Nervous System Basics

Nervous system parts, neurotransmitters & receptors

This lecture applies dynamics concepts…

We will quickly survey CNS anatomy and be introduced to the peripheral nervous system in preparation for the 1st drug lectures coming up. Most importantly, we will start learning the neurotransmitters affected by many, many drugs.

"There's someone in my head, but it's not me"

Chapter 1, *Incognito* by David Eagleman.

We all hear voices in our head. We argue and make deals with ourselves all the time. When we dream, we seem to hear others speak. So, why is it crazy when someone with a mental illness hears voices? And why does an antipsychotic help?

To try to understand how the drugs we will be discussing in the Nervous System Lecture Series affect the nervous system, you have to have a basic understanding, not only of the wiring (the anatomy), but also the interactions (the physiology) and the means by which the cells communicate (the neurotransmitters, autocoids and receptors).

The drugs will, by and large, be altering communication between cells. We will be looking mostly at neurons, but also other cells, such as certain white blood cells.

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Select Neurotransmitters (NT)

ACh	Acetylcholine. Found in all parts of nervous system.
DA	Dopamine – movement & motivation!
NE	Norepinephrine – Sympathetic NT, in CNS (sleep, mood, memory)
5-HT	Serotonin – in CNS (sleep, mood, vomiting), in GIT peristalsis!, in platelets (clotting)
GABA	Gamma amino butyric acid – inhibitory NT in CNS

"I must have a prodigious quantity of mind; it takes me as much as a week sometimes to make it up." Mark Twain

Image: National Library of Medicine

LEFT: Maxfield Parrish (1870-1966) poster for a chewing gum aid to stop smoking. This is one of many Patent Medicines that carried imagery of "Nobel Warriors," often American Indians. The imagery played to the public's innate desire to believe that native peoples somehow "have the answer" because they live "closer to the earth."

Modern advertising plays upon stereotypes as well. Look at a few ads, do you see themes having nothing to do with the medication? Also, do you see the long, technical information segment that is a part of all prescription drug marketing? Do you see any technical information on this old ad?

Image: National Library of Medicine

Patent Medicines in the era before FDA


Revised Retail Prices of

COCA WINE.

(ARMBRECHTS)

FOR FATIGUE OF MIND AND BODY.

And Consequent Affections, as

NEURALGIA,
SLEEPLESSNESS,
DESPONDENCY,

etc., etc.

TWELVE BOTTLES, 48s. TWENTY-FOUR BOTTLES, 94s.

Carriage Paid England and Wales, and Half for Ireland and Scotland. Remittance with Order.

Professional Price: 40s. per dozen; 21s. half-dozen.

(Carriage Paid as above.)

ARMBRECHT, NELSON & CO.,

Temporary Address: 2, Duke St., Grosvenor Square, London, W.

Telegraphic Address: "ARMBRECHT, LONDON."

A Sample Bottle free to Medical Men and Clergymen on receipt of professional card.

Patent medicine label from London, England, 1889. Image from the National Library of Medicine. http://ihm.nlm.nih.gov

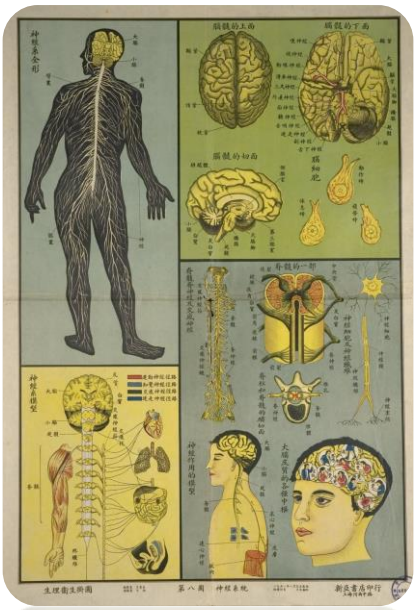
In the 1800's there were an enormous variety of Patent medicines, some of which continue to be marketed today (the sodas no longer make medicinal claims).

- Coca cola (contained coca),7 Up (contained lithium), others: Dr Pepper, Hires Root Beer, Angostura Bitters
- Bromo-Seltzer
- Luden's Cough Drops
- Teething syrups containing laudanum
- Cannabis plasters to cure corns

Because of the false claims and toxic contents of many patent medicines, the **Pure Food and Drug Act** was passed in 1906, which did not ban their sale; it just required they be truthfully labeled.

Autocoids or Neurotransmitters?

Histamine and serotonin both act as neurotransmitters (chemicals released by neurons to communicate with other cells) as well as autocoids (chemicals released by a cell to communicate with nearby cells).



Chinese Public Health Poster, National Library of Medicine

Histamine

Histamine receptors in the CNS originate almost exclusively in one part of the hypothalamus and radiate to all the other brain areas[1]. They modulate the activity of other neurons, including ACh, GABA, DA and NE among others. Some important modulated functions include wakefulness, arousal; anxiety; activation of the sympathetic nervous system; stress-related hormone release from the pituitary; and suppression of appetite and pain perception[1,2]. Histamine is also important in motion sickness.

