolyte balance
  - Response to stress and injury
Hormones

- Can be classified as drugs
- Exogenous sources can include animals and synthetic or semi-synthetic compounds
- Often used for replacement therapy; also used for therapeutic and diagnostic purposes
  - Replacement therapy during deficiency
  - To accentuate endogenous counter agents
  - Treatment of endocrine hyperactivity
  - Regulate normal function
Hormones

- Therapeutically useful hormones and related drugs include
  - Pituitary hormones
  - Thyroid hormones and thyroid inhibitors
  - Antidiabetic agents
  - Gonadal hormones
  - Adrenocorticosteroids
Pituitary Hormones

- Pituitary is subdivided into anterior, intermediate, and posterior lobes.
- Hormones divided based on site of secretion.
Pituitary Hormones

- Anterior pituitary
  - Protein molecules are used therapeutically
    - ACTH (adrenocorticotrophic hormone)/ Corticotropin
      - ↑ synthesis of adrenal steroid
      - Used to diagnose and differentiate primary and secondary adrenal insufficiency
    - TSH (thyroid-stimulating hormone/ Thyrotropin
      - ↑ synthesis of thyroid hormones
    - TRH (thyrotropin-releasing hormone)
    - GH (growth hormone)
      - ↑ growth and development of tissue
      - Stimulates protein, carbohydrate, and lipid metabolism
      - Somatrem, somatropin
Pituitary Hormones

Anterior pituitary (continued)

- Gonadotropins not available for therapeutic use
  - FSH (follicle-stimulating hormone)
    - Female: ↑ follicular development and synthesis of estrogen
    - Male: enhancement of spermatogenesis
  - LH (luteinizing hormone)
    - hCG (human chorionic hormone)
    - Female: ↑ ovulation; ↑ synthesis of estrogen and progesterone
    - Male: ↑ spermatogenesis, testosterone releasing
  - Menotropins (hMG/human menopausal gonadotropin)
    - High in FSH and LH-like activity; obtained from urine of postmenopausal women
    - Produce ovarian follicular growth and induce ovulation
    - Used to induce ovulation and pregnancy; induction of spermatogenesis in men
  - PR/LTH (prolactin/luteotropic hormone)
    - Initiation of lactation
Anterior pituitary hormones
Pituitary Hormones

Intermediate pituitary

- MSH (melanocyte-stimulating hormone)
  - No significant amounts produced in humans
  - No physiologic or pharmacologic significance

Posterior pituitary

- ADH (antidiuretic hormone)
  - Effects exerted on kidney; promotes reabsorption of water
  - Used to treat neurogenic diabetes insipidus
  - Vasopressin and desmopressin (DDVAP)

- Oxytocin
  - Stimulation of uterine contractions and lactation
  - Used to promote delivery by initiation and improving uterine contraction; control of postpartum bleeding or hemorrhage
Pituitary Hormones

Adverse effects

- Corticotropin
  - ADRS are rare; hypersensitivity
- Growth hormone
  - Development of antibodies to GH-typically do not interfere with treatment
- Menotropins (hMG)
  - Hypersensitivity, arterial thromboembolism, febrile reactions, ovarian enlargement hyperstimulation syndrome, hemoperitoneum
  - Gynecomastia in men
Thyroid Hormones

- Two hormones are thyroxine ($T_4$, levothyroxine) and triiodothyronine ($T_3$, liothyronine)
- Liotrix is a mixture of $T_4$ and $T_3$ (4:1)
- Iodine (Lugol’s solution)
- Antithyroid agents
  - Propylthiouracil (PTU), Methimazole, Sodium Iodide I 131
- $T_4$ is less potent than $T_3$ but has longer duration of action (6-7 days vs. 1-2 days)
Feedback control of thyroid function
Thyroid Hormones

Indications include

- Hypothyroidism
- Myxedema coma
- Cretinism
- Simple goiter
- Endemic goiter
- Thyrotopin-dependent carcinoma
Grave’s disease

- Hyperthyroidism caused by circulating antibodies to the TSH receptor.
- Associated with diffuse goiter.
- Autoantibodies bind to TSH receptor and mimic the action of TSH itself leads to persistent stimulation of thyroid and elevated levels of thyroid hormones.
Thyroid Hormones

