Overview of Lecture:  Endocrine systems & homeostasis
see the schedule for reading
and watching assignments

Bullet Points:
• - FA regulation and the Hypothalamic-Pituitary axis
• - FB and blood glucose regulation
• Endo-Para-Auto-Neuro Sys
• Receptors & ‘Meaning’
• Classic Hormones
• Steroid Hormones
• Peptide-Protein Hormones
• Prostaglandins-COX-Pain
• Caffeine - G-coupled
• Hypothalamus-Pituitary
• Testosterone –FB
• Endocrine Disrupters
• painkillers & testosterone
• the thrill of victory & the agony of defeat
• Stress & immune suppression
**Learning Goals:**

1. Be able to describe and explain the hormonal push-pull mechanisms that regulate blood glucose levels. Include the names of the organs or tissues and the hormones involved. Why does the brain have “a particular interest” in blood glucose regulation?

2. Be able to name and describe an example of (a) a classic endocrine hormone, (b) a paracrine signal, (c) a neuroendocrine releasing factor, (d) a neurotransmitter that is also released as an endocrine hormone.

3. Be able to compare and contrast the typical modes of action of water-soluble vs fat-soluble (steroid) hormones. Illustrate with an example of each.

4. Be able to describe and explain what “endocrine disruptors” are and what are possible modes of action? Give an example.

5. Be able to explain the feedback regulatory mechanism that leads from exogenous testosterone use to testicular atrophy.
Watch: Homeostasis and Feedback - PenguinProf

**Physiology Feedback Loops**

- **Input** → Any Body System → **Output**
- **Feedback**
  - Effector: Makes adjustments as directed.
  - Integrator: Compares what is happening now with what should be happening.
  - Sensor or Receptor: Senses the variable.

#penguinchat
Homeostasis and Feedback
Hormones whose secretion is regulated through the hypothalamus and pituitary regulate their own secretion through negative feedback inhibition. For example - hypothalamic CRH (corticotropin releasing hormone) and pituitary ACTH (adrenocorticotropic hormone).

Negative feedback inhibition keeps hormone levels within a particular appropriate physiological range. [homeostasis around the “set point”]
Blood Glucose Regulation as an Example of \{push-pull –FB\} Homeostasis

Blood glucose levels are regulated by complementary ‘push-pull’ negative feedback systems: (see text Fig 35.12)

- **insulin** pulls high blood glucose down
- **glucagon** pushes low glucose up

\[-FB\text{ systems like this tend to cycle}\]

When an animal takes in excess calories, liver & muscle store it as glycogen, a polymer of many glucose units. If the body’s glycogen depots are full, the excess is converted to fat. When fewer calories are taken in than are expended ...

the body expends liver glycogen, then muscle glycogen and fat. \[\text{released as glucose, into blood}\]

**Type 1 diabetes** mellitus:
loss of insulin-producing beta cells; autoimmune, juvenile onset

**Type 2 diabetes** is often due to reduced responsiveness to insulin, associated w/ obesity in adults
Because the brain relies exclusively on glucose as a fuel source, brain function is rapidly compromised when circulating glucose levels drop below the normal range. Consequently, hypoglycemia elicits a robust, integrated, and redundant set of counterregulatory responses (CRRs) that ensure the rapid and efficient recovery of plasma glucose concentrations into the normal range.

Components of the CRR include increased secretion of the hormones glucagon [pancreas alpha cells], epinephrine [adrenal medulla & sympathetic NS], and glucocorticoids [“stress hormones’ from adrenal cortex], inhibition of glucose-induced insulin secretion, increased sympathetic nervous system (SNS) outflow [as in “fight or flight”] …

Owing to this redundancy, … Only when multiple responses are blocked is the ability to recover from hypoglycemia significantly compromised … is perhaps unsurprising, given the threat to survival posed by hypoglycemia. The brain clearly plays a central role in this regulatory system …

Here, we report a crucial role for VMN neurons [neurons in the VentroMedial Nucleus of the brain act as a central control mechanism via autonomic NS; the neural and endocrine systems are tightly coupled]
The EndoParaAutoNeuroSecretory System regulates **homeostasis** & initiates **adaptive change**

Paracrine & Autocrine signals are local signals to nearby cells or self; ex: NO & vasodilation etc; immune sys signals: interferons, some interleukins & other cytokines are both paracrine & autocrine.

**Synaptic Neurotransmitters** act on receptors on neighboring cell, across tightly integrated synapse. ex: Ach at neuromuscular junction; more on NS later.

**NeuroEndocrine hormones** are released into the blood; ex: Hormones from **anterior pituitary** (ACTH, GH, TSH, LH, FSH, PRL, MSH) are under local control by ‘releasing factors’ from hypothalamus. Hormones from **posterior pituitary** (ADH & oxytocin) are neurotransmitters secreted from the hypothalamus. Hormones from **adrenal medulla** (epinephrine & norepi) are neurotransmitters from modified neural crest cells.
Chemical Signals and modes of action

A **signal molecule** has a specific shape *{the ‘key’}* that is recognized by a **receptor protein** *{lock}*

The binding of a signal molecule to a receptor protein triggers events within the target cell - **signal transduction** - that result in a response.

