BI 358 Lecture 2

I. **Announcements** Douglas Bovee, MD, Addiction & Internal Medicine Specialist next session! *NB*: Sign-in + e-feedback < 24 hr. Quiz 1 + Outline due next Tues. Q? Great drug overview for Quiz. U Utah Addiction website! [http://learn.genetics.utah.edu/content/addiction/](http://learn.genetics.utah.edu/content/addiction/)

II. **Medical Physiology in the News** Glymphatic System?

III. **Homeostasis Connections** BP e.g. Q? + Gain? G&H pp 7-8

IV. **Discussion Follow-up Addiction Medicine**

Cigarette smoking, nicotine & PADDs!

V. **Organization of the Nervous System**

G&H ch 45 pp 543-8, LS1/2 ch 5

A. Central vs peripheral, computer analogy fig 45-4 p 546
B. Neurons, neuronal classes, neuroglia, connections

VI. **Autonomic Nervous System**

G&H ch 60 pp 729-41 + LS +...

A. Sympathetic vs. parasympathetic fig 60-1,60-3 pp730-1
B. Neurotransmitters, receptors, actions tab 60-1 pp 731-7
C. Nicotine & adrenal hormonal disruption

VII. **Addiction Medicine: Homeostasis & Applications**
**Come see us!**

<table>
<thead>
<tr>
<th>Day &amp; Time</th>
<th>Instructor</th>
<th>Place</th>
<th>e-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>M 11 am-12n</td>
<td>Pat Lombardi</td>
<td>73A Klamath</td>
<td>lombardi</td>
</tr>
<tr>
<td>W 11:30-12:30am-pm</td>
<td>Tony Yang</td>
<td>15E Klamath</td>
<td>anthonyy</td>
</tr>
<tr>
<td>R 10-11 am</td>
<td>Conor O’Sullivan</td>
<td>206 LISB</td>
<td>conoro</td>
</tr>
<tr>
<td>F 2-3 pm</td>
<td>Emile Rutherford</td>
<td>360 ONYX</td>
<td>srutherf</td>
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</tbody>
</table>

*And by appointment.*

For Emile, please e-mail or call 541-346-4536.
For Conor, please e-mail or call 541-346-4536.
For Pat, please call 541-346-4536 or 541-346-6055.
Astrocytes

\~90\% of Cells w/in CNS are **Glial Cells/Neuroglia**!

1. Neuron spatial relationships.
2. Scaffolding during fetal development.
3. Induce capillary changes to establish **Blood-Brain Barrier**.
4. Transfer **nutrients** from blood to neurons.
5. Repair brain injuries & form neural scars.
6. Uptake & degrade **neurotransmitters**.
7. Soak up excess K+ to sustain normal **neural excitability**.
8. Communicate with neurons & each other electrochemically.

100 Billion Neurons \(\rightarrow\) 900 Billion Glial Cells!
What the Heck is the Glymphatic System? CNS Functional Waste Clearance Pathway!

Glymphatic Pathway Function

- Para-Arterial Influx
- Convective Flux
- Para-Venous Efflux

- Astrocyte
- Neuron
- Interstitial solute
- AQP4

http://www.sciencedaily.com/releases/2012/08/120815142042.htm
https://www.urmc.rochester.edu/labs/nedergaard-lab/projects/glymphatic_system
Balance is the Key to Life
Invariably, Negative Feedback

Feedback loop

Invariably, Negative Feedback
NB: Though most often negative feedback, there are exceptions:

Selected +FB e.g.:

LH Surge → Ovulation
Oxytocin → Uterine Contraction
Blood Clotting Cascade
cAMP Cascade
Na+ influx during AP

Nonpathological! Temporarily amplifies, but ultimately turned off by - FB!
Recovery of heart pumping caused by negative feedback after 1 liter of blood is removed from the circulation. Death caused by positive feedback when 2 liters of blood are removed.
Seated to Standing

Venous Pooling

Electrochemical Signal

CV Control Center

Brain Stem

Seated to Standing

BP Pooling

I

R

Baroreceptors/Pressure Receptors e.g., in Carotids & Aorta

NB: Corrective Change Opposes Original Input

O

Electrochemical Signal e.g., Symp Accelator N

E

BP

+ HR

VC

Ef

FB eg
How Effective is a System at Maintaining Relative Constancy? Feedback Gain?

Gain = \frac{\text{Correction}}{\text{Error}}

e.g., Transfuse large volume of blood into person with non-functioning Baroreceptor system

BP: 100 mm Hg \rightarrow 175 mm Hg

...into person with functioning system

BP: 100 mm Hg \rightarrow 125 mm Hg

G&H pp 7-8
Gain for Human Baroreceptor System?

