Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking

BIONB 4110
March 10th, 2014
Presented by: Gilbert Agyeman and Robert Guber

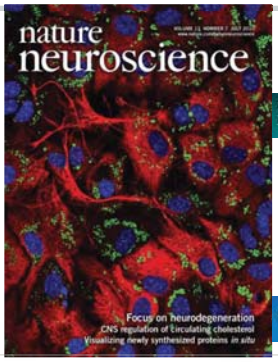
News article
http://www.ucsf.edu/news/2013/04/104831/laser-light-zaps-away-cocaine-addiction

Journal- nature

- Published Weekly (51 issues)
- Founded 1869- England
- Impact factor 38.597
- Multidisciplinary
- NPG has many different publications

Jan 31 2013 cover

Nature Publishing Group



nature REVIEWS NEUROSCIENCE
nature neuroscience
nature REVIEWS NEUROLOGY
Molecular Psychiatry
Neuropsychopharmacology

Dr. Billy T. Chen

- NIH Staff Scientist, within the National Institute on Drug Abuse.
- PhD at NY Langone- department of neurology
- Lead author of the study

Authors

Dr. Hau-Jie Yau

- Research Fellow NIDA/NIH
- PhD in Neuroscience.
- Post doctorate- NIDA and Northwestern University, Feinberg school of medicine.
- She helped to design experiments and run some.

Christina Hatch

- Post Baccalaureate fellow in the lab of Dr. Judith Walters.
- She performed experiments and helped analyze data.

Authors Continued

Ikue Kusumoto-Yoshida

- She works at NIDA
- Assisted with performing the experiments.
- Author on a paper titled: Olfactory Cortex Generates Synchronized Top-Down Inputs to the Olfactory Bulb during Slow-Wave Sleep
- She is from Japan

Dr. Saemi L. Cho

- Researcher at Ernest Gallo Clinic and Research Center,
- Department of Neurology, University of California San Francisco
- Assisted performing experiments in this project

F. Woodward Hopf, Ph.D.

F. Woodward Hopf

- Researcher at Ernest Gallo Clinic and Research Center, Ph.D.
- Department of Neurology, University of California San Francisco
- Adjunct assistant professor of neurology
- Staff Research Investigator

http://actg.galloresearch.org/Directorye6ab.html?profile=WoodF.
Woodward Hopf, Ph.D.

Dr. Antonello Bonci

- Has a medical degree from Sacred Heart School of Medicine- (Rome, Italy)
- He was the PI of the study
- Scientific Director of NIDA intramural research program
- Chief of synaptic Plasticity Section with the NIDA intramural research program.
- His lab mainly focuses on investigating drug-induced neuroadaptations, through various techniques.

Introduction

- Drug Addiction is major public health problem.
- There is no perfect treatment for cocaine addiction
- DMS IV defines addiction as: having both a loss of control as well continuing use despite the significant negative consequences.

Cocaine was removed in 1903

http://giocondalaw.blogspot.com/2013/08/fashionable-parodies-where-does-free.html

Addiction vs. Substance use disorder

Addiction

- May have cultural implications
- Stigma associated with being an addict

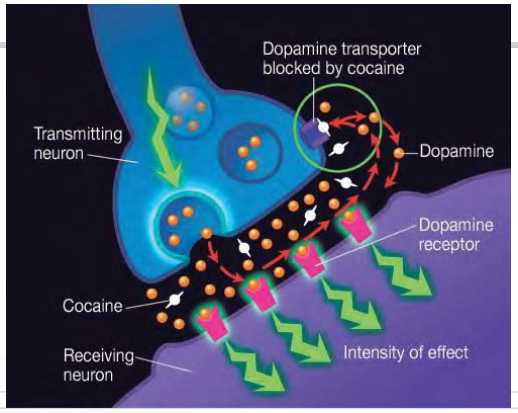
Substance use disorder

- This is a persistent chronic disorder.
- Brain circuitry changes
- Pathological pattern of behaviors

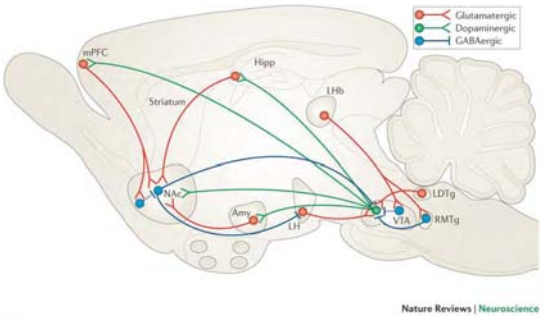
DSM V- Substance Use Disorder

- Divided into multiple overall classes of 11 different criteria.
- Group 1- Impaired control over substance use
  - Ex. Taking more than is meant to be taken, cravings
- Group 2- Social impairment
  - Failure to fulfill major obligations
- Group 3- Risky use
  - Using the drug even when it puts you in danger
- Group 4- Pharmacological changes
  - Tolerance and withdrawal