Functions include

- Metabolism of proteins, fat, and carbohydrates
- Maintenance and regulation of body heat
- Growth and development of normal bone
- Positive inotropic and chronotropic effects on myocardium
- CNS development
Thyroid Hormones

- MOA – not well understood
  - Control of DNA transcription and protein synthesis
  - Principle effect is increase of metabolic rate of body tissues
    - Increases in oxygen consumption, respiratory rate, body temp, cardiac output, heart rate, blood volume, enzyme system activity, fat, protein, and carbohydrate metabolism, growth and maturation
  - Administration increases basal metabolic rate
Thyroid Hormones

- Use contraindicated in acute MI
- Can exacerbate diabetes mellitus, diabetes insipidus, and adrenal insufficiency
- Adverse reactions
  - Overdose: palpitations, tachycardia, arrhythmias, angina, cardiac arrest, tremors, headache, diarrhea, vomiting, nervousness, insomnia, weight loss, menstrual irregularities, sweating, heat intolerance, fever
Thyroid Hormones

Drug Interactions
- Cholestyramine
- Colestipol
- Estrogens
- Anticoagulants
- Beta blockers
- Digoxin
- Theophylline
Thyroid Hormones

- Should not change from one brand to another without consulting physician or pharmacists
- Do not discontinue
- Taking levothyroxine on empty stomach will increase absorption
Thyroid Hormones

Iodine

- Lugol’s solution
- Adequate iodine intake required for normal thyroid function; large doses can inhibit $T_4$ and $T_3$ synthesis

Indications

- Adjunct therapy with anti thyroid drugs in hyperthyroid patients
Thyroid Hormones

Iodine (continued)

- Adverse effects
  - Skin rash, swelling of salivary glands
  - Iodism – metallic taste, burning mouth and throat, sore teeth and gums, head cold symptoms, upset stomach and diarrhea
  - Allergic reaction – fever and joint pains, swelling of parts of face and body, severe SOB
Gonadal Hormones

- Steroids that influence sexual and reproductive functions
- Release is controlled by hormones from hypothalamus and anterior pituitary
- Estrogen – produced in ovaries
  - Natural, Semi-synthetic, Nonsteroidal synthetic, Estrogen antagonists
- Progestin – produced in ovaries
  - Natural, Synthetic
- Androgens and anabolic steroids – produced in testes
Gonadal Hormones

Estrogen

- Primary estrogenic hormone is estradiol (Estrace)
- Antagonists or antiestrogens (e.g. Clomiphene and tamoxifen) are structurally related to estradiol but have different binding sites and functions
- Some estrogen responsive tissues include the vagina, uterus, mammary glands, anterior pituitary, and hypothalamus
Gonadal Hormones

Estrogens

- Indications
  - Oral contraception
  - Menopausal symptoms (vasomotor disorder, urogenital atrophy, psychological disorder)
  - Acne
  - Osteoporosis
  - Prostate cancer

- Antiestrogens used to treat estrogen dependent breast cancer (tamoxifen) or in induction of ovulation (clomiphene)

- SERMS (selective estrogen receptor modulators) for treatment and prevention of osteoporosis, e.g. raloxifene (Evista)
Gonadal Hormones

Adverse effects

- GI effects (GI distress, nausea, vomiting, anorexia, diarrhea)
- CV effects (hypertension, increased risk of thromboembolic diseases, stroke, MI)
- Fluid and electrolyte disturbances (increased fluid retention, increased TG)
- Migraines, nausea, vomiting, breakthrough bleeding,
Gonadal Hormones

• Estrogens
  • Drug interactions
    • Oral anticoagulants
    • Tricyclic antidepressants
    • P450 inducers – barbiturates, rifampin
    • Corticosteroids
    • Hydantoins
Gonadal Hormones

Progestins
- Natural – progesterone
- Synthetic - medroxyprogesterone and megestrol

Indications
- Oral contraception (alone or in combo with estrogens)
- Menstrual disorder (dysfunctional uterine bleeding, dysmenorrhea)
- Endometriosis

Adverse effects
- Gynecological (irregular menses, bleeding, amenorrhea)
- Weight gain and edema
- Exacerbation of breast carcinoma
- Insomnia, rash, breast changes, edema
Gonadal Hormones

