Pharmacology Review:
Endocrinology & Vitamins

Presented by:
A Nelson Avery, MD

Board Certified in Toxicology, Preventive Medicine and Internal Medicine

Clinical Professor and Director
Preventive Medicine Residency Program
navery@medicine.tamhsc.edu
Endocrine Agents
Insulin

- Beta cells $\rightarrow$ proinsulin $\rightarrow$ hydrolyzed into C-peptide (which has no function) and insulin $\rightarrow$ glucose

- Mechanism to release insulin:
  - In response to glucose and other sugars, certain amino acids (leucine, arginine) & vagus activity $\rightarrow$
  - $\uparrow$ Intracellular ATP levels $\rightarrow$ close ATP-dependent K$^+$ channels $\rightarrow$ $\downarrow$ outward K$^+$ efflux $\rightarrow$
  - Depolarization of $\beta$ cell and open voltage gated Ca$^{++}$ channels $\rightarrow$ influx of Ca$^{++}$ $\rightarrow$ triggers release of insulin
Insulin

- Insulin receptors function as transmembrane tyrosine kinases
- Activates cGMP
- Promotes glucose utilization in skeletal muscle and adipose and gluconeogenesis
- Promotes glycogen storage (liver and muscle)
- Fat synthesis (triglycerides) in liver and fat cells; lipolysis
- Amino acid uptake and protein synthesis
- Toxicity: hypoglycemia, lipoatrophy, insulin resistance
### Insulin: Types

<table>
<thead>
<tr>
<th>preparation</th>
<th>onset</th>
<th>duration</th>
<th>peak</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>0-15 mins</td>
<td>&lt;5 hrs</td>
<td>30-90 mins</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin</td>
<td>30-45 mins</td>
<td>5-7 hrs</td>
<td>2-4 hrs</td>
</tr>
<tr>
<td><strong>Intermediate:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lente or NPH</td>
<td>1-4 hrs</td>
<td>18-24 hrs</td>
<td>6-14 hrs</td>
</tr>
<tr>
<td><strong>Long:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td>4-6 hrs</td>
<td>24+ hrs</td>
<td>18-26 hrs</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oral Hypoglycemics: Sulfonylureas

- 1st generation: chlorpropamide, tolbutamide, tolaazamide, acetohexamide
- 2nd generation: glypizide, glyburide, glimepiride

- Mechanism: stimulate release of endogenous insulin (requires residual islet function; close (depolarize) K⁺ channels in beta cell membrane → open Ca²⁺ channel → influx of Ca²⁺ → insulin release)

- Side effects: hypoglycemia, leukocytosis, SIADH, disulfiram-type reaction with alcohol
Oral Hypoglycemics: Biguanides

Includes: **metformin**

- **Mechanism:** ↑ peripheral utilization, ↓ gluconeogenesis
- **Toxicity:** **lactic acidosis**
Oral Hypoglycemics: Glitazones

Includes: pioglitazone, rosiglitazone

- Mechanism: stimulate peroxisome proliferator-activated receptors (PPARs)
  - ↓ insulin resistance, ↑ glucose uptake,
  - ↓ gluconeogenesis

- Toxicity: weight gain, anemia, ↑ LFTs;
  - ↑ risk of cardiovascular events (MI, CHF) with rosiglitazone
Oral Hypoglycemics: Dipeptidyl-Peptidase-4 Inhibitor

Includes: *sitagliptin*, *saxagliptin*, *linagliptin*, *alogliptin*

Mechanism:

- DPP-4 is enzyme responsible for inactivation and degradation of the incretin hormones *GLP-1* and *GIP* (glucose-dependent insulinotropic polypeptide)
- Blockage of DPP-4 $\rightarrow$ allows GLP-1 and GIP to potentiate insulin synthesis and release and to decrease glucagon production
Oral Hypoglycemics: Sodium-glucose Co-transporter 2

Includes: **canagliflozin, dapagliflozin**

Mechanism:

- **SGLT2** is a membrane protein expressed mainly in kidney—involved in glucose reabsorption

- Blockage of SGLT2 $\rightarrow$ decreased glucose reabsorption, increased glucose excretion, lower blood glucose levels
Other Oral Hypoglycemic Agents

- **Meglitinides**: repaglinide, nateglinide
  - Mechanism: same as sulfonylureas
  - Rapid onset and return to baseline—have to take with each meal

- **α-glucosidase inhibitors**: acarbose, miglitol
  - Mechanism: inhibit intestinal villi α-glucosidases
  - Toxicity: GI symptoms
Other Oral Hypoglycemic Agents

- **GLP-1 like agent:** exenatide, liraglutide, albiglutide, dulaglutide
  - Mechanism: amino acid sequence similar to glucagon-like peptide-1; incretin mimetic; stimulates insulin secretion