The H3 receptor found in the CNS is recognized as a drug target for neuropathic pain, sleep-wake disorders, and cognitive impairment associated with ADHD, schizophrenia, Alzheimer's and Parkinson's[3]. But there are not any drugs currently on the market for these indications, they are all still in clinical trials[4].

In the PNS, histamine has several important roles in allergic responses and inflammation, nociception, vasodilation and activation of white blood cells. In the stomach, it stimulates gastric acid secretion.

1. **The physiology of brain histamine**. Brown RE, Stevens DR, Haas HL. Prog Neurobiol 2001 Apr;63©:637-72
2. **Histamine in Neurotransmission and Brain Diseases**. Nuutinen S and Panula P. Adv Exp Med Biol 2010; 709:95-107.
3. **The histamine H3 receptor: an attractive target for the treatment of cognitive disorders**. Esbenshade TA, et. al. Br J Pharmacol. 2008 Jul;154(6):1166-81.
4. **Histamine pharmacology and new CNS drug targets**. Tiligada E, Kyriakidis K, Chazot PL, and Passani MB. CNS Neurosci Ther. 2011 Dec;17(6):620-8.

Serotonin

In the CNS, 5-HT is involved in mood, anxiety, pain perception, wakefulness, nausea, vomiting, sexual behavior, motivation, memory, learning, body temperature and autonomic modulation.

In the periphery, its role is also complex. In the enteric nervous system, enterocromaffin cells in the gastrointestinal tract produce 5-HT to stimulate GIT smooth muscle and cause peristalsis. Excess 5-HT is absorbed into the blood where it is taken up and stored by platelets. The platelets will release 5-HT when activated to trigger activation of additional platelets in the formation of a clot. Any residual 5-HT left by the platelets goes to the brain and triggers nausea and vomiting by stimulating receptors on the Chemoreceptor Trigger Zone (CTZ).

Serotonin can trigger vasoconstriction. There are receptors in the vasculature of the brain that when activated, correlate with migraine headache relief. **Sumatriptan** is an agonist at these receptors and works to relieve migraine, but not as a prophylactic.

How do drugs change how cells communicate? And how does this treat disease?

As we learned in the Introduction lectures, drugs interact with receptors by either mimicking or blocking the activity of a naturally occurring chemical. At least MOST drugs work this way.

In this section we are going to apply this concept to a number of drugs, interacting with many different receptors.

We need first to recall that the receptors for neurotransmitters will fall into two basic categories for us; they will either be **GPCR**, like the ACh Muscarinic, the NE Adrenergic, the DA and most of the 5-HT receptors, or will be **LGIC** like the ACh Nicotinic and the 5-HT3 receptors. We will also have to recall the two basic types of interaction: a drug may be an **agonist** and mimic activity of the natural ligand, or it may be an **antagonist** and block the activity of the natural ligand.

We will look at drugs related to ACh, NE, DA, 5-HT and GABA, as well as Histamine, Opioids and Purines. Let's get started.

Acetylcholine

In the CNS, ACh is used mainly to modulate the activity of either NE or DA systems. Therefore, we find ACh having effects on learning, memory, arousal (as in waking up and staying awake) as well as reward functions. ACh triggers and maintains REM sleep.

Anticholinergic drugs cause effects that fall into the categories of the mnemonic: red as a beet (vasodilation), hot as a poker (no sweating), dry as a bone (no secretions), fast as a hart (tachycardia), mad as a hatter (delirium, hallucinations), blind as a bat (mydriasis, dilated pupils). Many of these effects are due to blocking the Vagus nerve and are therefore parasympatholytic effects, but the delirium (mad as a hatter) is a CNS effect. Anticholinergics can also cause problems with memory and a lack of CNS ACh is related to Alzheimer's disease.

The early stages of Alzheimer's may be treated with a drug (**Donepezil**, for instance) that elevates CNS ACh levels.

The archetypal anticholinergic, though, is **Atropine**, a "Belladonna" alkaloid originally isolated from the deadly nightshade plant. The term "belladonna" (literally, "pretty woman") comes from the fact that women would put drops of the alkaloid into their eyes to dilate their pupils and appear more sexually attractive (your pupils dilate when you see someone attractive). You may have had atropine eye drops yourself, when having an eye exam (and become "blind as a bat").

GPCR = G-Protein Coupled Receptor LGIC = Ligand-gated Ion Channel

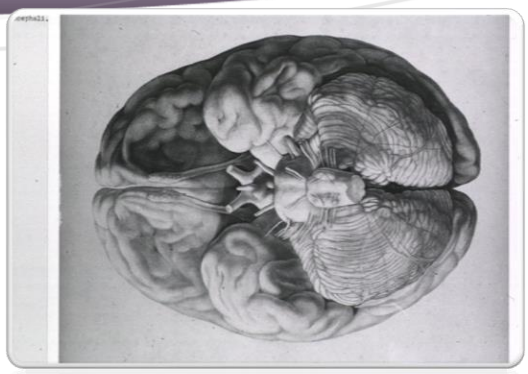


Image of the base of the brain by Samuel Thomas von Soemmerring, 1755-1830, from the National Library of Medicine

Medulla oblongata

The medulla oblongata is a part of the brainstem. It is at the junction of the brain and spinal cord. It is also the region of the brain important for the source of most of the outflowing neurons for the **Autonomic Nervous System**.

