How Opioids Work on the Brain

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Overview:
• Brief review of the current opioid epidemic
• Basic review of neuroanatomy, with a focus on key brain structures affected by opioids
• Discussion on how opioids are absorbed by the body, used by the brain, and eliminated from the body

Human Side

Motor Vehicle Accidents

U.S. population: ~330 million
How many people do you think die in a car accident in the U.S. each year?

Figure 1. National Drug-Involved Overdose Deaths*, Number Among All Ages, by Gender, 1999-2021

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021
Overdose Deaths vs. Homicide

Overdose = ~107,000
Homicide = ~26,000

Majority of Overdose Deaths Involve Opioids

Opioids
No opioids

25%
75%

Opioid Deaths in U.S

Pre-Covid (2019)
2021

Overdose Deaths NH

Year | State Ranking | Rate per 100,000
--- | --- | ---
2014 | 3rd most | 10
2015 | 2nd most | 20
2016 | 3rd most | 30
2017 | 5th most | 40
2018 | 6th most | 50
2019 | 9th most | 60
2020 | 22nd | 70
2021 | 23rd | 80

Lives Lost

Pre-Covid (2019)
2021

Number of Overdose Death in NH by Year

Types of Opioids Causing these Deaths

Opioids Originally Came from the Poppy Plant
Opium was listed in the Ebers Papyrus, which was written about 3,500 years ago in ancient Egypt.

In the 1800’s, opium became a major recreational drug in Europe and the United States. Available by mail order.

The discovery of morphine in 1803 as the principal active ingredient in opium revolutionized medical treatment of pain and chronic diseases.

Prior to the 1900’s opioids were widely available and were not regulated in the U.S.

In 1906 the Pure Food and Drug Act was passed, which stated that addictive drugs must be accurately listed on the product’s label.

In 1914 the Harrison Act was passed, which regulated and taxed the opiates and products made from coca leaves.

The Comprehensive Drug Abuse Prevention and Control Act of 1970, set up the five schedules of drugs that we still use today.

A few common opioids include:
- Codeine
- Fentanyl
- Heroin
- Hydrocodone (Vicodin)
- Morphine
- Oxycodone (OxyContin, Percocet)
- Subutex
- Tramadol

The Comprehensive Drug Abuse and Prevention Act of 1970, set up the five schedules of controlled substances we use today. Importantly, drug enforcement shifted from the Treasury Department to the Justice Department.

- Schedule I: Heroin
- Schedule II: Vicodin
- Schedule III: Subutex
- Schedule IV: Tramadol
- Schedule V: Low doses of codeine in cough syrup
### Primary effects of opioids
- Pain relief
- Euphoria
- Constipation
- Respiratory depression
- Decreased sex drive
- Skin flushed and warm
- Cough suppression

### Major Regions of the Brain

#### Parietal Lobe
- Located behind the central sulcus
- Sense of touch and pain
  - Primary somatosensory cortex
  - Pain is inhibited due to the disruption of neurons in this area.
- Also controls visual attention

#### Visuospatial Neglect

#### Somatosensory Cortex
**Location where the pain signal is processed**

#### Ascending Spinothalamic tract
- Somatosensory receptors synapse with neurons into two primary pathways that transmit information from the spinal cord to the thalamus and then the cortex.
- In both pathways information travels to the contralateral hemisphere.
- The two system carry different information to the brain
**Ascending Spinothalamic tract**

- **Ascending spinal-thalamic tract** – carries information related to **pain and temperature**.
- Information crosses to the contralateral side at the spinal cord.
- Travels parallel to the spinal cord.
- Pathway: Pain or temperature is felt → travels up the spinal cord → to the thalamus → primary somatosensory cortex.

**Temporal Lobe**

- Involved in hearing, language comprehension.
- The hippocampus is buried deep in the temporal lobe and plays a vital role in learning and memory.
  - Memory is often impaired while on opioids.

**Frontal Lobe: General Functions**

- Emotional control.
- Executive functions.
- Higher-order intellectual functions.
- Personality.
- Processing emotional memories.
- Voluntary movement.
- Verbal Fluency.
- Working memory.

**Frontal Lobe: General Functions**

- Origin of descending motor pathways.
- Involved in the initiation of voluntary movement.

**Medulla Oblongata**

- **Function:** Vitals
  - Respiration.
  - Blood pressure.
  - Heart rate.
  - Vomiting.
- Damage or inhibition of neurons.
  - Life-threatening.
**Ventral Tegmental Area & Nucleus Accumbens**

- Implicated in addiction
- Is the "reward circuitry" of the brain.
- The ventral tegmental area (VTA) is in the midbrain.
- The VTA projects to several areas of the brain, including the nucleus accumbens.
- There is structural volume loss in this region with repeated heroin administration.

**Neurons: Receptors**

- On neurons there are receptors for chemicals (neurotransmitters, opioids, etc.)
- Drugs bind to these receptors and allow ions in and out of the neuron. This movement of ion changes the electrical charge of a neuron.