- **Amylinomimetic agent:** pramlintide
  - Mechanism: suppresses postprandial glucagon and hepatic glucose output
Glucagon

- Produced by pancreatic A cells
- Mechanism: activation of glucagon receptors $\rightarrow$ cAMP with cardiac stimulation and relaxation of smooth muscle; hepatic glycogenolysis and gluconeogenesis
- Used for treatment of hypoglycemia, reversal of beta-blocker overdose, relaxation of bowel for x-ray or passage of retained object in esophagus
<table>
<thead>
<tr>
<th><strong>Hypothalamic Hormones</strong> (+ stimulate / - inhibit)</th>
<th><strong>Anterior Pituitary Hormones</strong></th>
<th><strong>Feedback</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone RH (+) somatostatin (−)</td>
<td>Growth hormone (GH) (somatotropin)</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Dopamine (−)</td>
<td>Prolactin</td>
<td></td>
</tr>
<tr>
<td>Corticotropin releasing hormone (+)</td>
<td>Adrenocorticotropic hormone (ACTH, corticotropin)</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Thyrotropin releasing hormone (+)</td>
<td>Thyroid stimulating hormone (TSH, thyrotropin)</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Gonadotropin releasing hormone (GnRH) (+)</td>
<td>Leuteinizing hormone (LH ♀) or Interstitial cell stimulating hormone (ICSH ♂)</td>
<td>Estradiol (in ♀)</td>
</tr>
<tr>
<td></td>
<td>Follicular stimulating hormone (FSH ♀ or ♂)</td>
<td></td>
</tr>
</tbody>
</table>
Hypothalamic: Growth Hormone

- **Growth hormone-releasing hormone:**
  - sermorelin (*all releasing hormones end in –relin*)
  - Used to evaluate GH responsiveness

- **GH-inhibiting hormone (= somatostatin):**
  - octreotide
  - Inhibits release of pituitary and GI hormones
  - Used to treat hormone-secreting tumors, persistent hypoglycemia from sulfonyl-urea overdose
Hypothalamic: TRH, CRH, GnRH

- **Thyrotropin-releasing hormone**: protirelin
  - Stimulates synthesis and release of thyrotropin and prolactin
  - Used to assess thyroid function

- **Corticotropin-releasing hormone**: corticorelin
  - Stimulates release of corticotropin (ACTH)
  - Used to evaluate pituitary function

- **Gonadotropin-releasing hormone**: see slide 25
Ant. Pituitary Hormones: GH, ACTH

Most of the anterior pituitary hormones end in –tropin

❖ Growth hormone: somatropin, somatrem, recombinant human growth hormone (rhGH)
  ► Adverse effect: development of glucose intolerance

❖ ACTH: corticotropin, ACTH, cosyntropin
  ► Stimulates release of adrenal hormones
  ► Used to evaluate adrenal function
  ► Adverse effect: Cushing’s syndrome
Ant. Pituitary: Prolactin Inhibitors

Include: **bromo(ergo)criptine, pergolide, cabergoline**

- These are **dopamine agonists** → inhibit lactation; treat amenorrhea and galactorrhea associated with pituitary adenoma
- Can also use bromocriptine and pergolide for Parkinson’s disease
Posterior Pituitary: Vasopressin

Also called anti-diuretic hormone (ADH)
► Used in ACLS protocol for v-fib that does not respond to defibrillation
► Potent vasoconstrictor; used to control bleeding from esophageal varices

Vasopressin analog: desmopressin
► Antidiuretic effect (in kidney activates cAMP)
► Used for:
  – Central diabetes insipidus
  – Raises clotting factor VIII (Hemophilia A) and von Willebrand’s factor
  – Treat childhood bedwetting (enuresis) (DDAVP)
  – Ventricular fibrillation or pulseless V-tach
  – Esophageal variceal bleeding
Thyroid Hormones

Include: **thyroxine (T4), triiodothyronine (T3)**

- Signs of overdose or thyroid storm: ↓ weight, ↑ HR, palpitations, ↑ BP, diaphoresis, angina, CHF, atrial fibrillation, anxiety, HA, confusion, heat intolerant, warm, flushed, sleep disturbance
Antithyroid Drugs

- Radioactive iodine: $^{131}\text{I}$
- Iodinated radiocontrast media: ipodate
- Iodide salts and iodine: NaI, KI, I$_2$
- Beta blockers: propranolol

- Thioamides: propylthiouracil (= PTU) & methimazole
  - Mechanism: thioureas inhibit coupling of thyroid hormone synthesis; PTU also decreases peripheral conversion of T4 to T3
  - Toxicity: skin rash, agranulocytosis (1 in 1500), aplastic anemia, hepatotoxic
Oral Contraceptives