When you hear: ventral surface of the medulla (VSM), you should think Autonomic Outflow.

The Vagus nerve (Cranial nerve X) originates in the medulla along with virtually all of the many Sympathetic neurons. The Vagus is the principal Parasympathetic nerve that we cover.

This means that the medulla is critical for homeostasis, since that is the function of the autonomic nervous system.

Autonomic neurons are themselves enervated by sensory neurons from the periphery, other autonomic neurons, and cortical neurons (through the thalamus, a relay section of the brain). Hormones, released from a number of glands, including the hypothalamus and pituitary, also modulate ANS functions.

(continued)

Norepinephrine

In the CNS, NE is important, along with Serotonin, in wakefulness, attention, appetite and mood. It is also involved in Sympathetic Nervous System (SNS) feed back.

Along with Serotonin, NE balances out ACh in modulating other neurons.

The most common adrenergic receptors in the CNS are alpha 2, which tend to have the opposite effect of alpha 1 receptors. **Clonidine** is an alpha 2 agonist active in the CNS. It acts to lower blood pressure.

In the Peripheral Nervous System (PNS), NE is the neurotransmitter for the SNS. This aspect will be covered in another lecture.

Dopamine

Dopamine is vastly more important in the CNS than in the PNS where it really is only present in very small amounts. But, it is the most common catecholamine in the CNS[1]. In the CNS, DA is critical in two very fundamental brain activities: movement and motivation. These two functions are considered to be very ancient activities of the brain. But these are not the conscious aspects of "I shall move" or the behavior of seeking something you "want." It is the brain activity BEHIND those events.

DA is also important in a few other key areas:

- It is the controlling factor that inhibits the secretion of the hormone Prolactin;
- There are DA receptors on the Chemoreceptor Trigger Zone (CTZ) which when activated will trigger nausea and vomiting;
- There are DA receptors in the kidneys that trigger vasodilation and the synthesis of prostaglandins by the cells of the macula densa. This will become important as one step in the pathway for renin secretion, an enzyme produced by the kidney to produce Angiotensin, a critical chemical the body uses to raise blood pressure.

Patients with schizophrenia and depression often have elevated DA levels, so early Antipsychotics hinged on an ability to block DA2 receptors. Because of this, the typical (old) antipsychotics have a number of serious side effects, including sexual dysfunction due to the elevated levels of prolactin they cause! They also often cause a condition called EPS, or Extrapyramidal Symptoms, that are movement disorders similar to Parkinson's, a disease caused by the loss of DA neurons in the CNS.

Treating Parkinson's with drugs that are DA agonists present their own challenges. Many of these drugs cause problems in reward-seeking behavior (patients become gamblers, sex addicts…). They can also cause hallucinations (doesn't that sound like psychosis?).

Opioid receptors

Opioids modulate pain perception, nausea and vomiting, respiration rate and feelings of wellbeing and addiction[2].

Purine receptors

In the CNS, purine receptors initiate and maintain sleep, hence why the caffeine in your morning beverage wakes you up (caffeine blocks purine receptors). Purines also modulate the activity of most neurons in the CNS[3].

1. **Structure and function of dopamine receptors**. Vallone, et.al. Neurosci Biobehav Rev 2000 Jan;24(1):125-32.

2. **Current research on opioid receptor function**. Feng et. al., Curr Drug Targets 2012 Feb;13(2):230-46.

3. **Receptors for Purines and Pyrimidines**. Ralevic and Burnstock. ASPET Pharm Rev 1998 Sep;50(3):413-492.

We know a lot, but we really know almost nothing about how the brain actually *works*.

When we look at brain activity by hooking people up to electrodes, or running them through any of a nearly a dozen different types of brain imaging devices, it is like looking at a star through a portable telescope. Yes, you can see the star better, but you still can't see its surface or even if it has planets in orbit. Imaging falls into two basic types: structural to diagnose large scale injuries and diseases (like tumors) and functional used to examine metabolism and relatively large-scale cellular activity.

Tracking how and where drugs exert their actions in the brain at the Lexington Hospital, Addiction Research Center. Image from the US National Library of Medicine

Homework and Exercises

1. Read the "START HERE" announcement in Laulima for updates and instructions.
2. Read Chapter 21 **CNS Overview** in Adams & Urban, PHARMACOLOGY Connections to Nursing Practice.
3. Review the Powerpoints and listen to the audio from the face-to-face lecture. You may opt to watch the appropriate videos for the Nervous System Basics lecture. Review any handouts available for this lecture in the *Course Index*.
4. Complete the SLO Practice Set in Tasks, Tests and Surveys.
5. Use "Chat," "Discussions and Private Messages" or the lecture "Forum" to ask questions and find answers or assistance.
6. Complete the online quiz in Laulima Tasks, Tests and Surveys.

If you have any questions, email me at abeale@hawaii.edu