Biology and Behavior: Neuroadaptations to Opioids and their Consequences for Addiction

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Educational Objectives

• At the conclusion of this activity participants should be able to:
  ▪ Identify acute effects of opioids on the cAMP system
  ▪ Understand the role of the locus coeruleus in the opioid withdrawal syndrome
  ▪ Explain how changes in the extended amygdala and prefrontal cortical areas underlie behavioral changes to chronic opioids
  ▪ Recognize key changes underlying the development of hyperalgesia
Target Audience

• The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.
Today I will discuss three areas of neurobiological adaptation caused by chronic opioids resulting in known clinical features of addiction:

• Development of Opioid Tolerance and Opioid Withdrawal

• Modifications of Glutamate Neurotransmission in the Prefrontal Cortex and Extended Amygdala

• The Phenomenon of Opioid-Induced Hyperalgesia
The Cycle of Addiction

- Preoccupation to obtain
- Persistent problems

Preoccupation Anticipation

- Persistent desire
- Using more than expected

Binge Intoxication

- Tolerance/Withdrawal
- Soc/Occ/Rec Sequelae

Withdrawal Negative Affect

Acute Effects of Drugs of Abuse

Drugs that block the dopamine pump:
- Cocaine
- Amphetamine

Drugs that activate or inhibit channels:
- Alcohol
- PCP, ketamine

Drugs that mimic neurotransmitters by activating receptors:
- Morphine
- Nicotine
- Marijuana
Progression Construct for Addiction

Abuse
Down arrow
Dependence
Impulse Control Disorder
Down arrow
Compulsive Disorder
Down arrow
Positive Reinforcement (Reward)
Down arrow
Negative Reinforcement (Avoidance)

A well-defined behavioral model with which we elucidated a neurochemical mechanism and then a clinically effective treatment
Signs and Symptoms of Opioid Withdrawal

- Dysphoric mood
- Nausea or vomiting
- Muscle aches/cramps
- Lacrimation
- Rhinorrhea
- Insomnia
- Hypertension
- Can use standardized scales to measure: e.g.: COWS, OOWS

- Pupillary dilation
- Sweating
- Gooseflesh
- Diarrhea
- Yawning
- Tachycardia

DSM-5
The Locus Coeruleus
In vivo Electrophysiological Recordings of LC In an Opioid-Dependent Rat in Withdrawal
The cAMP Cascade in Chronic Opioid Action in the LC

The cAMP Cascade in Acute Opioid Action in the LC

LC Glutamate Levels Rise During Opioid Withdrawal

Neuroanatomical Sites of Action in Opioid Withdrawal

Neurocircuitry of Opioid Withdrawal

- Lateral Paragiganto-cellularis
- Locus Coeruleus
- Behavioral Excitation

Glutamate → Norepinephrine

Acute Opiate → cAMP (AC, PKA) → Tolerance → Withdrawal
Neuroanatomical Sites of Action in Opioid Withdrawal

Implications for Clinical Treatment of Withdrawal

• Clonidline is effective in reducing somatic symptoms of opioid withdrawal.

• Agents targeting the rise in glutamate and/or NMDA antagonists might also prove helpful.

• The emotional effects of opioid withdrawal appear little addressed by LC-focused therapies.
The fear and distress associated with opioid withdrawal goes beyond what one would expect from the somatic symptoms.

“Doc, I’ll do anything, but don’t let me be sick.”
Addiction is Driven by much more than Acute Reward or Fear of Withdrawal

• The majority of the time, the addict is neither high nor in withdrawal, he/she is preoccupied with staying away from the drug or thinking about getting it. That preoccupation robs the addict of their productive life.

• The preoccupation phase moves to drug use because of failures of executive function, impulse control and judgment, and misplaced motivation.
Opioid Receptor Imaging with Positron Emission Tomography and $^{18}$F[Cyclofoxy

Kling et al. (2000) J Pharmacol Exp Ther. 295: 1070
Addiction Involves Many Areas of the Brain

- Orbitofrontal Cortex
- Subcollosal Cingulate
- Motivation
- Planning, judgement
- Prefrontal cortex
- Frontal cortex
- Nucleus accumbens
- Medial forebrain bundle
- Ventral tegmental area
- Emotions, conditioned effects
- Amygdala
Three Types of Reinstatement

• Drug-induced Reinstatement – Don’t put yourself in risky situations, *and* “I can have just one hit.” A dose that would not be addicting triggers addictions in the former addict.

• Cue-induced Reinstatement – People, places and things. Something paired with prior use triggers relapse.

• Stress-induced Reinstatement – The links between the HPA dysregulation, glutamate and relapse.
Glutamatergic Mechanisms of Relapse

- PFC to Nac and eAM (glutamate) - drug-induced reinstatement
- bIAM to Nac and eAM (glutamate) - cue-induced reinstatement
- Ventral striatal-palladal-thalamocortial loops (compulsive drug seeking)
- Now “cues” associated with drug use activate the reward and withdrawal circuit

Glutamate/GABA Modulation of the Mesolimbic Dopamine Pathway
Neurocircuitry of Drug-Seeking Behavior

Extended Amygdala

- VTA
  - Arcuate Nucleus

- NAc
  - BNST
  - ceAM

- Amygdala nuclei
  - PFC subregions

- Pontine Nuclei
- Hip, VP, LH

Motor Response (Behavioral Output)
Addiction Involves Many Areas of the Brain, so…

- Treatment of opioid withdrawal or blockade of acute intoxication is unlikely to treat behavioral abnormalities of the opioid addict, and thus, achieve sustained sobriety.
- Well described behavioral interventions such as CBT, MET, TSF can “retrain” behaviors gone awry from prefrontal hypofunction, and conditioned fear responses driven by the extended amygdala.
- Novel glutamatergic or peptidergic* targets may counter changes in the extended amygdala.
- As in all substance use disorders, there is much to do!
A Brief Overview of Opioid-Induced Hyperalgesia (OIH)

Another “Dark-Side” to Opioid Pain Medications
Tolerance or OIH?