● Androgens and anabolic steroids
  ● Primary natural androgen is testosterone
    ● Used for androgenic and anabolic effects
    ● Anabolic steroids only differ slightly in structure from testosterone
      ● e.g. oxandrolone
  ● Indications
    ● Androgen-replacement therapy
    ● Breast cancer and endometriosis
    ● Female : hypopituitarism, in combo with estrogen therapy; metastatic cancer
    ● Anabolic therapy (in those with negative nitrogen balance)
    ● Anemia
Gonadal Hormones

Androgens and anabolic steroids

- Adverse effects
  - Fluid retention
  - Increase in LDL and decrease in HDL cholesterol
  - Psychological changes
  - Liver disorders
  - Development of masculine features in females
  - Decreased fertility in males
  - Amenorrhea in females
Prolactin

- Stimulates breast development and lactogenesis
- May be involved in development of Leydig cells in pre-pubertal males
- Immunomodulatory effects—stimulates T cell functions
  - Prolactin receptors in thymus
Oxytocin: uterine contractions

- Reflexes originating in the cervical, vaginal and uterus stimulate oxytocin synthesis and release via neural input to hypothalamus
- Increases in plasma at time of ovulation, parturition, and coitus
- Estrogen increases synthesis and lowers threshold for release
Adrenocorticosteroids

- ACTH (adrenocorticotropic hormone)
  - Corticotropin and Cosyntropin
  - Indications
    - Diagnostic testing of adrenocortical function
    - Thyroiditis
    - Hypercalcemia associated with cancer
    - Acute exacerbations of multiple sclerosis
    - Tuberculous meningitis
    - Same manner as glucocorticoids in many conditions
Adrenocorticosteroids

- ACTH (adrenocorticotropic hormone)
  - MOA – is secreted from anterior pituitary and stimulates release of adrenocortical hormones by adrenal cortex
  - Cosyntropin is a synthetic derivative which exhibits full corticosteroid activity
    - Less allergenic
    - Only used diagnostically
Adrenocorticosteroids

- ACTH (adrenocorticotropic hormone)
  - Adverse effects
    - Infections – pneumonia, abscess and septic infection, GI and GU infections
    - CV – HTN, CHF, anginitis
    - Derm – impaired wound healing, acne, petechiae and ecchymoses
    - CNS – convulsions, vertigo, headache, increased intracranial pressure with papilledema
    - Electrolyte – sodium and fluid retention, loss of potassium and calcium
Adrenocorticosteroids

ACTH (adrenocorticotropic hormone)

- Adverse effects
  - Endocrine – menstrual irregularities, Cushingoid state, decreased carbohydrate tolerance and latent DM, hirsutism, suppresses growth in children
  - GI – pancreatitis, peptic ulceration, ulcerative esophagitis
  - Musculoskeletal – muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures
  - Cataracts, glaucoma, hypersensitivity (dizziness, nausea, vomiting, shock, skin reactions)
“Buffalo Hump”

“Moon Face”
Antidiabetic Agents/Pancreatic Hormones

- Pancreas secretes two hormones - insulin and glucagon (also somatostatin & digestive enzymes)
- Needed for regulation of blood glucose; release is in turn stimulated by glucose concentrations in blood vessels
- Glucagon is secreted by α-cells
  - Stimulates release of glucose from storage sites in liver
- Insulin is secreted by β-cells
  - Removes glucose from blood and facilitates its storage in liver and muscle; normalizes glucose levels
Antidiabetic Agents/Pancreatic Hormones

Glucagon

- Indications:
  - Antidote for hypoglycemia

- Adverse reactions
  - Hypotension, urticaria, nausea, vomiting, respiratory distress

- Drug interactions
  - Anticoagulants- may increase possibility of bleeding

- Typically advised for DM patients to carry preparation in case of needed administration for insulin shock
Antidiabetic Agents/Pancreatic Hormones

- **Insulin**
  - Indications for insulin preparations
    - Treatment of diabetes mellitus not controlled by diet alone
    - Duration of actions varies based on preparations (i.e. Regular, Semilente, NPH, Ultralente)
  - Adverse effects
    - Hypoglycemia: sweating, tachycardia, hunger; convulsions in presence of insulin shock
    - Hypersensitivity
    - Local irritation at injections site
Regulation of Insulin Secretion from the Pancreas