**Adrenal medulla epinephrine** (aka adrenalin)

Different receptors → different cell responses

**“fight-or-flight”**

(a) Intestinal blood vessel
(b) Skeletal muscle blood vessel
(c) Liver cell

Different intracellular proteins → different cell responses

**Acetylcholine**

**Skeletal Motor neuron**

Nicotinic acetylcholine Receptor

(a) Contraction of a skeletal muscle cell

**Parasympathetic: vagus**

(a) Relaxation of a heart muscle cell
Endocrine hormones: lipid-soluable: (1) steroids; thyroxine
water-soluable: (2) polypeptides < 100 amino acids
(3) glycoproteins > 100 amino acids + a carb.
(4) amines from tyrosine

Hypothalamus: ‘releasing hormones’
control anterior pituitary
melatonin: widespread effects;
Ducrest et al. 2008
Tree 23:502-510
thyroxine, calcitonin
parathyroid hormone

Adrenal medulla: epinephrine
norepinephrine
cortex: aldosterone, cortisol

insulin, glucagon
estrogens, progesterone
androgens

Pituitary:
posterior: ADH, oxytocin
anterior: GH, ACTH, PRL, MSH
TSH, LH, FSH

mysterious ‘thymosins’
important in early development of the immune system

+ many new signaling molecules that fall between endocrine & paracrine,
ex: atrial natriuretic hormone erythropoietin (kidneys), etc.;
many hormones from fat cells can potentiate inflammation and cause insulin resistance contributing to type 2 diabetes
Fat-soluble steroids (and thyroid hormones)

Supplemental stimulation of testosterone receptors upregulates genes coding for muscle proteins.

note: lipid-soluble means water-insoluble; a carrier protein suspends these in aqueous plasma.

Supplemental stimulation of testosterone receptors upregulates genes coding for muscle proteins.

{-FB ‘side-effects’ later}
Water-soluble (polar, non-steroid) hormones


**G-protein-coupled receptors (GPCRs)** ... one of the largest gene families in the animal genome ... members have been identified in ancient **eukaryotes**, such as slime molds (Dictyostelium) and sponges.

{up to 60% of all medications act on G-protein-coupled receptors}

NATURE NEWS BLOG 10 Oct 2012

**G-protein-coupled receptors take chemistry Nobel**

Nearly every function of the human body, from sight and smell to heart rate and neuronal communication, depends on G-protein-coupled receptors ...

When nociceptors {pain nerves} are exposed to injury and inflammation, their excitability is altered. The figure highlights the vanilloid receptor VR1 [stimulated by heat & chemicals like capsaicin to ↑ Na+ influx and nerve signaling] enhance nociceptor excitability: ↑ Na+ influx @ TTX-R {note: G-coupled}

Prostaglandins at PGE₂ enhance nociceptor excitability: COX-1 maintains prostaglandin synthesis in the stomach, kidneys, and platelets.

Non-selective NSAIDs inhibit COX-1 & COX-2

COX-2 maintains prostaglandin production predominately in inflamed tissue

COX-2 inhibitors selectively inhibit COX-2 but ↑ risk of heart attacks!

Prostaglandins at PGE₂

Prostaglandins: widespread & diverse lipid paracrine signals 1st found in seminal fluid, from prostate: stimulate contraction of uterine smooth muscle {of another person!}

… are one of the chemical signals (cytokines) that recruit phagocytes to wounds and potentiate pain - to get your attention.

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Caffeine

is an alkaloid … in cola nuts, coffee, tea & other plants

Alkaloids

are nitrogenous secondary compounds

that plants produce to poison herbivores.

The LD-50 for coffee varies from 50 to 200 cups.

Adenosine and Sleep

... adenosine {a neurotransmitter, but also a paracrine signal produced by active tissues from degraded ATP} promotes sleep.

{note double negative: caffeine inhibits inhibition of adenylyl cyclase by adenosine}

Caffeine has a withdrawal syndrome featuring headache and nausea. Caffeine is used to relieve headaches.

[see: https://www.smithsonianmag.com/science-nature/this-is-how-your-brain-becomes-addicted-to-caffeine-26861037/ ]

Caffeine

and

Alkaloids
The **Hypothalamus** is ‘The Master Puppeteer,’ but monitors feedback & other inputs from brain. [homework: get to know]

Alcohol inhibits ADH secretion,

{ADH is also a neurotransmitter in brain aka vasopressin – more later}
Consider the role of testosterone in the FB loop from testes to hypothalamus, that regulates secretion of gonadotropins FSH & LH, that regulate gonads.

What do you suppose happens when blood testosterone (or mimic) levels are raised by external supplements?

**Anabolic-androgenic steroids (AAS),** are synthetic derivatives of testosterone, used by body builders and weightlifters to increase lean muscle and decrease fat.

Consider the role of testosterone in the FB loop from testes to hypothalamus, that regulates secretion of gonadotropins FSH & LH, that regulate gonads.

