Addiction, OCD, & riding a bike: how opiates control your brain

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what you are in for…

1. What are opiates?

2. Where is ‘opiate addiction’ in the brain?

3. What does that place normally do, and why does opiate action cause addiction?

4. What does OCD and riding a bike have to do with any of this?

5. How does my research fit into this?
~3400 BC

The opium poppy is cultivated in lower Mesopotamia

opium poppy

‘joy plant’

Lachryma papveris
‘poppy tears’
~330 AD
Alexander the Great introduces opium to the peoples of Persia and India.
~1700

Smoking opium with tobacco becomes popular (it had previously only been ingested)
1841 – 1856
The Opium Wars
1804

Friedrich Sertturner isolates the psychoactive chemical in opium. He names it ‘morphine’ after the Greek god of sleep ‘Morpheus’.

~3400 BC  ~330 AD  ~1700  1804  1841-56
1898

Bayer synthesizes a morphine derivative that it claims has the rewarding effects of morphine without the addictive side effects!
1909-1919
Widespread opium, morphine, & heroin addiction leads to first international drug prohibition treaty
2007

Prescription painkillers are responsible for more overdose deaths than all other drugs combined (including heroin, cocaine, crystal meth, etc…)

hydrocodone (Vicodin), oxycodone (OxyContin, Percocet), codeine, etc…
20th century: we started to figure out the brain!
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How is morphine (and its derivatives) acting on the brain to so powerfully modulate behavior?
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Possibility 1:
Opiates change how a neurotransmitter is signaling between cells.
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e.g. cocaine, MDMA
How is morphine (and its derivatives) acting on the brain to so powerfully modulate behavior?

Possibility 1: Opiates change how a neurotransmitter is signaling between cells

Possibility 2: Opiates actually binding receptors themselves to cause unnatural signaling between cells

e.g. cocaine, MDMA

e.g. nicotine,
How is morphine (and its derivatives) acting on the brain to so powerfully modulate behavior?

Possibility 1:
Opiates change how a neurotransmitter is signaling between cells

Possibility 2:
Opiates actually binding receptors themselves to cause unnatural signaling between cells

e.g. cocaine, MDMA

e.g. nicotine,
1973
Candace Pert discovers the opiate receptor!

“Any crazy caper you can get up to, any great meal you can think of, any combination of children or idea of how to raise them — somebody’s already thought of. But nobody’s ever discovered an opiate receptor before.”

- Candace Pert
How is morphine (and its derivatives) acting on the brain to so powerfully modulate behavior?

Possibility 1: Opiates change how a neurotransmitter is signaling between cells

Possibility 2: Opiates actually binding receptors themselves to cause unnatural signaling between cells

The fact that there are opiate receptors means there most also be ‘natural’ opiates produced by your body!

e.g. cocaine, MDMA

e.g. nicotine, caffeine, morphine
1973 – 1980
The discovery of the endogenous opioid system

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu-receptor</td>
<td>enkephalin, endorphins, endomorphin</td>
</tr>
</tbody>
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**Opiate**: any substance found in opium that acts on opioid receptors

**Opioid**: any substance that acts on opioid receptors

opioids

- opiates: morphine, codeine
- endogenous: enkephalins, endorphins, endomorphins
- synthesized: heroin, oxycodone
1971 – 1980
The discovery of the endogenous opioid system

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Morphine binds mu-receptors

Where are mu-receptors in the brain?
Mu-receptors are abundant in a brain area called the striatum.

What kinds of information does the striatum process?

How does activating mu-receptors change the way this information is processed?
Summary

1. Addiction to opioids has single-handedly started wars, sparked the first international laws on drugs, and is responsible for more overdose deaths in the USA than every other drug of abuse combined.

2. Opiates are chemicals found in the plant opium that bind opioid receptors in the brain.

3. Opioids includes any molecule (endogenous, in nature, synthesized) that bind opioid-receptors.

4. Morphine binds to mu-receptors

5. Mu-receptors normally bind the neurotransmitters enkephalin, endorphin, or endomorphin

Questions?
Mu-receptors are highly expressed in a brain area called the striatum.

What kinds of information does the striatum process?