How cocaine works



Addiction Pathway



Nucleus Accumbens

- Plays a central role in the reward circuit.
- Operation based chiefly on dopamine, which promotes desire, and serotonin whose effects include satiety and inhibition.
- Maintains close relations with other centers involved in the mechanisms of pleasure and with the ventral tegmental area (VTA).
- Sometimes called brain's pleasure center.
- Link in brain pathways that cause addiction and depression

http://thebrain.mcgill.ca/flash/i/i_03/i_03_cr/i_03_cr_par/i_03_cr_par.html

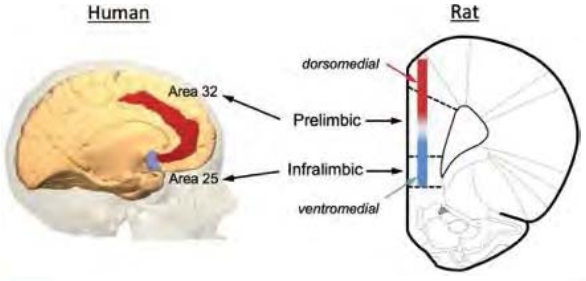
http://www.slideshare.net/krirytter/nucleus-accumbenspresentation

The Prefrontal Cortex

- Drug addicts have implicated disruption of PFC activity in ventral, dorsal medial and lateral regions
- Regions believed to underlie inflexible behavior addicted subjects express when faced with conditioned cues
- Ventromedial PFC (BA 11, BA 25) is implicated in the disruption in inhibitory control that results in impulsivity and poor control over behavior in addicts

Kalivas and Volkow, 2011 ***Molecular Psychiatry***

Medial Prefrontal Cortex



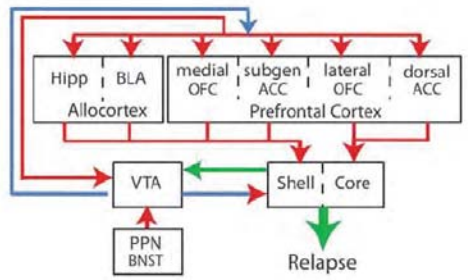
Gass and Chandler, 2013 *Frontiers in Psychiatry*

Prelimbic Cortex

- Can inhibit or augment desire to perform a particular behavior.
- Inhibition increases compulsive cocaine seeking; stimulation prevented compulsive cocaine seeking
- May have role in controlling desire for seeking out cocaine.

Kalivas and Volkow, 2011 *Molecular Psychiatry*

Figure 1



Red- Glu
Blue- DA
Green- GABA
Two colors means both

Kalivas and Volkow, 2011 *Molecular Psychiatry*

Purpose/Hypothesis

- "…Chronic cocaine use induces prelimbic cortex hypoactivity, and that compromised prelimbic cortex functions in turn impairs inhibitory control over compulsive drug seeking"

Methods

- They used male Winsar Rats
- Model of addiction was from Pelloux et al., 2007 *Pharmacology*
- Mice underwent Catheter surgery and Stereotaxic surgery (for optogenetics)

Surgeries

Catheter implantation

Stereotaxic

Cocaine Self-Administration

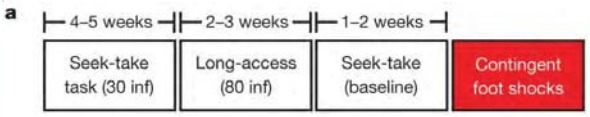


Figure 1

Cocaine Self-Administration

The model was a Seek-Take model

1. Acquisition of the taking response
   1. **Take lever gives reward**
2. Training of the seek-take chain
   1. Seek lever → take lever out→ reward→ begin again.
      1. Only one lever out at a time.
   2. Random interval (RI)
3. Extended training
   1. 8 sessions only take lever max 80 infusions
   2. Within only take were more seek-take trials or RI60
4. Punishment
   1. On the seek lever press shock administered

Random Interval Description

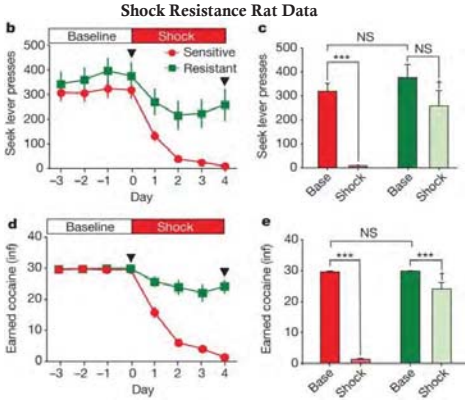
- Three RI schedule uses RI5, RI30 and RI60
- Press seek lever → initiate RI → all presses of seek during RI result in no retraction → after RI next seek press resulted in removal of seek lever and insertion of take lever → take lever press =Reward
- Animals progressed between the RI durations.
- 10 min. to complete cycle.