Gain = \frac{-50 \text{ mm Hg}}{+25 \text{ mm Hg}} = -2

cf: Gain for Human Body Temperature = -33
Cigarettes ≡ Patient-Assisted Drug-Delivery System
Inhaling Bypasses the Systemic Circulation
& Is Powerfully Reinforcing!
SMOKING $\equiv$ ASTHMA?

Petri-dish Effect

Ugh!!
Cough!!
Cough!!
Tracing the Route of Cigarette Smoke
Puff to Brain Time 5 to 8 seconds!!

Mouth
  ↓
Pharynx
  ↓
Larynx
  ↓
Trachea
  ↓
Bronchi
  ↓
Bronchioles
  ↓
Alveoli

Blood

Pulmonary Veins
  ↓
Left Atrium
  ↓
Left Ventricle
  ↓
Aorta

Heart

Respiratory Membrane

Systemic Circulation

Brain
Not only the Lungs, Heart & Brain, but 100s of Other Tissues & Organs are Adversely Affected!

So sorry I was forced to deliver!
Cigarette + Smoke: > 7000 Chemicals; ~600 Tobacco Company Additives
Atherogenic, Carcinogenic (C), Tumor Initiating, Tumor Promoting (TP),
Toxic (T) Cornucoppia of Unknowns, Synergistic, Reactive...?

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Source</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>4-aminobiphenyl</td>
<td>C</td>
<td>140 ng per cigarette...</td>
</tr>
<tr>
<td>benz(a)anthracene</td>
<td>C</td>
<td>40-200 ng</td>
</tr>
<tr>
<td>benzene</td>
<td>C</td>
<td>400 μg</td>
</tr>
<tr>
<td>benz(o)pyrene</td>
<td>C</td>
<td>40-70 ng</td>
</tr>
<tr>
<td>carbon monoxide</td>
<td>T</td>
<td>26.8-61 mg</td>
</tr>
<tr>
<td>formaldehyde</td>
<td>C</td>
<td>1500 μg</td>
</tr>
<tr>
<td>hydrazine</td>
<td>C</td>
<td>90 ng</td>
</tr>
<tr>
<td>hydrogen cyanide</td>
<td>T</td>
<td>14-110 μg</td>
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<tr>
<td>2-napthylamine</td>
<td>C</td>
<td>70 ng</td>
</tr>
<tr>
<td>nitrogen oxides</td>
<td>T</td>
<td>500-2000 μg</td>
</tr>
<tr>
<td>N-nitrosodimethylamine</td>
<td>C</td>
<td>200-1040 ng</td>
</tr>
<tr>
<td>N-nitrosodiethanolamine</td>
<td>C</td>
<td>43 ng</td>
</tr>
<tr>
<td>N-nitrospyrrolide</td>
<td>C</td>
<td>30-390 ng</td>
</tr>
<tr>
<td>phenol</td>
<td>TP</td>
<td>70-250 μg</td>
</tr>
<tr>
<td>polonium 210</td>
<td>C</td>
<td>0.5-1.6 pCi</td>
</tr>
<tr>
<td>quinoline</td>
<td>C</td>
<td>15-20 μg</td>
</tr>
<tr>
<td>O-toluidine</td>
<td>C</td>
<td>3 μg</td>
</tr>
</tbody>
</table>

**SOURCES:** US Surgeon General's Office, American Cancer Society, American Heart Association.
Absorbs H₂O
Preserves tobacco
Antifreeze & de-icing
Polyester compounds
Artificial smoke in
Theater & electric cigarettes
American Cancer Society
What's in tobacco?

US Food & Drug Administration
Constituents in tobacco?

http://livealittlelonger.wordpress.com/tobacco/whats-inside-that-cigarette/
http://www.smokefree.gov/
Arsenic 33

- Shotgun pellets
- Metal for mirrors
- Glass, lasers
- Light emitting diodes(LED)
- 74.9216

Polonium 84

- Nuclear batteries
- Neutron source
- Antistatic agents
- Film cleaner
- (209)
TOBACCO ADDITIVES

The tobacco industry has acknowledged that nearly 600 chemicals are added to cigarettes. It is not clear, however, how much of the various additives are used or which combinations appear together. Some of the chemicals among cigarette additives most questioned by tobacco opponents include:

- **Megastigmatrienone**: A flavoring that tobacco companies contend is found naturally in grapefruit juice.
- **Dehydromenthofurolactone**: A flavoring that tobacco companies say is found in peppermint.
- **Ethyl furoate**: Found naturally in coffee, kiwi and peanuts.
- **Maltitol**: A sweetener used in chewing gum and diabetic candy.
- **Sclareolide**: A synthetic form of a naturally occurring tobacco element.
- **Ammonia**: A processing aid.
- **Methoprene**: An insecticide that toxicologists say is biodegradable.
- **Other additives**: Yeast, wine, caffeine, beeswax, beta carotene, chocolate, coconut oil.
Ammonia converts nicotine, the addictive agent in tobacco, into a more volatile form, Pankow said. “Ammonia is the thing that helps tobacco companies hook the smoker by providing a means of delivering the nicotine.”

Last October a former tobacco industry employee revealed that secret industry documents indicated that ammonia was added to tobacco to double the impact of nicotine. The Oregon Graduate Institute study confirms the contention that
Tobacco-free Campus

For better health, smoking and use of tobacco products are prohibited everywhere on our property.

September 1, 2012

For a healthier community and cleaner environment, the University of Oregon will be smoke and tobacco-free.

UO's Josh Buehler  U.S. Surgeon General Regina Benjamin
Discussion/Questions?
Nervous System

CNS

PNS

input

output

Systems Level
~99% of all neurons in humans!
CNS ~100 billion interneurons!!
A single nerve cell may have as many as 200,000 inputs!
Figure 45-5  Typical anterior motor neuron, showing presynaptic terminals on the neuronal soma and dendrites. Note also the single axon.
Nerve cell with multiple axons grown by adding a mitogen/neurogen \( \equiv \) nerve growth factor!

Courtesy Fengquan Zhou
UNC Chapel Hill
Sensory nerves especially, come in all shapes & sizes!
LS2 2006 fig 5-1 p 110
Figure 45-4  Block diagram of a general-purpose computer, showing the basic components and their interrelations.
CNS Connections: The Central 7!

- **Fore-**
  - 1. Cerebrum
  - 2. Diencephalon – Hypothalamus + Thalamus

- **Mid-**
  - 3. Midbrain

- **Hind-**
  - 4. Cerebellum
  - 5. Pons
  - 6. Medulla – Brain Stem
  - 7. Spinal Cord
Ice Cream Cone Evolution Analogy

- Brain Stem
  - Medulla
  - Pons

- Cerebellum

- Cerebrum
  - Basal Nuclei
  - Cerebral Cortex

- Diencephalon
  - Hypothalamus
  - Thalamus
Homeostasis is a dynamic balance between the autonomic branches.

- **Parasympathetic**
  - Rest-and-digest: Parasympathetic activity dominates.

- **Sympathetic**
  - Fight-or-flight: Sympathetic activity dominates.

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D Silverthorn 2010
Autonomic Neurotransmitters & Receptors

Cholinergic
- Nicotinic
- Muscarinic

Adrenergic
- $\alpha = \text{Alpha}$
- $\beta = \text{Beta}$

Acetylcholine

Norepinephrine

G&H 2011 p 731-3
**Parasympathetic**

Ach = Acetylcholine

= Nicotinic Receptor

= Muscarinic Receptor

**Sympathetic**

NE = Norepinephrine

= α Receptor (α₁, α₂)

= β Receptor (β₁, β₂)
Nicotine activates both Sympathetic & Parasympathetic post-ganglionic neurons!

Problem?

Like hammering the gas pedal & brake at the same time!!
Nicotine also triggers the release of adrenalin & cortical hormones & causes generalized adrenal disruption!

80% Epinephrine/Adrenaline (E)
20% Norepinephrine (NE)

Output to blood

Adrenals = Paired organs above kidneys

Break for discussion/questions!
VI. **Addiction Medicine: Homeostasis & Applications**

G&H ch 45, 58 & 60 + DLN section B

A. Neurotransmitter balance: Mood/Diseases/Addiction?
B. Synapses, classes, NT release, homeostasis?
   - G&H fig 45-5, 45-6 pp 546-48
C. Neurotransmitters prominent in addiction medicine
   - G&H tab 45-1 p 550, LS2 2006 fig 4-15
D. Brain neurohumoral systems fig 58-2, 58-3 pp 712-13
   - locus ceruleus (NE+), substantia nigra (D/-/+), raphe nuclei (SI-) large cells of RAS (Ach+) + cocaine
E. Limbic system G&H ch 58 p 714-20 fig 58-4 + LS1 & LS2
   1. Hypothalamus headquarters, reward & punishment
      - G&H fig 58-5, fig 58-6 pp 714-6; 11th ed fig 58-8 p 735
Neurotransmitter (NT) Balance: Diseases/Addictions/Moods?