Chronic Opioid Exposure

Tolerance

Opioid-Induced Hyperalgesia

Pronociception

see Mao J (2008) Pain Clinical Updates.16:1-4
Animal Data Supporting the Existence of OIH

Pain Threshold (sec)

DAYS

Opioid Infusion

Paw Withdrawal Latency

Initial Analgesia

Increased Pain Sensitivity

0 1 2 3 4 5 6 7 8 9 10 11 12
Opioid-Induced Hyperalgesia in Humans

Alternative Explanations for OIH

- Tolerance - more opioid needed to prevent breakthrough pain
- Undetected Disease Progression
- Variable Exposure to Opioids – compliance issues, use of different opioids with variable tolerance
- Allodynia – perception of previously non-painful stimuli as painful
Proposed Mechanisms of OIH and/or Tolerance

1. **Chronic opioids elevate CCK, which activates efferents from the rostroventral medulla, which raises spinal dynorphin and glutamate, activating spinal NMDA receptors (pro-nociceptive); NMDA antagonists block development of OIH and tolerance.**

2. **Increased activity of central nociceptive pathways or of facilitative descending pathways as a homoeostatic response to pain suppression.**

3. **Decreased activity of central descending inhibitory pathways (non-homeostatic).**
The Result …

A need for increased doses of opioids for pain control.

BUT

If it is OIH, increasing the opioid will worsen the pain.

OPTIONS:

• Opioid rotation
• Change opioid to methadone, buprenorphine?
• Reduction in opioid and addition of non-opioids
• Addition of behavioral interventions
• NMDA antagonism (?ketamine)
Increased Pain with Taper of Chronic Opioids

- Reduction in Tolerance and OIH
  - Pain Spike
  - Dose Reduction

Reduction in Tolerance and OIH
Addiction Viewed as Drug-Induced Neuoplasticity

- Reuptake transporters
- Receptors
- Channels
- Second messengers & protein phosphorylation
- Regulation of many cellular processes
- Nucleus
- Transcription factors
- Target genes
- dFosB in Nac
- Stable adaptations in neural function
- CREB in NAC
- CREB in cAM
- NPY
- κ-op rec

- Reward
The drug-dependent state represents not just a perturbation of the homeostatic state, but the establishment of a new allostatic state, dysfunctional but stable.

Per Koob and colleagues
Case Vignette

- 54-year-old-retired mechanic, on long-term disability, who is transferring care from out of state to a new PCP. He suffers failed-back syndrome s/p two lumbar fusion attempts, and has been maintained on OxyContin 240 mg per day and oxycodone 10 mg q 4 hours for breakthrough pain, along with diazepam 10 mg per day, cyclobenzaprine 10 mg tid, and the NSAID meloxicam 15 mg q AM.

- The PCP consults you, an addiction psychiatrist, on whether he should continue this opioid regimen.

- Wife and patient both confirm the patient is in pain up to a 10/10 every day, and he spends most of his time lying down on the couch watching TV.
Case Vignette

• The patient’s main concern today is whether you will approve continuing his opioid pain medications, as they are “the only thing that work.”

• The patient only has a three day supply of opioids left.

• The patient indicated physical therapy and other physical activity only make his pain worse.

• The patient hopes blood work isn’t needed as he finds venipuncture excruciatingly painful.

• What are your next steps?
1. Discuss with PCP if there are prior records or a release to discuss prior history with the previous provider. Was the patient compliant, were urine toxicologies being obtained, were there aberrant use behaviors?

2. Given potential adverse interaction, find out why diazepam was prescribed.

3. You learn the patient has been compliant, has had regular u-toxes that did not reveal any unexpected drug use, and had no aberrant behaviors. Diazepam was prescribed years ago as a muscle relaxant.

4. Take your own history to rule out a history of past or present opioid use disorder or other substance use disorder.

5. Is there a co-morbid psychiatric diagnosis impacting pain control? (You conclude ‘no.’).
6. You conclude opioids *could* be continued based on risks EXCEPT for 2 things. First, there is co-prescription of a benzodiazepine and an opioid, and 2) you see no evidence pain control has been adequate or that function has been improved.

7. You recommend benzodiazepines be tapered off over a 4-week period, and a muscle relaxant such as methocarbamol be used if not too sedating and if needed.

8. You recommend a slow taper of opioids be commenced, starting with 20 mg OxyContin per week. You advise the patient you are making this recommendation based on the lack of efficacy and evidence he has a component of OIH (sensitivity to blood draws and other history you obtain).
Case Vignette

9. You explain that pain will increase a bit but this would be temporary, and advise the PCP you would assist with symptomatic control of opioid withdrawal symptoms if needed.

10. You advise the PCP that a plan must be developed for pain control as opioids are tapered, including non-opioid pain medications, CBT with a psychologist with whom you work, and recommendations for complementary and alternative medicine including exploring options for yoga, meditation etc.
References


PCSS MAT is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA) and American Society of Addiction Medicine (ASAM).

For More Information: [www.pcssmat.org](http://www.pcssmat.org)

Twitter: [@PCSSProjects](https://twitter.com/PCSSProjects)

Funding for this initiative was made possible (in part) by Providers’ Clinical Support System for Medication Assisted Treatment (1U79TI024697) from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.