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

THE FOLLOWING PREVIEW HAS BEEN APPROVED FOR ALL AUDIENCES

Bullet Points:
• FB regulation and the Hypothalamic-Pituitary axis
• FB and blood glucose regulation
• Endo-Para-Auto-Neuro Sys
• Signals, Receptors & ‘Meaning’
• Classic Hormones
• Steroid Hormones
• Peptide-Protein Hormones
• Prostaglandins-COX-Pain
• Caffeine - G-coupled
• Hypothalamus-Pituitary-Axis
• 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

Sensor or Receptor

Senses the variable.

Effector

Makes adjustments as directed.

Integrator

Compares what is happening now with what should be happening.

#penguinchat

Homeostasis and Feedback
Hormones whose secretion is regulated through the hypothalamus and pituitary regulate their own secretion through negative feedback inhibition. For example -

Negative feedback inhibition keeps hormone levels within a particular appropriate physiological range. 

[homeostasis around a dynamic “set point”]
Blood glucose levels are regulated by complementary 'push-pull' negative feedback systems: (see text Fig).

- **Insulin** pulls high blood glucose down
- **Glucagon** pushes low glucose up

FB systems like this tend to cycle 'set point'.

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**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

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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. 
  
  [released as glucose, into blood]

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**Blood Glucose Regulation as an Example of {push-pull-FB} Homeostasis**

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. 
  
  [released as glucose, into blood]
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.
Endocrine System, part 1 - Glands & Hormones: Crash Course A&P #23
The EndoParaAutoNeuroSecretory System regulates **homeostasis** & initiates **adaptive change**

**Hormones** secreted into blood by **endocrine glands & other tissues**

Circulate widely and act on specific **receptor proteins** which determine consequences inside **target cells**;

**Paracrine & Autocrine** signals are local signals to

**Synaptic Neurotransmitters** act on receptors on

**NeuroEndocrine hormones** are released into the blood;

Hormones from **posterior pituitary** (ADH & oxytocin)

Hormones from **adrenal medulla** (epinephrine & norepi)

**Pheromones** are chemical signals to the neuroendocrine system of other individuals!
Chemical Signals and modes of action

A **signal molecule** has a specific shape *(the ‘key’)* that is recognized by a **receptor protein** *(lock)* in the **plasma membrane** *(water soluable)* or **cytoplasm** *(lipid soluable)* of the **target cell**

The binding of a signal molecule to a receptor protein

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**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

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**Acetylcholine**

- **Skeletal Motor neuron**
- **Parasympathetic: vagus**

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**Nicotinic acetylcholine Receptor**

(a) Contraction of a skeletal muscle cell
(b) Relaxation of a heart muscle cell
**Endocrine hormones:**

- **lipid-soluble:** (1) steroids; thyroxine
- **water-soluble:** (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

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

**Adrenal medulla:** epinephrine
  norepinephrine

**cortex:** aldosterone,
cortisol

- insulin, glucagon

- estrogens,
  progesterone
- androgens

**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

**From:** The Rheumatologist, August 2011

**What Fat Does to Arthritis**
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*

The hormone-receptor complex

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

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

Evolution, structure, and activation mechanism of family 3/C **G-protein-coupled receptors**.

**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]

Prostaglandins at PGE₂ enhance nociceptor excitability: ↑ Na⁺ influx @ TTX-R {note: G-coupled}

Opiates & cannabinoids can counteract the increase in excitability of the nociceptor.

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.

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!
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.

Caffeine's stimulating characteristics stem from its action as an 'adenosine disrupter': it prevents adenosine from binding to cells at a G-coupled receptor.

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

Anterior Pituitary controlled by

Posterior Pituitary

ADH is also a neurotransmitter in brain aka vasopressin – more later

THE PHYSIOLOGY OF THE HANGOVER
http://ist-socrates.berkeley.edu/~jmp/LO2-HCG.html
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?

Hormone therapy: A dangerous elixir?

Nature 431, 500 - 501 (30 September 2004)

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 substances 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]
EU shifts endocrine disrupter research into overdrive

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...


J. R. Rochester. 2013. Reproductive Toxicology 42, 132–155

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

Life begins ... but for western couples the process is becoming more and more difficult. Photograph: Mark Evans/Getty Images

Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism
DM Kristensen et al. 2018. PNAS January 23, 2018 vol. 115 no. 4

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]

Several studies have shown that mild analgesics exposure during fetal life is associated with antiandrogenic effects and congenital malformations, [we will learn more about this when we study development] but the effects on adult men remain largely unknown.

Through a clinical trial with young men exposed to ibuprofen, we show that

[The negative feedback regulatory system between the anterior pituitary & gonads cranks up the release of more LH from the pituitary to stimulate the production of increased testosterone from testes, but impaired testes can’t completely compensate.]
Testosterone changes during vicarious experiences of winning and losing among fans at sporting events
Bernhardt et al. 1998 Physiol & Behav 65: 59-62

Effects of competition outcome on testosterone concentrations in humans: [among players including women]
An updated meta-analysis.
SN Geniolea et al. Available online 6 October 2016
... winners had elevated testosterone relative to losers.
Immunosuppression w/ steroids (ex Prednisone) is used for treatment of inflammation, allergy, MS & other autoimmune problems.


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