- NT Lack
  - Depression
  - Parkinson’s

Balance

+ NT Excess
  - Serotonin/Norepinephrine
  - Dopamine
  - Euphoria?
  - Suicidal Ideation?
  - Schizophrenia
  - Cocaine Addiction

Continuum
Figure 45-6  Physiologic anatomy of the synapse.
Synapse Animations

http://outreach.mcb.harvard.edu/animations/synaptic.swf

Balance!

http://thebrain.mcgill.ca/flash/i/i_08/i_08_m/i_08_m_dep/i_08_m_dep_isrs.html#3
### Table 45-1 Small-Molecule, Rapidly Acting Transmitters

<table>
<thead>
<tr>
<th>Class I</th>
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<tbody>
<tr>
<td>Acetylcholine</td>
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<table>
<thead>
<tr>
<th>Class II: The Amines</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
</tr>
</tbody>
</table>

**Prominent in reward pathways & chemistry of addiction.**

<table>
<thead>
<tr>
<th>Class III: Amino Acids</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma-aminobutyric acid (GABA)</td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td></td>
</tr>
<tr>
<td>Aspartate</td>
<td></td>
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<table>
<thead>
<tr>
<th>Class IV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitric oxide (NO)</td>
<td></td>
</tr>
</tbody>
</table>
**Locus ceruleus** = “Blue/azur spot”

**Substantia nigra** = “Black substance”

**Raphe nuclei** = “Nut seam/line”

---

**Norepinephrine** = NE

**Dopamine** = D?

**Serotonin** = SI

---

G&H 2011 p 713
Cocaine prevents re-uptake of Dopamine (1\textsuperscript{st} discovery), Norepinephrine (2\textsuperscript{nd}...) & Serotonin (3\textsuperscript{rd}...) & alters the plasticity of all 3 pathways!!!


Nerve cells eg: Ventral Tegmentum (Substantia Nigra) to Nucleus Accumbens (Limbic System)

http://learn.genetics.utah.edu/content/addiction/
4th Pathway Releases Acetylcholine!

Cortical Alertness!

To diencephalon and cerebrum

Substantia nigra (dopamine)

Gigantocellular neurons of reticular formation (acetylcholine)

Locus ceruleus (norepinephrine)

Nuclei of the raphe (serotonin)

Mesencephalon

To cerebellum

Pons

Medulla

To cord

G&H 2011 p 713
Reticular Activating System (RAS)
Overall Cortical Alertness!

Radiations to cerebral cortex

Visual impulses

Reticular formation

Pons

Auditory impulses

Spinal cord

Descending motor tracts

Ascending sensory tracts

Cerebellum

Wake up!
Back row!
Hypothalamus
< 1% of Brain Mass
Hormone Master Controller
100s of Functions!

Good Things Come in Small Packages!
POSTERIOR
Dorsomedial nucleus
(GI stimulation)

Posterior hypothalamus
(Increased blood pressure)
(Pupillary dilation)
(Shivering)

Perifornical nucleus
(Hunger)
(Increased blood pressure)
(Rage)

VENTROMEDIAL NUCLEUS
(Satiety)
(Neuroendocrine control)

Mamillary body
(Feeding reflexes)

Arcuate nucleus and periventricular zone
(Neuroendocrine control)

LATERAL HYPOTHALAMIC AREA (not shown)
(Thirst and hunger)

ANTERIOR
Paraventricular nucleus
(Oxytocin release)
(Water conservation)

Medial preoptic area
(Bladder contraction)
(Decreased heart rate)
(Decreased blood pressure)

Posterior preoptic and anterior hypothalamic areas
(Body temperature regulation)
(Panting)
(Sweating)
(Thyrotropin inhibition)

Optic chiasm (Optic nerve)

Supraoptic nucleus
(Vasopressin release)

Infundibulum

- = Reward
- = Punishment

midbrain
FIGURE 5-18

Limbic system
This partially transparent view of the brain reveals the structures composing the limbic system.
Memory
Emotion
Motivation
Sociosexual Behavior

Limbic system
Enraged BI 358 student post Quiz 1?

Really, Jose Delgado, Yale University!
Reward Centers = Hypothalamus, lateral & ventromedial n.

Punishment Centers = Mesencephalon, central gray area, Hypothalamus & Thalamus, periventricular zones

Animal will self-stimulate $\geq 5000x/hr$ if electrodes planted in reward center!


G&H 11th ed only p 735