- **Estrogen component**: ethinyl estradiol
- **Progestogen components**: norethindrone, levonorgestrel, norgestimate, norgestrel

Complications:

- **Thromboembolic disease** (↑ prothrombin (II) and factors VII, VIII, IX & X) (risk ↑ with age, beginning at 30)
- **Coronary artery disease** (risk is primarily in older smokers; as much as 5x ↑ risk of MI)
- **↑ BP**
- **↑ Triglycerides**
**Uterine Drugs: Oxytocics**

- **Cause uterine contraction:** oxytocin
  - Posterior pituitary hormone
  - Used to induce labor—stimulates uterine muscle; control post-partum hemorrhage

- **Prostaglandins:** dinoprostone (PGE$_2$), carboprost (PGF$_{2\alpha}$)
  - Used to induce abortion; soften cervix before induction of labor

- **Ergots:** ergonovine, methylergonovine
  - Used to prevent post-partum bleeding
Uterine Drugs: Tocolytics

- **Cause uterine relaxation:**
  - magnesium sulfate
    - Used to prevent premature labor

- **Beta-2 agonist:** terbutaline
  - Used to prevent premature labor

- **NSAIDs**
  - Relief of cramps (dysmenorrhea)
Gonadotropin Releasing Hormone

- **GnRH agonists:** leuprolide, goserelin, nafarelin
  - Used continuously: causes suppression of pituitary gonadotropins (↓ FSH & LH) → ↓ ovarian and testicular steroidogenesis; used for prostate cancer, endometriosis
  - Used in pulsatile fashion: agonist; used for infertility
  - Side effects: antiandrogen, N/V, multiple births

- **GnRH antagonists:** (releasing hormone antagonists end in –relix)
  - Cetrorelix, ganirelix: used for rapid suppression of FSH, LH to prevent ovulation, endometriosis
  - Degarelix: used for rapid medical castration for advanced prostate cancer
Selective Estrogen Receptor Modulators (SERMs)

Tamoxifen (used for breast cancer)
- Block estrogen binding to ER+ cancer cells
- Side effect: hot flashes

Clomiphene
- Blocks estrogen negative feedback → ↑ output of pituitary gonadotropins → ↑ ovulation
- Side effects: hot flashes, breast discomfort, HA, N/V/abdominal discomfort, 10% multiple births, ovarian enlargement
Antiprogestins: Mifepristone

Also known as **RU486**

- Anti-progestogen (competitive inhibitor at progesterone receptor)
- With a prostaglandin (**misoprostol**) used to **induce abortion** (oxytotic effect) up to 56th day of pregnancy
- Side effects: hot flashes, alopecia, N/V, abdominal pain
Antiprogestins: Danazol

- Suppresses the pituitary-ovarian axis
- Used in female for endometriosis, fibrocystic disease
- Side effects: androgen-like effects, disturbed menses
Treat Osteoporosis: Biphosphonates

Include: **alendronate**, **ibandronate**, **risedronate**

- **Mechanism:** affinity for **hydroxyapatite**; inhibit osteoclast activity, reduce bone resorption
- **Toxicity:** **osteonecrosis of jaw**, **esophageal problems**
Treat Osteoporosis: Raloxifene

► Has estrogen-like effects on bone and anti-estrogen effects on uterus and breast.

► Causes a ↓ risk of invasive breast cancer in postmenopausal women and lowers LDL cholesterol.

► Side effects: hot flashes, ↑ risk of pulmonary emboli
Androgens

Agents: **testosterone, methyl-testosterone, oxymetholone, oxandrolone, stanozolol, fluoxymesterone**

- (+) Nitrogen balance $\rightarrow$ ↑ muscle and bone mass; ↑ basal metabolism; ↑ RBCs
- Will allow descent of testicles in cryptorchidism
- In female used for treatment of endometriosis and fibrocystic breast disease by suppressing FSH and LH
- Toxicity: peliosis hepatitis, cholestatic hepatitis, liver tumors, psychological changes, MI, virilization of women
Androgen Suppression

**Finasteride, dutasteride** (used for prostate cancer)
► Inhibits 5α-reductase (which converts testosterone to DHT) → rapid ↓ DHT (dihydrotestosterone) → ↓ prostate size and ↓ PSA
► Does not affect hypothalamus-pituitary-testicular axis

**Flutamide, bicalutamide, nilutamide** (used for prostate cancer)
► A nonsteroidal competitive inhibitor of androgens at the testosterone receptor
► Can cause hepatic injury, gynecomastia, hot flash
Treat Erectile Dysfunction

