Overview of Lecture: Endocrine systems
Read: Text ch 45

Bullet Points:
- endocrine system
- Para-Neuro-Endo Sys
- Prostaglandins-COX-Pain
- Feedback & Fever
- Receptors & 'Meaning'
- Ancient Origins
- Classic Hormones
- Steroid Hormones
- Endocrine Disrupters
- Peptide-Protein Hormones
- Caffeine - G-coupled
- Hypothalamus-Pituitary
- Pheromones
The EndoParaAutoNeuroSecretory System regulates **homeostasis** & initiates **adaptive change** & tissues (Fig 45.10) act on **receptor proteins** which determine consequences inside **target cells**; Table 45.1: “classic hormones”

nearby cells or self; ex: NO & vasodilation etc; interferons, some interleukins & other cytokines are both paracrine & autocrine.

neighboring cell, across tightly integrated synapse. ex: Ach @ neuromuscular junction; more on NS later.

ex: Hormones from **anterior pituitary** (ACTH, GH, TSH, LH, FSH, PRL, MSH) are under local control by ‘releasing factors’ from hypothalamus (Fig 45.17 & 18). Hormones from **posterior pituitary** (ADH & oxytocin) are secreted by neurons from hypothalamus (Fig 45.15). Hormones from **adrenal medulla** (epinephrine & norepi) are neurotransmitters from modified neural crest cells.

**Pheromones** are chemical signals to

When nociceptors \(\text{pain nerves}\) are exposed to injury and inflammation, their excitability is altered. The figure highlights the vanilloid receptor \(\text{VR1}\) \{stimulated by heat & chemicals like capsaicin to \(\uparrow\) Na\(^+\) influx\}.

**Prostaglandins at \(\text{PGE}_2\)** enhance nociceptor excitability: \(\uparrow\) Na\(^+\) influx @ TTX-R can counteract the increase in excitability of the nociceptor. {note: G-coupled}

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 & \(\uparrow\) risk of heart attacks!

**Prostaglandins:** widespread & diverse group of paracrine signals

1st found in seminal fluid, from prostate: stimulate contraction of uterine smooth muscle.
A taste for pain

Three peptides isolated from the venom of the West Indian tarantula ... promote pain and inflammation by activating the same neuronal receptor as capsaicin, the hot component of chilli peppers. ...

News and Views: Physiology: Channelled pain

The newly isolated peptides are dubbed 'vanillotoxins' because of their action on the TRPV1 vanilloid receptor...

Letter: Spider toxins activate the capsaicin receptor to produce inflammatory pain

Editor's Summary 4 October 2007

Hit where it hurts

Most local anaesthetics indiscriminately block sodium channels in neural membranes. Binshtok et al. report that the lidocaine derivative QX-314 can be targeted to pain-sensing neurons ... by coupling it to capsaicin, allowing it to enter via the TRPV1 {aka VR1} channel found only in pain-sensing neurons.

Letter: Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. AM Binshtok et al. | Full Text |
Omega-3 fatty acids, which are essential polyunsaturated fatty acids, have been associated with beneficial health effects. One mechanism for their anti-inflammatory effect is via competitive inhibition of the enzymatic activity of cyclooxygenase (COX), which is the rate-limiting step in the biosynthesis of prostaglandins.

Massaro et al. (2006 Proc. Natl. Acad. Sci. U.S.A. 103, 15184) report that exposure of vascular endothelial cells to the omega-3 fatty acid docosahexaenoate (DHA) for long enough for it to be incorporated into cellular membranes inhibits prostaglandin production from arachidonic acid by COX-2 in response to the proinflammatory signal interleukin-1 (IL-1).

Bacon That's Good For You? Researchers Create Pigs That Produce Heart-healthy Omega-3 Fatty Acids

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ScienceDaily (Mar. 27, 2006) ... cloned transgenic livestock.