Cocaine Self-Administration

The model was a Seek-Take model

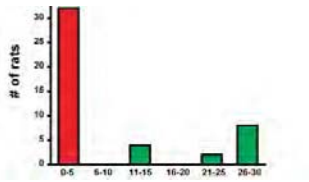
1. Acquisition of the taking response
   1. **Take lever gives reward**
2. Training of the seek-take chain
   1. Seek lever → take lever out→ reward→ begin again.
      1. Only one lever out at a time.
   2. Random interval (RI)
3. Extended training
   1. 8 sessions only take lever max 80 infusions
   2. Within only take were more seek-take trials or RI60
4. Punishment
   1. On the seek lever press.

Shock Resistance Rat Data



Rats that were addicted to cocaine had a smaller drop in seek presses while being shocked and earned much more cocaine than the control.

Shock resistance

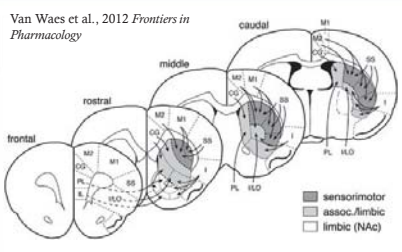


Shock sensitive (red) less than 5 rewards on final shock day
Shock resistance (green) greater than 10 rewards on final shock day.

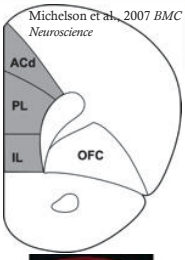
ex Vivo electrophysiology

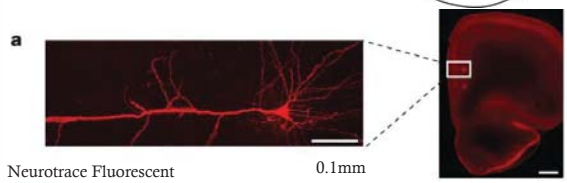
- Is the study of the electrical properties of biological cells and tissues.
- Involves measurements of voltage/ current change across single ion channels or organs.
- Was performed outside of tissue to measure prefrontal/prelimbic activity

Van Waes et al., 2012 *Frontiers in Pharmacology*



Michelson et al., 2007 *BMC Neuroscience*



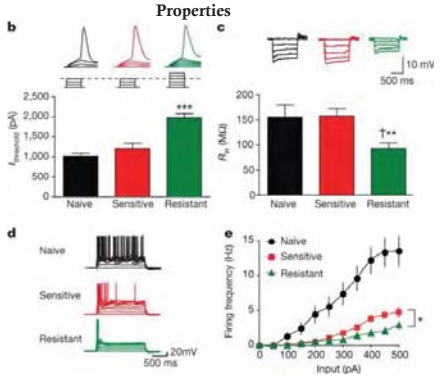


Neurotrace Fluorescent
Nissl Stain

0.1mm

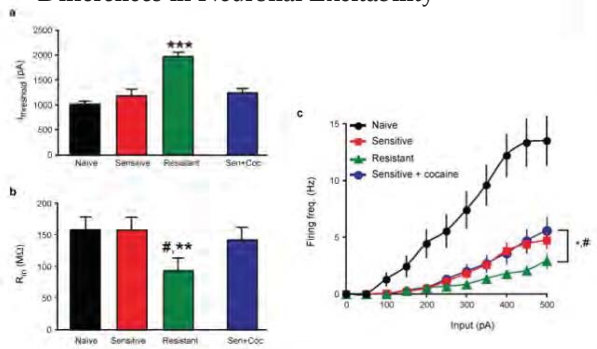
1.0mm

Affect of Cocaine Addiction on Neuron Properties



Resistive properties of membrane have changed. The resistant cell has more leaky channels.

Differences in Neuronal Excitability



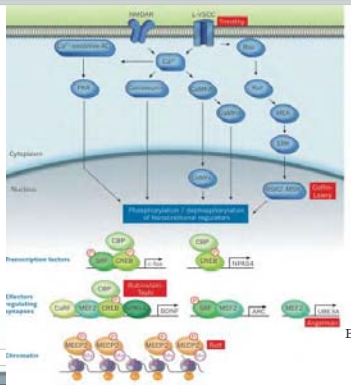
Quantity of cocaine infusions was not responsible for firing adaptations of shock resistant rats.