**Opioid receptors are found throughout the brain**

- Opioid receptors are found in many areas of the brain.
  - Brainstem
  - Medulla
  - Pons
  - Midbrain
  - Amygdala
  - Hippocampus
  - Hypothalamus
  - Thalamus
  - Cerebellum
  - Nucleus accumbens
  - Ventral tegmental area
  - Frontal, parietal, temporal, and occipital lobes
  - Regions of the prefrontal cortex

**Opioids work by making changes to neurons**

- **Resting Potential**: slight electrical imbalance caused by different ions inside and outside the neuron.
- Some ions want to enter into the neuron and some want to leave. The Cell Membrane helps maintain this balance.
- At rest the inside of the neuron is negative at about -70mV.

<table>
<thead>
<tr>
<th>Inside the Axon</th>
<th>Positive charge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside the Axon</td>
<td>Negative charge</td>
</tr>
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When opioids bind to receptors on neurons, they make the neuron more negative which prevents them from firing.

**Opioids work by making changes to neurons**

- A neuron activating or firing is called an action potential. The figure below shows the change in electrical activity when a neuron fires.

![Opioids work by making changes to neurons](Image of Opioids and Neurons)

![Graph showing voltage and time in milliseconds](Image of Voltage and Time Graph)
Opioids work by making changes to neurons

- Opioids force the membrane potential to below its normal resting state of -70 mV. When a stimulus occurs, the neuron does not reach the threshold and therefore does not fire.

<table>
<thead>
<tr>
<th>Voltage in millivolts</th>
<th>Time in milliseconds</th>
</tr>
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<tbody>
<tr>
<td>Resting potential</td>
<td>0</td>
</tr>
<tr>
<td>Stimulus occurs</td>
<td>5</td>
</tr>
<tr>
<td>Threshold</td>
<td>1</td>
</tr>
<tr>
<td>Opioid is working on a receptor</td>
<td>3</td>
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Let’s apply this to the real world

- David just injected heroin. The drug reaches the brain in about 10 seconds and has lowered the membrane potential of neurons in the primary auditory cortex.
- "David, are you OK?" No response.
- Or screaming “David, are you OK?” Some sounds but unintelligible.

Endogenous neurotransmitters & their receptors

- There are four different types of opioid receptors in the body and the brain.
- There are five different endogenous (made by the body) neurotransmitters.

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<th>Receptor activates</th>
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Opium

- The part of the brain that allows us to hear is called the primary auditory cortex (also called Heschl’s gyrus).
- The primary auditory cortex is located on the temporal lobe.
- When we hear a sound neurons in the primary auditory cortex fire.

Opioids

- Opioids can be divided into three broad categories:
  - Natural compounds that can be extracted from opium.
  - Compounds that can be created by making specific changes in the chemical composition of these natural compounds.
  - Compounds synthesized in the laboratory.

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**Half-lives of different opioids**

- **Half-life:** The amount of time it takes for the body to eliminate half of a given blood level of a drug.

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<th>Half-life</th>
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<tr>
<td>Morphine</td>
<td>2 hours</td>
</tr>
<tr>
<td>Heroin</td>
<td>Less than 8 minutes</td>
</tr>
<tr>
<td>Codeine</td>
<td>3 hours</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2.5 to 3 hours</td>
</tr>
<tr>
<td>Methadone</td>
<td>12 to 150 hours</td>
</tr>
<tr>
<td>Buprenorphine (Subutex)</td>
<td>98 hours (sublingual)</td>
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**Opioid metabolism**

- Some opioids are broken down into inactive metabolites and some are broken into active metabolites. Some of these metabolites are more potent than the original drug.

**Elimination**

- Opioids are primarily metabolized by the liver.
- There are two phases of opioid metabolism.
  - Phase #1 – The drug is changed by the enzymes CYP3A4 & CYP2D6
  - Phase #2 – The drug or metabolite combines with a hydrophilic (water-loving) substance.

**Tolerance**

- Effective dose of heroin (~15 mg)
- Lethal dose of heroin for a non-tolerant individual (~50 mg)
- After several months of use, consumption can increase 10 fold or more!

**Receptor changes with repeated administration**

-Because the drug reduces neuronal activity, with repeated administration, your brain tries to adapt by reducing sodium-potassium pump activity; thereby increasing excitability and counteracting the drug effect.

**Receptor changes with repeated administration**

- Acute tolerance: Almost immediately after drug administration the number of opioid receptors decreases.
Methadone – a long-lasting opioid agonist
  - Its long duration of action prevents withdrawal symptoms for 24 hours or more. Therefore, it can be administered once a day.
  - High affinity for binding to mu receptors, therefore if someone takes heroin while on methadone, they won’t get the usual high.

Suboxone – contains both buprenorphine and naloxone (a opioid antagonist)
  - Through oral administration, buprenorphine can easily enter into the general circulation. Naloxone, on the other hand, is poorly absorbed into the general circulation through oral administration.
  - If Suboxone is snorted or injected, the naloxone reaches the general circulation and the brain and therefore counteracts the effects of buprenorphine.

Naloxone – A competitive antagonist for opioids.