- Insulin
- Glucose
- Glucose
- GLUT-2
- ATP
- K^+
- Ca^{2+}
- Glucokinase
- Glucose-6-Phosphate
- Depolarization
Normal Insulin Function: Fuel Storage

- Glucose Storage
- Gluconeogenesis
- Glucose and FFA Uptake
- Glucose Uptake
- Gluconeogenic amino acid release to liver

Pancreas

Muscle
Diabetes Mellitus

- Compare Type I and Type II Diabetes
- use insulin preparations and hypoglycemic drugs
- The three main classes of hypoglycemic agents
  1. $\alpha$-glucosidase inhibitors
  2. sulfonylureas and meglitinides
  3. Insulin sensitizers (Metformin)
  4. Thiazolidinediones
Chronic Complications of Diabetes

- **Retinopathy**: Most common cause of blindness in people of working age.

- **Nephropathy**: 16% of all new patients needing renal replacement therapy.

- **Erectile Dysfunction**: May affect up to 50% of men with long-standing diabetes.

- **Coronary and cerebrovascular Disease**: 2–4 fold increased risk of coronary heart disease and stroke; 75% have hypertension.

- **Foot Problems**: 15% of people with diabetes develop foot ulcers; 5–15% of people with diabetic foot ulcers need amputations.
Insulin Products

- Purified Animal Insulins (porcine, bovine) purified by gel filtration, single peak purity, few contaminants

- Recombinant human insulins (Humulin) Extremely low-risk of insulin allergy

- “Designer Insulins” – biochemical modifications of human insulins altering their absorption profile, duration of action
Insulin

- Ultra-short acting
  - Lispro (Humalog)
- Short-acting
  - Regular (Humulin)
  - Semilente
- Intermed-acting
  - Lente
  - NPH
  - Mixture
- Long-acting
  - Ultralente
  - Glargine
Insulin Resistance: Causes and Associated Conditions

- Obesity and inactivity
- Genetics
- Type 2 diabetes
- Hypertension
- Dyslipidemia
- Aging
- Medications
- Rare disorders
- Atherosclerosis
- Insulin Resistance
Sites of Action of Agents Used in the Treatment of Type II Diabetes

Plasma Glucose

Liver

Gut

Muscle

Pancreas

Fat

Food Intake

Glucose Absorption

Glucose uptake & utilization

Thiazolidinediones

α-glucosidase inhibitors
Acarbose, miglitol

Metformin

Gluconeogenesis & glycogenolysis

Liver

Sulfonylureas

Inulin

Insulin

Gluconeogenesis & glycogenolysis

Food Intake
Sulfonylureas

1\textsuperscript{st} Gen
- Acetohexamide
- Chlorpropamide
- Tolazamide
- Tolbutamide

2\textsuperscript{nd}/3\textsuperscript{rd} Gen
- Glipizide (GLUCOTROL)
- Glyburide (DIABETA/MICRONASE)
- Glimepiride (AMARYL)
Sulfonylureas: Mechanism of Action

1. Intestine: glucose absorption
2. Muscle and adipose tissue: glucose uptake
3. Pancreas: insulin secretion
   - Sulfonylureas
   - ↑ insulin secretion
4. Liver: hepatic glucose output

Blood glucose → Insulin resistance

Lebovitz HE. In Joslin’s Diabetes Mellitus. 1994:508-529.
Sulfonylureas: Mechanism of Action

Pancreatic β cell

Insulin granules

GLUT2

Na⁺

K⁺

Ca²⁺

Voltage-gated Ca²⁺ channel

Sulfonylureas

Vm

- 

Sulfonylureas: Mechanism of Action

Pancreatic β cell

Insulin granules
**Sulfonylureas**

- MOA = bind to ATP-sensitive K-channels on pancreatic β-islet cells → release insulin
- **Frequent episodes of** hypoglycemia
**DRUG-DRUG INTERACTIONS**