Have a headache? No aspirin or ibuprofen handy? Try some olive oil - Phytochemistry: Ibuprofen-like activity in extra-virgin olive oil

Beauchamp et al. Nature 437, 45-46 (1 September 2005)
Fever is an adaptive & regulated rise of temperature mediated by paracrine signals (cytokine interleukins) released from macrophages the body behaves as if its thermostat has been reset at a higher temperature.

Bits of bacterial antigen (LPS endotoxin) are phagocytosed by macrophage leucocytes. {MΦ}

which then release 'cytokines' incl. interleukins IL-1 & IL-6 into local tissue and circ. sys.

Locally: recruit immune cells & inflammation

At neurons in anterior hypothalamus which regulate body temp 'set point': act as 'endogenous pyrogens' by increasing synthesis of prostaglandin E2 (PGE2) which acts on hypothalamic neurons in a way that increases the regulated temperature 'set point'.

The new setpoint is maintained by heat regulating mechanisms

Aspirin reduces fever by inhibiting the synthesis of prostaglandins in the hypothalamus.

Fever is beneficial; the increased temp accelerates immune responses, incl. antibody production, & inhibits bacterial multiplication by stimulating liver and spleen to sequester iron needed by bacteria.
Chemical Signals and modes of action (see ch 11)

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

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

The distribution of receptors determines which cells ‘get the message.’

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**Adrenal epinephrine (aka adrenalin)**

Different receptors → different cell responses

- **Epinephrine**
  - α receptor
  - Vessel constricts
  - (a) Intestinal blood vessel

- **Epinephrine**
  - β receptor
  - Vessel dilates
  - (b) Skeletal muscle blood vessel

- **Epinephrine**
  - β receptor
  - Glycogen deposits
  - (c) Liver cell

**Acetylcholine**

**Skeletal Motor neuron**

- **Nicotinic acetylcholine**
  - Receptor
  - Contraction of a skeletal muscle cell

**Parasympathetic: vagus**

- **Acetylcholine**
  - Relaxation of a heart muscle cell
Endocrine hormones:
(see Table 45.1)

Hypothalamus:
‘releasing hormones’
control anterior pituitary

- melatonin: widespread effects;
  Ducrest et al. 2008
  Tree 23:502-510

- thyroxine, calcitonin
- parathyroid hormone
  see Fig 45.20

Pituitary:
posterior:
- ADH, oxytocin

anterior:
- GH, ACTH, PRL, MSH
- TSH, LH, FSH

Adrenal
medulla:
- epinepherine
- norepinephrine

cortex:
- aldosterone,
  cortisol
- estrogens,
  progesterone
- androgens

Insulin, glucagon
(fig 45.12)

Major endocrine glands:
Hypothalamus

Pineal gland

Pituitary gland

Thyroid gland

Parathyroid glands (behind thyroid)

Adrenal glands (atop kidneys)

Pancreas

Kidney

Ovaries (female)

Testes (male)

Mysterious ‘thmosins’
important in early development of the immune system

+ many new signaling molecules that fall between endocrine & paracrine,
ex: atrial natriuretic hormone erythropoietin (kidneys), etc.

Table 1: Proinflammatory molecules released from adipose tissue.1

<table>
<thead>
<tr>
<th>Class of molecules</th>
<th>Key molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines, chemokines, and growth factors</td>
<td>TNF-α, IL-6, plasminogen activator inhibitor-1, migration inhibitory factor, macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>Complement factors</td>
<td>C3, C1 inhibitor, complement factors B and D</td>
</tr>
<tr>
<td>Adipokines</td>
<td>Leptin, adiponecin, resistin, visfatin/PBEF, omentin, C1q/TNF-related protein-3</td>
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</tbody>
</table>
**Fat-soluble steroids** (and thyroid hormones) diffuse through lipid plasma cell membrane, receptor proteins are inside the cell.

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

The **hormone-receptor** complex

Supplemental stimulation of existing receptors upregulates existing genes for muscle proteins.}{-FB ‘side-effects’ later}
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
nuclear estrogen receptor (ER) α & β & plasma membrane ERs
{recently discovered}.
... found in 95% of urine samples, in maternal & fetal tissue & in the milk of nursing mothers...

