Drug Addiction, Animal Models, and the Neural Circuitry Involved

Osher Lecture Series
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Kimberly Thibeault & Veronika Kondev
PhD Candidates, Vanderbilt Center for Addiction Research
Massachusetts reports 2nd vaping-related death

The second resident to die was a woman.

Science News

Drug overdose deaths in CT doubled in 6 years

Date: October 29, 2019
Source: University of Connecticut
Summary: Opioid overdose deaths in Connecticut doubled in the past 6 years, largely driven by use of multiple drugs together, according to a team of researchers.

Drug deaths rising in Finland

Latest figures show a steady year-on-year increase, as criticises under-funded services.

Deaths linked to vaping often involved THC products, not nicotine, CDC says

By Michael Nedelman, CNN
Updated 4:49 PM ET, Mon October 28, 2019

Record drug overdose deaths announced in Virginia

Deaths linked to vaping often involved THC products, not nicotine, CDC says

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Addiction is a national and global problem.
Addiction is a chronic psychiatric disorder

“Addiction is a complex condition, a brain disease that is manifested by compulsive substance use despite harmful consequence”

Substance Abuse: use of any drug in a manner that deviates from the approved medical or social patterns within a given culture

Addiction: indicates severe degree of drug abuse
...but addiction was not always viewed as a disease.

1830’s
1959: American Public Health Associations adopt official statement saying alcoholism is a disease
1976: American Medical Association defines alcoholism as an illness
1994: DSM-IV updates definition of substance dependence

Addiction as choice
RESEARCH
Addiction as disease
Drugs of abuse can alter the neurochemistry of the brain

Di Chiara & Imperato (1988)

**Dopamine Facts**

Molecular Structure: \( \text{C}_{8}\text{H}_{11}\text{NO}_2 \)

Where Produced: Many brain regions

Controls: Pleasure, emotions, movement, motivation, cognition

Too Much: Overload of pleasure-reward system

Too Little: Inability to feel pleasure, depression, Parkinson’s disease

Activities that Boost Levels: Exercising, cooperating, having healthy relationships, eating sweet foods

Di Chiara & Imperato (1988)
Drugs of abuse can alter the **physical structure** of the brain

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**Legend:**
- Glutamate
- Heteromeric NMDA receptor
- Heteromeric AMPA receptor
- Post synaptic density
- Actin Filament

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Drugs of abuse can change the size and shape of dendritic spines

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Russo, et al. (2010)
The mesolimbic pathway is involved in addiction

Also called the “reward pathway” of the brain

The VTA sends dopamine projections to the nucleus accumbens

The nucleus accumbens shows increased dopamine levels in response to rewarding stimuli
Multiple brain regions and circuits are involved in addiction. All of these circuits have to be considered in developing strategies to effectively treat addiction.

How can we study how different brain regions and interacting circuits result in addiction?

All of these circuits have to be considered in developing strategies to effectively treat addiction.
Using animal models to study addiction

Using behavioral paradigms, we can model different aspects of addiction:

- Learning of drug-related cues
- Conditioned associations between drug and environmental stimuli
- Classical Conditioning: Associate an involuntary response and a stimulus
- Operant Conditioning: Associate a voluntary behavior and a consequence
- Motivational state
- Drug seeking
- Drug taking
Conditioned Place Preference is used to study the learning of reward-related cues

Box with two different sides: different gradients on floor, different patterns on walls, different odors, etc.

Pair one side of box with injections of saline (vehicle) and one side with drug across several days

Test day: (drug free); allow rodent free access to both sides and see which side it spends more of its time on

Olive & Kalivas (2010)
Combining CPP with Calcium Imaging

**Calcium imaging** takes advantage of calcium indicators to visualize changes in intracellular calcium.

**GCaMP**: genetically encoded calcium indicators - fluoresces when calcium binds - used as proxy for neural activity

Calipari, et al. (2016)
Combining CPP with Calcium Imaging

Calipari, et al. (2016)
Using operant conditioning in the lab to model drug-seeking and drug-taking

• Operant Conditioning ~ Instrumental conditioning
  – Comes from Skinner’s emphasis on how an organism learns to “operate on” its environment to produce an effect
• Operant (behavior)
  – Is a behavioral response that has some effect (consequence) on an organism’s environment
• Operant Chamber- Skinner Box
  – A chamber containing a bar or key that an animal can manipulate to obtain a food or water reinforcer, with an attached devices to record the animal’s rate of response
Components of Operant Conditioning