Agents: **sildenafil, tadalafil, vardenafil**

- Inhibits cGMP phosphodiesterase $\rightarrow$ ↑ cGMP, smooth muscle relaxation in the corpus cavernosum, ↑ blood flow, and penile erection

- Toxicity: HA, flushing, hypotension (if taking nitrates is dangerous)
Vitamins
Vitamins $B_1$ & $B_2$

**Thiamine ($B_1$)**
- Links glycolysis to the Krebs cycle (co-enzyme in pyruvate metabolism)
- Deficiency: *beriberi*; in alcoholic → **Wernicke’s encephalopathy, Korsakoff’s psychosis**

**Riboflavin ($B_2$)**
- Deficiency: cheilosis, seborrhea
Vitamin $B_3$ (Niacin)

- Deficiency: **pellagra**
- Used to treat hyperlipidemia
- Side effects: **flushing**, HA, **rhabdomyolysis** if mixed with HMG-CoA reductase inhibitors
Vitamin $B_6$ (Pyridoxine)

- Co-enzyme in nitrogen metabolism, in metabolism of tryptophan, enhance transport of amino acids and K+ into cells, formation of heme in RBCs, energy transfer in brain
- Deficiency (or excessive dose): **peripheral neuropathy**
- Used to treat INH overdose
Vitamins $B_{12}$ & Folate

Cyanocobalamin ($B_{12}$)

► Deficiency: pernicious anemia

Folic acid

► Used to treat folate deficiency; prophylaxis for neural tube defect
► It is necessary for the synthesis of nucleic acid; co-enzyme in purine metabolism; critical in RBC division
► Deficiency: glossitis, diarrhea, anemia
► As leucovorin used for methotrexate rescue
**Vitamin A (Retinol)**

- Fat soluble
- Deficiency: **blindness** (principle cause in the world), slow growth in child
- Toxicity: ↑**ICP** with bulging fontanelles in child, **pseudotumor cerebri** (in adults), alopecia, **bone pain**, hepatomegaly
Vitamins C & D

**Vitamin C (ascorbic acid)**
- Water soluble
- Deficiency: **scurvy**
- Excess can cause **kidney stones**

**Vitamin D**
- Fat soluble
- Deficiency: **rickets**, osteomalacia
- Toxicity: hypercalcemia, **kidney stones**
Vitamin E (Tocopherols)

- Fat soluble
- Tissue antioxidants, influence heme and porphyrin synthesis, retard RBC hemolysis, enhance vitamin A use needed for fertility
- Toxicity: N/D, HA, antagonizes vitamin K
**Vitamin K**

- Fat soluble
- Production of clotting factors: prothrombin II, VII, IX, and X by gamma carboxylation of glutamate
- It is used as the antidote for oral anticoagulants, which cause accumulation of vitamin K 2,3-epoxide (inactive form of vitamin K)

Vitamin K (active) $\xrightarrow{\text{coumadin}}$ epoxide reductase (in liver) $\xrightarrow{\text{(in liver)}}$ Vitamin K—2,3-epoxide (inactive)
Study Questions: Endocrine

1. Which pituitary analog can be used to raise levels of clotting factor VIII and von Willebrand’s factor? [desmopressin, DDAVP, related to ADH]

2. What effect does warfarin have on oral hypoglycemics? [warfarin displaces oral hypoglycemics from protein binding \(\Rightarrow\) worsen hypoglycemia]

3. What is the toxic effect with high mortality that occurs with biguanides (oral hypoglycemics)? [lactic acidosis]
Study Questions: Vitamins

1. Which vitamin deficiency causes beriberi? [vit. B1, thiamine]
2. Which vitamin deficiency causes pellagra? [vit. B3, niacin]
3. Which vitamin if taken in too high a dose acutely causes flushing? [vit. B3, niacin]
4. Which vitamin deficiency causes a megalocytic anemia that should not be given alone for pernicious anemia? [folic acid]
5. Which vitamin deficiency causes pernicious anemia? [vit. B12, cyanocobalamin]
6. What physical finding might you have in a young infant with acute vitamin A toxicity? [anorexia, vomiting, ICP, bulging fontanelles, drowsy or irritable]
Study Questions: Vitamins

7. What vitamin deficiency is the principal cause of blindness in the world?  [vitamin A]

8. What effect does vitamin A have on intracranial pressure in adults?  [↑ CSF with intracranial hypertension and papilledema = pseudotumor cerebri]

9. Name two vitamins if taken in excess chronically could lead to kidney stones.  [vit. C; vit. D]

10. Which vitamin deficiency causes scurvy?  [vit. C]

11. What vitamin is given to newborns to prevent hemorrhage?  [vit. K]