Supplemental figure 5

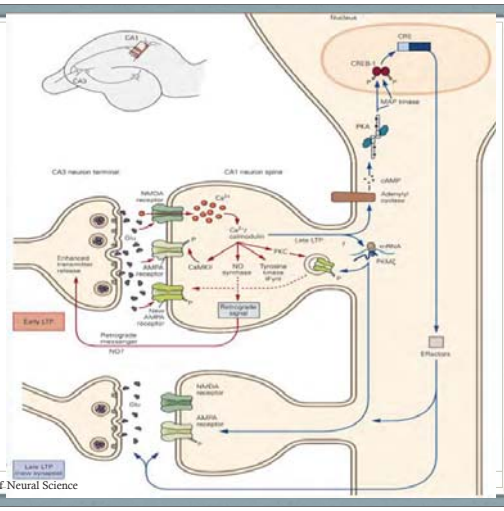
Optogenetics

- They had their stereotaxic into the prelimbic cortex.
- They added ChR2-eYFP to at the promoter of Camk2a which is the promoter for CaMKIIa
- Or mice were given eNpHR3.0

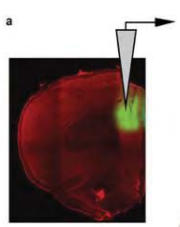
Why Camk2a?



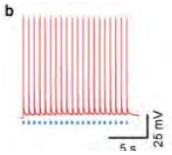
Ebert and Greenberg, 2013 *Nature*



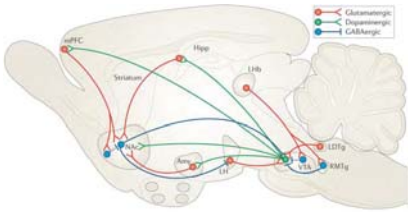
Kandel et al., Principles of Neural Science

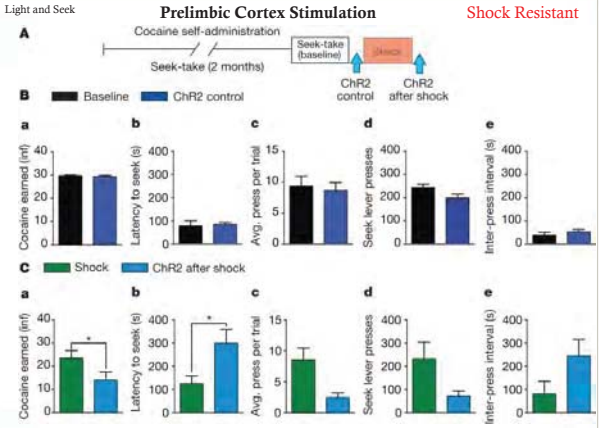


Neurotrace Fluorescent
Nissl Stain

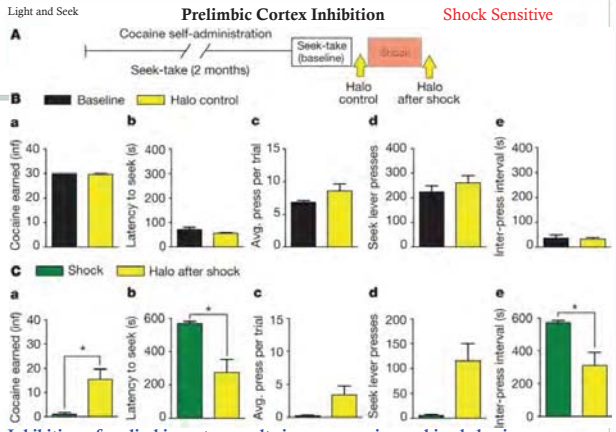


Optogenetic
activation





Stimulation of prelimbic cortex area results in inhibited cocaine seeking behavior



Inhibition of prelimbic cortex results in more cocaine seeking behavior

Discussion

- Long-term cocaine self administration reduced prelimbic cortex excitability, with a much more pronounced effect in compulsive rats.
- Prolonged cocaine use depressed prelimbic cortex excitability
- Profound prelimbic cortex hypo activity drove compulsive cocaine seeking.
- By hyper activating the neurons, leads to shock sensitive animals while inhibiting the neurons in the prelimbic cortex leads to shock resistant animals

Conclusion

- Decreased prelimbic excitability can lead to compulsive behavior.
- What other diseases do you expect that you would see this hypo activity.

Discussion Questions

- 1. How does cocaine affect the brain initially, and what brain regions are most affected?
- 2. Why did the authors chose the prelimbic cortex as the region of interest, and what are the main roles of the prelimbic cortex? What brain areas in humans did they say it might be similar to?
- 3. What promoter region did the authors use for their optogenetic experiments, and why was this promoter region chosen?
- 4. What is the difference between ChR2 and eNpHR3.0? Why did the authors choose these two?