Reinforcers vs. Punishers

Increases the probability that a response will occur
Strengthens the behavior it follows

Decreases the frequency that a response will occur
Weakens the behavior it follows

Positive Reinforcer  Negative Reinforcer
Positive Punisher  Negative Punisher
Components of Operant Conditioning

i.e. “reward”
- sugar, drugs of abuse

i.e. remove unpleasant stimulus
- shock, loud sounds

Thibeault, et al. (2019)
Punishment

• Presents an aversive stimuli or removes a pleasant stimuli to decrease the frequency of a behavior

• Disadvantages
  • It doesn’t eliminate behavior merely suppresses it
  • Not effective unless it immediately follows the behavior
  • Punishment becomes associated with the punisher-so the punisher is feared
  • Organism being punished may learn to relate to others in an aggressive way
  • Punishment makes clear what behaviors are incorrect, but doesn’t provide any demonstration of desired behaviors
Punishment

• Can work if used wisely...
  – Punish the behavior not the person
  – Punish immediately
  – Use a severe enough punishment to eliminate the behavior
  – Explain and reinforce more appropriate behaviors
Punishment or Negative Reinforcement?

TIP FOR IDENTIFYING CONTINGENT RESPONSES

WHAT IS THE BEHAVIOR DOING?

Increasing?
- Give Positive Stimulus?
  - POSITIVE REINFORCEMENT

Decreasing?
- Take Away Negative Stimulus?
  - NEGATIVE REINFORCEMENT

- Give Negative Stimulus
- Take Away Positive Stimulus
  - PUNISHMENT
Forming and Strengthening Operant Behavior

• Shaping
  – An operant conditioning process in which successive approximations of a behavior are reinforced until the desired behavior pattern emerges
  – i.e. “step by step”
Forming and Strengthening Operant Behavior

• Secondary Reinforcement (Conditioned)
  – Primary reinforcers—an innately satisfying reinforcing stimulus, such as one that satisfies a biological need (food, water, pain relief)
  – Conditioned or secondary reinforcer—a stimulus that gains its reinforcing power through its association with a primary reinforcer. (MONEY)
Forming and Strengthening Operant Behavior

• Delay, size, and schedule of reinforcement
  – Operant conditioning is strongest when the delay in receiving a reinforcer is short and the reinforcer is large
Animals Regulate Intake

Rats regulate their consumption by varying their rate of responding

0.75 mg/kg/inj

1.5 mg/kg/inj
Self-Administration Models

• Understanding different self-administration schedules can help you to model addiction
  – Self-administration in the face of negative consequences
    • Punishment + reinforcement

• Animal models of addiction can model many aspects of human addiction
  – Tolerance
  – Withdrawal
Channelrhodopsin as a novel tool to study neural circuitry

Channelrhodopsin (ChR2): light-gated channel

- Shining blue light “turns neurons on”
- ChR2 ~ “on/off switch”


Adapted from: Kayser
Channelrhodopsin as a novel tool to study neural circuitry

Using viral-mediated strategies, you can effectively target and express ChR2 in specific brain regions

Typical Experiment:

Inject ChR2-virus into brain region of choice

Allow 4-8 weeks for virus to infect neurons

Implant fiber optic to allow delivery of light (either into same brain region that the virus was injected = somatic; or another brain region = projections)

Shen, et al. (2019)
Combining self-administration and Channelrhodopsin: ICSS

Intracranial Self-Stimulation: Will rodents self-administer for delivery of light directly into the brain?

Shen, et al. (2019)
Combining Self-Administration with Channelrhodopsin

Shen, et al. (2019)
Addiction is a chronic, psychiatric disease that involves many brain regions and several different neural circuits.

WHERE ARE WE NOW?

- Rodent Behavior
- Calcium Imaging (GCaMP)
- Channelrhodopsin (ChR2)
The role of the nucleus accumbens

Part of the mesolimbic “reward” pathway

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Neural Ensembles

Stress
Nucleus Accumbens and Neural Ensembles

Ensembles: population of cells

- “Encode information”

Do ensembles exist in the nucleus accumbens to encode information about the drug or drug-related cues?

Can we manipulate these ensembles to prevent drug seeking behavior?

Use calcium imaging to look at activity of populations of cells during behaviors
Nucleus Accumbens May Contribute to Stress Susceptibility

Mice susceptible to stress paradigm show decreased neural activity in nucleus accumbens

Stress is a huge precipitator of relapse!