The Nervous System and Neurotransmission

PHRM 203
Allison Beale
Basic NS Anatomy

CNS
- Brain
- Spinal cord

PNS
- Autonomic Involuntary
  - Parasympathetic
    "Rest & digest"
  - Sympathetic
    "Fight or flight"
- Somatic Voluntary
  - Motor neurons
    Skeletal Muscle

Maybe better:
Sex, sandwiches and sleep
The Major CNS Areas

- Cerebrum (four lobes)
- Diencephalon
  - Thalamus
  - Hypothalamus
- Brainstem
  - Midbrain
  - Pons
  - Medulla
- Cerebellum
- Spinal cord

[Diagram of the brain with labeled areas]

www.medem.com/MEDEM/images/ama/ama_brain_stroke_lev20_thebraineffectsstroke_01.gif
Cerebral lobes
Cognition, planning, execution, recognition

- **FRONTAL LOBE**
  - Higher mental functions
    - Planning, judgment, emotional expression, creativity, inhibition
- **TEMPORAL LOBE**
  - Association area
    - Short term memory
    - Emotion
    - Equilibrium
- **OCCIPITAL LOBE**
- **PARIETAL LOBE**
How homeostasis is maintained

- **Thalamus**
  - Relays info to cerebral cortex from other areas of the brain

- **Hypothalamus**
  - Controls homeostatic and reproductive functions
    - Autonomic nervous system connections
    - Cortical connections for behavior, emotion
    - Connected to pituitary gland
      - Pituitary gland = critical endocrine gland
      - Secretes hormones

Pituitary gland

Thalamus
The Hindbrain parts

• Cerebellum
  – Overlies the dorsal aspect of the brainstem
  – Coordination and planning of movement
  – Learning motor and cognitive tasks

• Brainstem
The Brainstem parts

- **Midbrain**
  - Continuous with hypothalamus and thalamus
  - Motor, visual & auditory system relays
  - Source of CN III, IV

- **Pons ("bridge")**
  - Connects medulla to cortex
  - Source of CN V, VI, VII, VIII

- **Medulla oblongata**
  - Controls autonomic function
  - Source of CN IX, X, XII
  - Relays motor signals from brain to spinal cord

- **Reticular formation**
  - Network of neuronsoverlaying brainstem
  - Critical for consciousness
Brainstem

• Most Cranial nerves start and end in the brainstem in cranial nerve nuclei
  – Motor nuclei medial
  – Sensory nuclei lateral
  – Rostral-caudal order pretty much matches innervated anatomy

1. Olfactory
2. Optic
3. Oculomotor
4. Trochlear
5. Trigeminal
6. Abducens
7. Facial
8. Vestibulocochlear (Auditory)
9. Glossopharyngeal
10. Vagus
11. Spinal Accessory
12. Hypoglossal
The Spinal Cord anatomy

• Starts in brainstem, at medullary-spinal junction
• Peripheral nerves (spinal) arise from the SC’s 31 pairs of spinal nerves
  – 8 cervical
  – 12 thoracic
  – 5 lumbar
  – 5 sacral
  – 1 coccygeal

Cranial nerves exit the CNS through the cranium (skull).

Spinal nerves are the nerves that exit the spinal cord (the CNS) into the periphery. Spinal nerves may be autonomic or somatic.
Basic CNS Principles

• Neurons synapse on other neurons
  – **Excitatory** or **inhibitory**
  – Many different types of neurons may synapse on another
  – Neurons may secrete several neurotransmitters
  – Neurons may have receptors for several neurotransmitters
• “Pacemaker” or basal activity
• Fast versus slow neurotransmitters
  – Fast - GABA, glutamate, **ACh** on ion channels
  – Slow - NE, 5-HT, **ACh** on G-protein coupled receptors
• **Modulation, protection, feeding**
  – Glial cells
• “Insulation”
  – Oligodendrocytes (CNS) and Schwann cells (PNS)
A single brainstem neuron (secreting NE) may synapse on 100,000 cortical neurons