**Hormone therapy: A dangerous elixir?**


Testosterone therapy jacks up vigour, sex drive and mental acuity - or so proponents claim.

But … testosterone replacement might increase the likelihood that latent cancerous cells in the prostate gland will transform into tumours. …
Endocrine disruptors are chemicals that may interfere with the body’s endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. A wide range of consumer products can cause endocrine disruption, including pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and plasticizers such as bisphenol A. Endocrine disruptors may be found in many everyday products - including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides.

The NIEHS supports studies to determine whether exposure to endocrine disruptors may result in human health effects …

… endocrine disruptors may pose the greatest risk during prenatal and early postnatal development when organ and neural systems are forming. [more on this when we study development]

75 studies link BPA to many adverse perinatal, childhood, and adult health effects.

EU shifts endocrine disrupter research into overdrive

Lorenz S. SCIENCE 300 (5622): 1069-1069 MAY 16 2003

The European Union is embarking on a massive new effort to pinpoint the harmful effects of hormone-mimicking chemicals. ...

Endocrine disruptors and reproductive health: The case of bisphenol-A


BPA is used in the manufacture of plastics and resins ... used in milk and food containers, baby formula bottles ... dental resins ...

BPA leaches from these materials ...

**BPA**, one of the most ubiquitous endocrine disruptors ... **binds both estrogen receptor (ER) α & β** ...

**... found in 95% of urine samples, in maternal & fetal tissue & in the milk of nursing mothers** ...

<table>
<thead>
<tr>
<th>Brain (ER α or ER β)</th>
<th>Tissue organization of sexually dimorphic structures and cellular phenomena (gene induction)</th>
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</thead>
<tbody>
<tr>
<td>Mammary Gland (ER α or ER β)</td>
<td>Tissue organization and cellular phenomena (gene induction)</td>
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<tr>
<td>Weight gain</td>
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<tr>
<td>Reproductive Tract (ER α or ER β)</td>
<td>Tissue organization and cellular phenomena (gene induction)</td>
</tr>
</tbody>
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**{data mostly from mice}**

- **ALtered Sexual Differentiation**
- **Advanced Puberty**
- **Altered Estrous Cycles**
- **Altered Pituitary Hormone Homeostasis**
- **Altered Ovarian Homeostasis**

- **Altered Ductal Invasion at Puberty**
- **Altered Remodeling of Terminal End Buds**
- **Increased Number of Progesterone Receptor Positive Cells and Ductal Cells**
- **Increased Lateral Branching**
- **Increased Number of Alveolar Structures**
- **Altered Response to Estradiol**

- **Decreased Weight of the Vagina**
- **Increased Proliferation in Endometrial Glands**
- **Increased Endometrial Expression of ER and PR**
- **Increased Anogenital Distance in Males**
- **Increased Prostate Size**
- **Malformations in the Urethra**
- **Decreased Sperm Production and Quality**
The infertility crisis is beyond doubt. Now scientists must find the cause

News last week that sperm counts in western men have halved confirmed what experts already knew. The real problem is that no one knows why.

Much concern has been raised over declining male reproductive health, [see Trends of male factor infertility, … J Hum Reprod Sci. 2015 8(4): 191–196.] and the disruption of male endocrinology has been suggested to play a central role. **Male reproduction and general health rely on androgens**, as well as on other hormones, which are mainly **produced by testicular Leydig and Sertoli cells**. In addition to the testis, **the androgens act in many somatic organs, producing anabolic effects on muscle mass and influencing cognitive functions**.

**Luteinizing hormone (LH)** produced by the pituitary stimulates testosterone production, and the testosterone/LH ratio is used as a clinical marker of Leydig cell function. **When Leydig cell function is compromised, normal or nearly normal testosterone levels can often be sustained by augmented LH levels, as observed in the clinical entity termed “compensated hypogonadism”**.
The so-called “over-the-counter” mild analgesics (hereafter called “analgesics”), such as acetaminophen/paracetamol, acetylsalicylic acid/aspirin, and ibuprofen, are among the most commonly used pharmaceutical compounds worldwide. These are meant to interfere with the production of prostaglandins.
Testosterone changes during vicarious experiences of winning and losing among fans at sporting events
Bernhardt et al. 1998 Physiol & Behav 65: 59-62

... mean testosterone level increased in the fans of winning teams and decreased in the fans of losing teams.

Effects of competition outcome [among players including women] on testosterone concentrations in humans: An updated meta-analysis.
SN Geniolea et al. Available online 6 October 2016

... winners had elevated testosterone relative to losers.
Interactions Between Mental States, Physiology, and Immunity

A Dynamic Psychoneuroimmunologic Network

by Duncan Smith-Rohrberg

Stress or flight

Current Directions in Stress and Human Immune Function.
Curr Opin Psychol. 2015 Oct 1; 5:13-17. JN Morey et al.

Immunosuppression w/ steroids (ex Prednisone) is used for treatment of inflammation, allergy, MS & other autoimmune problems.

Stress and the brain: from adaptation to disease

... chronic stressors [chronic cortisol to brain] can cause neuronal disturbances that resemble the changes that are observed in the brain during depression.