How does activating mu-receptors change the way this information is processed?
The cortex is subdivided into areas that are responsible for different functions.
The cortex is subdivided into areas that are responsible for different functions.
The **striatum** integrates many types of information and provides feedback to the cortex to conduct **appropriate, coordinated, goal-directed** behaviors.
Ventral striatum is the location of reward
Dorsal striatum is thought to encode habits
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The **striatum** integrates many types of information and provides feedback to the cortex to conduct **appropriate, coordinated, goal-directed** behaviors.

The **striatum** accomplishes this task, in large part, by being sensitive to communication of **enkephalin** via **mu-opioid receptors** which provides a signal of reward.
When opioids are smoked, ingested, or injected, the amount of mu-receptor activation is WAY more than what is normally experienced.
When opioids are smoked, ingested, or injected, the amount of mu-receptor activation is **WAY** more than what is normally experienced.
When opioids are smoked, ingested, or injected, mu-receptors are activated WAY more than usual.

This is why we say opioids ‘hijack’ the natural reward system.
Obsessive-compulsive disorder (OCD) is characterized by persistent intrusive thoughts (obsessions) and repetitive actions (compulsions).
Obsessive compulsive disorder is correlated with hyperactivity of inputs into ventral (‘reward’) striatum.
Summary

1. Mu-receptors are highly expressed in a brain area called the striatum.
2. The striatum integrates many types of information and provides feedback to the cortex to conduct appropriate, coordinated, goal-directed behaviors.
3. The ventral striatum is especially rich in mu-receptors where it signals reward to reinforce specific behaviors.
4. Reinforced behaviors gradually move to the dorsal striatum, where they become encoded as habits.
5. This system is hijacked and overloaded by drugs of abuse to cause addiction.
6. This system is abnormally active in conditions such as OCD.

Questions?
Break
What’s going on with those spots in dorsal striatum…
What’s going on with those spots in dorsal striatum…
Neurons with mu-receptors in the dorsal striatum define these curious compartments called ‘patches’.

Mu-receptor signaling in patches does not appear to be as rewarding as in ventral striatum. So what are they doing there?
The ligand for **mu-receptors** in the striatum is **enkephalin**. Enkephalin is only released by neurons outside of the patches!

Perhaps **enkephalin** release is a way for the two compartments to communicate with either—maybe to control behavioral flexibility or execution of habits.
How does enkephalin change the information transfer between neurons?

Enkephalin released by neurons outside the patch will decrease communication between cells inside the patch.
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4. What does OCD and riding a bike have to do with any of this?

5. How does my research fit into this?
Thank you!

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The Harvard/MIT COOP

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Questions?
Conclusion

?!@!#!* I don’t get it…
~1700

John Cabot (founder of the Boston Cabot family) makes a fortune importing opium
Ventral striatum is the location of reward
Dorsal striatum is thought to encode habits
dorsal

input → HABIT → REWARD → behavior

ventral

learning
How the striatum learns behavior...

• Ventral to Dorsal – reward to habit
Recap: the striatum

- Action selector etc…
- Dorsal to ventral
Break

• Coming up next...
• What do opioids do in ventral striatum.
• What do opioids do in dorsal striatum?
• Why haven’t we talked about riding a bike or OCD yet?
Here’s what you are in for…

1. What are opiates?
Morphine

2. Where is ‘opiate addiction’ in the brain?
Major site is striatum.

3. Once we find that place, what are the opiates actually doing there?

4. What does OCD and riding a bike have to do with any of this?
• “Addiction is a state characterized by compulsive engagement in rewarding stimuli, despite adverse consequences.”
Addiction is a state characterized by compulsive engagement in rewarding stimuli, despite adverse consequences.

- T.V. (binge)
- Caffeine
- Tobacco
- Prescription pain killers (opiates) (morphine, codeine, oxycotin, purkesettes, etc…)
- Alcohol
- Heroin (opiates)
# Addiction is expensive

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>$316 billion</td>
</tr>
<tr>
<td>Addiction</td>
<td>$193 billion</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$174 billion</td>
</tr>
<tr>
<td>Smoking</td>
<td>$157 billion</td>
</tr>
<tr>
<td>Obesity</td>
<td>$147 billion</td>
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