Note: Locus coeruleus (blue location, LC) is a NE nucleus in the pons whose fibers innervate the hypothalamus, cortex, cerebellum, spinal cord, other areas of the brainstem, thalamic relay nuclei, and the amygdala. It receives afferent signals from the hypothalamus, amygdala and spinal cord. NE is primarily an excitatory NT, and the efferents from the LC mediate arousal and memory functions. They allow integration of environmental, emotional and cognitive signals with autonomic (sympathetic) output and are almost completely silenced during REM sleep.
The Peripheral Nervous System

- **Autonomic**
  - **Parasympathetic**
    - "Rest & digest"
    - Cholinergic Nicotinic
      - ACh Muscarinic
  - **Sympathetic**
    - "Fight or flight"
    - Cholinergic Nicotinic
      - NE Adrenergic
  - **Motor neurons**
    - Cholinergic Nicotinic

- **Somatic Voluntary**

- **Enteric**
  - NANC
    - Neuropeptide Y
    - Vasoactive Intestinal Peptide
    - Enkephalin
    - Substance P
    - 5-HT
    - ATP or Adenosine
    - Nitric Oxide (NO)

- **At Ganglion**
  - At End organ
Somatic Nervous System

- Somatic motor neurons
  - Long axon
  - Myelinated
  - Cholinergic with nicotinic LGIC receptor at the effector
    - Neuromuscular Junction (NMJ)
  - Effector organ = skeletal muscle
  - Under conscious control

There are many forms of the nicotinic receptor. The CNS version differs from the somatic one.
Autonomic Nervous System

• Homeostasis
  – 1\textsuperscript{o} parasympathetic

• Emergency Response
  – 1\textsuperscript{o} sympathetic

• Act together to modulate
  – Respiration
  – Circulation
  – Digestion
  – Metabolism & Excretion
  – $B_t$ & Sweating
  – Exocrine and some Endocrine gland function

Generally, the “basal tone” of an organ is determined by the parasympathetic enervation

SNS stimulated by “E” situations:
- EMERGENCY
- Embarrassment
- Excitement
- Exercise
Afferent Neurons

- Both Autonomic and Somatic
  - Sensory - return info to CNS, may be reflex (spinal).
    - Long axon
    - Various transmitters
  - Stimulated by many things
    - Temperature
    - Pressure
    - Chemicals (e.g., oxygen tension or carbon dioxide)
    - Tension or stretch

Sensory neurons covered in “Pain & Inflammation”

Efferent neurons are “motor” neurons and may be Cranial nerves, or autonomic or somatic spinal nerves.
Chemical signaling mechanisms

NTs

Autocoids

Hormones

(A) Synaptic

Paracrine

Endocrine

(B)

Signaling cell

Signal

Receptor

Target molecule

Response

Activated receptors

Target molecules

Capillary

Target molecules in distant cells

Blood flow

Neuroscience, Fourth Edition

Edited by Dale Purves, George J. Augustine, David Fitzpatrick, William C. Hall, Anthony-Samuel LaMantia, James O. McNamara, and Leonard E. White

Published by Sinauer, 2008
Types of Ion channels
1. Passive
2. Voltage-gated
3. Ligand-gated
4. Mechanically-gated

Ions: Na⁺, K⁺, Ca²⁺, Cl⁻, protein anions (A⁻)

4 Categories of Cell Receptors

Neuroscience, Fourth Edition
Edited by Dale Purves, George J. Augustine, David Fitzpatrick, William C. Hall, Anthony-Samuel LaMantia, James O. McNamara, and Leonard E. White
Published by Sinauer, 2008

E.g. Tyrosine Kinase, Serine/Threonine Protein Kinase, & Guanylate cyclase

“Nuclear” Receptors detect steroids & thyroid hormone, Etc. Control development, metabolism, & homeostasis.

www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=.04Y-VIL8-_xuO10VyKZVDs9JT1o-qnEKGWUPwU
Small molecule NTs include:
- Biogenic amines (e.g., ACh, NE, DA…),
- Some Peptides (see next slide),
- Purines (e.g., ATP…),
- Amino acids (e.g., GABA, glycine…)
Peptide NTs include:

- Vasopressin
- Somatostatin
- Neurotensin
- Leutinizing hormone
- Insulin
- Substance P

Are also hormones
Neurons may release more than one type of transmitter.
Neuropeptides stored with NTs