- ACE inhibitors $\uparrow$ efficacy
- Androgens $\downarrow$ blood glucose in diabetics but not non-diabetics
- Antacids $\uparrow$ absorbance
- Estrogens, progestins, or oral contraceptives: $\downarrow$ Decrease the hypoglycemic efficacy by impairing glucose tolerance
- Salicylates, by inhibiting prostaglandin synthesis, can indirectly increase insulin secretion.
- Thiazide diuretics, carbonic anhydrase inhibitors and corticosteroids, may $\downarrow$ the hypoglycemic effects of anti-diabetic agents by producing an $\uparrow$ in blood glucose levels.
Insulin Secretagogue: Meglitinides

- Chemically Unrelated to Sulfonylureas but same mechanism of action
- Rapid absorption with half-life of 1 hr.
  - Can be taken right before meal
  - Less likely to cause hypoglycemia
- Metabolized by liver (contraindicated in patients with hepatic insufficiency
- Repaglinide and Nateglinide (Starlix)
Biguanides

- (Phenformin)
- Metformin (GLUCOPHAGE)

- **MOA=**
  - Suppresses hepatic glucose output by inhibiting gluconeogenesis
  - **Stimulates insulin-mediated** glucose uptake by muscle & other tissues

- **Lactic acidosis:** fatal in 50% of cases
  - Renal insufficiency
  - Iodinated contrast media
2nd Generation Biguanide

Metformin: Mechanism of Action

1. Intestine: glucose absorption
2. Muscle and adipose tissue: glucose uptake
   Metformin \( \uparrow \) glucose utilization
3. Pancreas: insulin secretion
4. Liver: hepatic glucose output
   Metformin \( \downarrow \) HGO

Insulin resistance
Blood glucose

METFORMIN

• Major mechanism of action: ↑AMP-dependent kinase.
  
  - Inhibits conversion of acetyl CoA to malonyl CoA, by acetyl-CoA carboxylase, the rate-limiting step in lipogenesis. Net result is a faster rate of fatty Acetyl-CoA influx into the mitochondria where it undergoes oxidation to ketone bodies
  
  - Increases expression or activity of glycolytic enzymes and GLUT-4, decreases activity of gluconeogenic enzymes
  
  - Net: ↓hepatic glucose Production and ↑Glucose uptake in muscle and adipose.

• Can reduce plasma glucose levels by 25% and decrease hemoglobin A$_{1c}$ by 1-2%. Also Lowers plasma triglyceride levels

• Does not lead to hypoglycemia when used alone I.e. is anti-hyperglycemic

• Adherence to prescribing guidelines is crucial to minimize risk of metabolic acidosis. (reason why phenformin taken off the market)
**METFORMIN**

**CONTRAINDICATIONS**

Parenteral radiographic contrast administration: may cause acute renal failure and lactic acidosis in patients on metformin. Must withhold metformin just prior to and for 48 hours after the completion of the procedure.

Metabolic acidosis, lactic acidosis, and diabetic ketoacidosis.

Metformin is substantially eliminated by the kidney and is contraindicated for use in patients with renal failure or renal impairment (CrCl < 60 ml/min or serum creatinine above normal value for gender and age).

**DRUG-DRUG Interactions:** Similar to those for sulfonylureas.
Thiazolidinediones: “glitazones”

- Troglitazone
- Rosiglitazone (AVANDIA)
- Pioglitazone (ACTOS)

**MOA**

- Reduce hepatic output of glucose by inhibiting gluconeogenesis
- Increase peripheral uptake
  - Hepatic toxicity
α-Glucosidase Inhibitors

- Acarbose, Miglitol, Voglibose
- MOA: inhibit brush border enzyme α-glucosidase → prevent metabolism of polysaccharides into smaller units for absorption
- Flatulence, bloating, malabsorption
- Hepatic toxicity (acarbose)
NEW CLASSES OF HYPOGLYCEMICS

**Incretin**: Glucagon-like peptide (GLP-1 released from the gut to augment glucose-dependent insulin secretion.

Incretin is rapidly broken down by dipeptidyl peptidase IV enzyme (DPP-IV)

**Byetta**: Incretin Mimetic

**Januvia** (sitagliptin): DPP-IV Inhibitor

**Amylin**: 37-aa peptide produced by beta cells and cosecreted with insulin. Inhibits glucagon secretion, delay gastric emptying, and suppress appetite.

**Pramlintide (SYMLIN)**: Modified amylin peptide with decreased tendency to self-aggregate into amyloid plaques.