Bisphenol A
alters early oogenesis and follicle formation in the fetal ovary
of the rhesus monkey.
Prenatal phthalate exposure and reduced masculine play in boys.

... concentrations of ... phthalate metabolites in the mothers' urine were statistically associated with decreased masculine play behavior in boys who were an average of 5 years-old at the time of the assessment. There were no strong associations ... with girls' play behavior.


... there are strong and rather consistent indications that phthalates increase the risk of allergy and asthma and have an adverse impact on children’s neurodevelopment reflected by quality of alertness among girls, less masculine composite score in boys and attention deficit hyperactivity disorder.

In all the reviewed studies, exposure to phthalates adversely affected the level of reproductive hormones (luteinizing hormone, free testosterone, sex hormone-binding globulin), anogenital distance \{pelvic morphology\} and thyroid function.
Endocrine Disrupters Trigger Fertility Problems in Multiple Generations

A fungicide and a pesticide known to be toxic to animals, have an even darker side: On page 1466, researchers report that the two chemicals cause fertility defects in male rats that are passed down to nearly every male in subsequent generations.

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility

Anway et al. Science 3 June 2005: 1466-1469. [[Full Text]

Transient exposure of a gestating female rat ... to the endocrine disruptors vinclozolin (an antiandrogenic compound): a commonly used fungicide ... metabolized into compounds with high affinity to androgen receptors, or methoxychlor (an estrogenic compound): a pesticide to replace DDT; metabolized into active compounds with ER\(\alpha\) (estrogen receptor \(\alpha\)) agonist, ER\(\beta\) antagonist, and anti-androgenic activity induced an adult male phenotype in the F1 \{next\} generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility.

These effects were transferred through the male germ line to nearly all males of all subsequent generations examined. The effects correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor to reprogram the germ line has significant implications for evolutionary biology and disease etiology.
Water-soluble (polar, non-steroid) hormones bind to receptor proteins on the surface of the lipid plasma membrane.

... generally changes the metabolism of cells but can alter transcription.

see ch 11 for more info on receptors & transduction

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.

{see Fig 11.7: - 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 …
G-Protein Coupled Receptors

G protein-coupled receptors (GPCRs) are membrane proteins that are involved in a broad range of biological processes, and a large number of clinically used drugs elicit their biological effect(s) via a GPCR. Structural information about GPCRs was very limited until 2007, and papers describing...
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.

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.
The Hypothalamus is ‘The Master Puppeteer,’ but monitors feedback & other inputs from brain. \{Figs 45.16 & 18\}

**Anterior** Pituitary controlled by

- FSH (follicle-stimulating hormone)
- LH (luteinizing hormone)
- TSH (thyroid-stimulating hormone)
- ACTH (adrenocorticotropic hormone)

**Posterior** Pituitary

- Neurosecretory cells of the hypothalamus

**Tropic effects only:**
- FSH
- LH
- TSH
- ACTH

**Nontropic effects only:**
- Prolactin
- MSH (melanocyte-stimulating hormone)

**Nontropic and tropic effects:**
- GH (growth hormone)

Alcohol inhibits ADH secretion, the kidneys fail to retain water and the person excretes large volumes of urine.

\{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?**


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. …
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.
De Dreu et al. (Science 11 June 2010: 1408-1411) have discovered a role for **oxytocin**, a neuropeptide produced in the hypothalamus, in regulating parochial altruism during human intergroup competition and conflict. **Oxytocin is already known to play a role in trusting behavior**, and naturally occurring genetic variants of the oxytocin receptor exist within the human population.

**Subjects who received a dose of the social-bonding hormone oxytocin**

**Oxytocin and Intergroup Conflict**

Human society is organized into groups, such as those based on nationality or religion, which can lead to intergroup conflicts, with sometimes devastating consequences. Intergroup conflict engages a human behavior termed parochial altruism: For example, a soldier who fights to protect their country is a parochial altruist.