<table>
<thead>
<tr>
<th>NT</th>
<th>Neuropeptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh</td>
<td>Galanin, Substance P and VIP</td>
</tr>
<tr>
<td>DA</td>
<td>Cholesystokinin, Neurotensin</td>
</tr>
<tr>
<td>EPI</td>
<td>Neuropeptide Y, Neurotensin</td>
</tr>
<tr>
<td>GABA</td>
<td>Somatostatin, Cholesystokinin, Neuropeptide Y</td>
</tr>
<tr>
<td>NE</td>
<td>Enkephalin, Galanin, Neuropeptide Y</td>
</tr>
<tr>
<td>5-HT</td>
<td>Enkephalin, TRH, Substance P</td>
</tr>
</tbody>
</table>

ATP almost always present, too
FATE OF NT’s AFTER RELEASE:

1. **Reuptake**
   - Serotonin
   - Dopamine
   - NE

2. **Breakdown**
   - ACh by AChE
   - Choline is taken back up by neuron and reused.

3. **Diffusion** or **uptake** by Glial cells
   - Neuroactive peptides

www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=0T9hWUVX1htY3zEx1nXgs5H-f4891nocX-XwOo
Receptors for Neurotransmitters

In the Peripheral Nervous System (Autonomic portion)

- **Adrenergic (NE)**
  - Sympathetic
    - $\alpha_1$ & $\beta_1$ ⊕
    - $\alpha_2$ & $\beta_2$ ⊗
    - $\beta_3$ - fat

- **Cholinergic (ACh)**
  - Parasympathetic, Sympathetic or Somatic
    - ⊕ or ⊗
    - Nicotinic (ganglia & NMJ)
    - Muscarinic (mostly parasympathetic effectors)

⊕ = stimulate; ⊗ = block

http://microvet.arizona.edu/Courses/VSC401/autonomicNervous.html
Select Neurotransmitters

- **ACh**
  - Muscarinic or Nicotinic
- **GABA**
  - A or B or C
- **Glutamate, aspartate**
  - NMDA, AMPA, Kainate (Ion)
  - mGluR (metabotropic)
  - Excitatory
- **Glycine, taurine**
  - GlyR
  - Inhibitory
- **ATP, ADP, Adenine, UTP, UDP**
  - at least 12 “P2Y” (GPCR) receptors, also P2X (ion)
- **DA**
  - 1-5
- **NE**
  - $\alpha_{1-2}$ and $\beta_{1-2}$ and $\beta_3$
- **5-HT**
  - 1-4
- **Histamine**
  - 1-3
- **Opioid peptides**
  - $\mu$, $\delta$, $\kappa$
- **Calcitonin gene related peptide (CGRP)**
- **Tachykinins (Neurokinins A&B, Substance P, etc.)**
  - NK1-3

**Amino acids**

**Purines**

**Biogenic amines**

**Peptides**

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Background
• **Receptors**
  - Muscarinic (GPCR)
  - Nicotinic (LGIC)
  - ACh is generally *excitatory*

• **Central**
  - ACh important *neuromodulator* for neurons related to learning and memory as well as arousal and reward functions
  - Alzheimer’s memory loss may be due to loss of ACh neurons
    – *Donepezil* (Aricept) = centrally acting AntiAChE agent

• **Peripheral**
  - Autonomic ganglia (nAChR) and PSNS effectors (mAChR)
    – *Bethanechol* (muscarinic agonist) and *Atropine* (muscarinic antagonist)
  - Somatic NMJ – triggers skeletal muscle contraction
    – Myasthenia gravis - Ab made to & destroy ACh receptors
      » AntiAChE agents (*neostigmine*) improve muscle tone
    – Paralytic agents for surgery
      » Neuromuscular blocking agents (*pancuronium* and *succinylcholine*)
• Amino acids
  – Most **inhibitory** CNS synapses use GABA or glycine⁰.