... chronic or repeated stressors can cause neuronal disturbances that resemble the changes that are observed in the brain during depression.
Pheromones are chemical signals released by an individual into the environment which affect the physiology or behavior of other members of the same species.

Many insects use pheromones to attract mates (usually female signaling to male)
We have figured out how to synthesize many of these, especially for ‘pests,’ and use them to lure one sex (usually males) into traps.

**Safer Japanese Beetle Traps**
Be prepared for the arrival of Japanese beetles with this dual-scented lure trap. …
The floral lure attracts the females while the pheromone lure brings in the males.
Regulation of ovulation by human pheromones.
Stern K, McClintock MK
NATURE 392: (6672) 177-179 MAR 12 1998

Here we investigate whether humans produce compounds that regulate a specific neuroendocrine mechanism in other people without being consciously detected as odours (thereby fulfilling the classic definition of a pheromone).

We found that odourless compounds from the armpits of women in the late follicular phase of their menstrual cycles

… this study provides definitive evidence of human pheromones.

… sniffing different concentrations of … 4,16-androstandien-3-one (AND) … increased positive mood in women compared to men, and had sympathetic-like effects in women and parasympathetic-like effects in men.

Male axillary extracts contain pheromones that affect pulsatile secretion of luteinizing hormone and mood in women recipients.


we extracted underarm secretions from men and placed the extract under the nose of women while monitoring serum LH and emotion/mood. Pulses of LH are excellent indicators of the release of GnRH from the hypothalamus.

In women, the positive influence of GnRH on LH affects the menstrual cycle and fertility.

Here we show that extracts of male axillary secretions have a direct effect upon LH-pulsing and mood of women.

In our subjects, the putative male pheromone(s) advanced the next peak of LH after its application, reduced tension, and increased relaxation.
The testosterone derivative 4,16-androstadien-3-one (AND) and the estrogen-like steroid estra-1,3,5(10),16-tetraen-3-ol (EST) are candidate compounds for human pheromones. AND is detected primarily in male sweat, whereas EST has been found in female urine.

In a previous positron emission tomography study, we found that smelling AND and EST activated regions covering sexually dimorphic nuclei of the anterior hypothalamus, and that this activation was differentiated with respect to sex and compound. In the present study, the pattern of activation induced by AND and EST was compared among homosexual men, heterosexual men, and heterosexual women.

In contrast to heterosexual men, and in congruence with heterosexual women, homosexual men displayed hypothalamic activation in response to AND. Maximal activation was observed in {areas} highly involved in sexual behavior. Common odors were processed similarly in all three groups of subjects ...

These findings … suggest a link between sexual orientation and hypothalamic neuronal processes.

Brain response to putative pheromones in lesbian women.
Berglund, H. 2006. PNAS 103 pp. 8269
Women's tears contain chemical cues

Female weeping dampens sexual arousal in men.

Janelle Weaver

Tears shed by women contain chemical signals that decrease sexual arousal and testosterone levels in men, according to a study. The result, discovered by Noam Sobel, a cognitive neuroscientist at the Weizmann Institute of Science in Rehovot, Israel, and his colleagues, is published today in *Science* 

*Punchstock*
Powerful urine is mind-altering

**Alpha-male pheromones cause females** \( \text{mice} \) **to make brain cells.**

Urine is rich in the sex pheromones that many animals use to recognize and choose their mates.

Samuel Weiss ... and his colleagues ... housed adult female mice with soiled litter for a week.

**Animals exposed to urine from dominant males** showed a 25% increase in new neurons in two brain regions.

Those exposed to clean bedding, or urine from females or subordinate males showed no such increase.

**Neurons grew in the hippocampus,** a brain region involved in learning and memory, and the olfactory bulb, which is involved in smell.

**Both regions make new neurons throughout life;**

We don't know whether pheromones trigger neuron formation in humans ...

**whether a subconscious whiff of an alpha-male's urine could turn a woman's head** is still a matter of speculation.

Derek P et al. Alpha males win again.