  – **GABA - A, B or C**
    • A & C are **inhibitory** LGICs
    • B are **excitatory** GPCRs
    • - **GABA_A** allosteric agonists
      – Baclofen, benzodiazepines, barbiturates, alcohol, neuroactive steroids, inhaled anesthetics, propofol, etomidate, niacin

  – **Glycine, taurine - inhibitory**
    • LGIC, very widespread

⁰glycine more important in brainstem & spinal cord
Glutamate/aspartate

- Amino acids
  - Glutamate, aspartate - excitatory
    - ~ 1/2 of all CNS synapses use glutamate
    - NMDA*, AMPA*, Kainate*, and mGluR
      - NMDA receptor
        » Unique in that it's both ligand-gated and voltage-gated
        » Requires both glutamate and glycine (or serine)
        » Antagonists include Dextromethorphan (anti-tussive), ketamine (dissociative), memantine (Alzheimer’s) and tramadol (analgesic)
  - ↑↑[glutamate] kills neurons!
    - Glial cells take up glutamate
      » They make glutamine that is transferred back to neuron.
      » Neuron synthesizes glutamate from glutamine

Autoimmune Ab
To AMPA, then see Epilepsy
To NMDA, then see Lupus, epilepsy
To mGluR, then see ataxia

Insufficient Glutamate at NMDA receptors implicated in schizophrenia
Dopamine - DA

- All GPCR
  - 2 families
    - $D_1$-like ($D_1$ & $D_5$)
    - $D_2$-like ($D_2$, $D_3$, $D_4$)

Two major areas of interest for us:
1. Initiation & coordination of movement
   - Parkinson’s disease
2. Motivation, reward, reinforcement pathways
   - Drug addiction
   - Depression, schizophrenia, ADHD
     - Elevated DA levels
     - Antipsychotics block DA receptors ($D_2$) - as well as many other types of receptors

- Brain ($D_1, 2, 3, 4, 5$)
  - Hypothalamus/Pituitary ($D_2$)
    - Inhibits prolactin secretion
  - Midbrain & striatum ($D_{1,2}$)
    - Movement, pain processing
  - Ventral tegmental area/amygdala ($D_{1,2}$)
    - Reward, pleasure, addiction
  - CTZ ($D_{1,2}$)
    - Vomiting, nausea
  - Frontal lobes ($D_{1,2}$)
    - Memory, attention, problem solving

- CV ($D_1, 2, 4, 5$) & Heart ($D_4$)
  - Increased BP & HR

- Kidneys ($D_{1,2}$)
  - Increases $H_2O$ and $Na^+$ loss
  - Vasodilation
  - Stimulation of PGE2 synthesis

Drug-induced movement disorders, called Extrapyramidal symptoms (EPS) are due to decreased DA availability.
• NE - $\alpha_{1-2}$ and $\beta_{1-2}$
  – All GPCR
  – Sleep/wakefulness, attention, appetite, mood, autonomic (sympathetic) functions
  – Agonists
    • Peripheral – Phenylephrine ($\alpha_{1-2}$ agonist)
    • CNS – Clonidine ($\alpha_{2}$ agonist), Amphetamine targets the NE Transporter (NET) preventing reuptake
  – Antagonists
    • Peripheral – Doxazosin ($\alpha_{1}$ blocker), Propranolol ($\beta_{1-2}$ blocker), Metoprolol ($\beta_{1}$ blocker)
    • CNS - Reserpine
Serotonin – 5-HT

• 5-HT, 5-hydroxytryptamine, Serotonin
  – Mood, anxiety, appetite, autonomic modulation, pain perception, sleep/wakefulness, nausea, vomiting, sexual behavior, addiction, memory, learning, body temperature,
  – Receptors are LGIC (excitatory postsynaptic) only at 5-HT₃, otherwise all GPCR
  – Agonists
    • Triptans (migraine), Buspirone (anxiety), SSRIs (depression)
  – Antagonists
    • Clozapine (atypical antipsychotic), Ondansetron (antiemetic)

Serotonin receptors are common on GIT smooth muscle (5-HT₃), on platelets and in the CNS
Histamine

- **All GPCR**
  - $H_1$
    - Smooth muscle & CNS
      - Vasodilation, allergy, motion sickness
      - Diphenhydramine
  - $H_2$
    - Mostly gut
      - Stimulate gastric acid secretion
      - Ranitidine
  - $H_3$
    - Mostly CNS – blocks NE, ACh and 5-HT release
  - $H_4$
    - Basophils, viscera - WBC chemotaxis
Peptide Neurotransmitters

• Peptides loosely grouped into 4 categories:

  1. Brain/gut peptides ★
     • Tachykinins - 1-3
       – Substance P – Pain Perception
     • Calcitonin gene related peptide (CGRP)
     • Appetite-regulating peptides - ghrelin, neuropeptide-Y, orexin, leptin

  2. Opioids (often co-located with GABA and 5-HT in the CNS) ★
     • μ, δ, κ, - e.g., endorphins, enkephalins and dynorphins

  3. Pituitary peptides ★
     • E.g., Melanocyte-stimulating hormone

  4. Hypothalamic releasing hormones ★
     • E.g., Adrenocorticotropic
Other Neurotransmitters

– Gases - NO \((\text{Guanlylate cyclase})\), CO \((\text{heme, mGluR})\)

– Endocannabinoids ★

– Purines - adenosine, ATP, GTP, etc.

  • All synaptic vesicles contain ATP

  • Receptors widely distributed \((\text{P2Y}^\bullet, \text{P2X}^*)\)

    – Xanthines (caffeine & theophylline) block adenosine receptors

    – P2Y\(_2\) - drug target for Cystic Fibrosis

    – P2Y\(_{11}\) - 20% of whites have type predisposing to MI

    – P2Y\(_{12}\) - drug target for clopidogrel (Plavix)

Adenosine levels build through the day leading to sleepiness. Caffeine blocks adenosine receptors in the CNS.

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Background
Drugs Affecting Transmission

• Activate postsynaptic receptors (agonists)
  – Bethanechol - stimulate muscarinic-type receptors
  – Nicotine - stimulate nicotinic-type receptors
  – Albuterol, epinephrine - stimulate adrenergic receptors

• Block postsynaptic receptors (antagonists)
  – Atropine - blocks muscarinic receptors
  – Pancuronium - blocks nicotinic NMJ receptors
  – Phentolamine - blocks \( \alpha \)-adrenergic receptors
  – Propranolol - blocks \( \beta \)-adrenergic receptors
Drugs Affecting Transmission

• Inhibiting neurotransmitter synthesis
  – Hemicholinium - inhibits ACh synthesis by \( \times \) choline uptake
  – Metyrosine - inhibits catecholamine (NE, E, DA) synthesis

• Prevent neurotransmitter storage in vesicles
  – Vesamicol - causes a non-competitive and reversible block of the intracellular transporter responsible for carrying newly synthesized ACh into storage vesicles in the pre-synaptic nerve terminal
  – Reserpine - inhibits intracellular monoamine transporter responsible for carrying NE, E, DA into vesicles. MAO degrades the free monoamines, leading to catecholamine depletion.
Drugs Affecting Transmission

• Block ion channel or pump
  – $\text{Na}^+$/K$^+$ ATPase
    • Digoxin
  – Voltage-gated $\text{Na}^+$ channel
    • Local anesthetics, saxitoxin
  – $\text{Ca}^{++}$ channels
    • Amlodipine, verapamil, diltiazem
      – (calcium channel blockers, CCB)
Drugs Affecting Transmission

- Inhibit release of transmitter
  - Botulinum toxin - taken into axon terminal where it binds to SNARE proteins required for exocytosis.
  - Bretylium - blocks NE release.

BoNT = botulinum toxin
TeNT = Tetanus toxin
Both bind to SNARE proteins, interfering with exocytosis
Drugs Affecting Transmission

• Stimulate release of transmitter
  - **Black widow venom** ($\alpha$ Latrotoxin) - large protein toxins that bind to a G-Protein coupled receptor, opening a Ca++ channel “pore” allowing ACh to flood the synapse.
  - **Amphetamine** - affects all catecholamines, but not at all receptors. It increases the release of transmitter both directly and by inverting the action of the transmitter reuptake system.

Drugs Affecting Transmission

- Inhibit reuptake of neurotransmitter
  - Antidepressants (SSRI’s) and cocaine
- Inhibit metabolism of neurotransmitter
  - Anti-Cholinesterase agents
  - MAO inhibitors

Cocaine Mechanism

www.cnsforum.com/imagebank/item/MAO_cocaine/default.aspx
MAO inhibition by selegiline (Eldepryl), a drug used to treat Parkinson’s disease, depression and senile dementia.

www.pharmainfo.net/reviews/parkinsons-disease