This is your brain on drugs...

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NeuroFest 2019
When I say addict....who do you see?
Overdose is Only the End

• First-time users do not overdose on opioids, addicts do.

• Everyone is talking about the overdose epidemic, but not addiction itself.

• Efforts to prevent overdose deaths are only treating a symptom of this epidemic.

So what really is an opioid addiction?
What is Addiction?

• Not merely liking or using a drug
• No diagnostic tests
• Clinical syndrome
• Characterized by loss of control
  – High motivation to obtain drug
  – Disruption of normal activities
  – Persistent use despite negative consequences
  – Difficulty stopping drug use
• Progressive, chronic disease
  – Extended experience is usually necessary
  – High rate of relapse

“DSM V” criteria
The Cycle of Substance Abuse

Acute Drug Use → Tolerance Develops → Increase Intake → Stop Using → Withdrawal Symptoms → Acute Drug Use

“I feel bad when I’m not on my drug.”

“I need more drug than before to feel the same way.”

- Fever
- Chills
- Sweating
- Muscle Pain
- Vomiting
- Diarrhea
- Anxiety
- Depression
- Insomnia
Big Picture Scientific Questions:

Why do we get addicted to painkillers but not our endorphins?

Why do only some people become addicted?

The Scientific Goals:

1. What changes in the brain are important for the side effects versus the beneficial effects of opioid drugs?

2. Can we reverse or block the side effects without compromising therapeutic utility?
What are opioids; where do the work?

The “lock” is the mu opioid receptor

So, why isn’t endorphin addictive?

Your body’s opioids (“the key”) are peptides

Nature gave us a gift that fits the lock

Endorphin

Morphine
Endorphins don’t produce tolerance or dependence

So, why isn’t endorphin addictive?

No tolerance to Endorphin

No dependence to Endorphin

If we can figure out why endorphin isn’t addictive, we can do better!
How do endorphin and morphine “signal” the mu opioid receptor?

A (G protein)

B (Arrestins)

Endocytosis

Endorphin: balanced or “unbiased”

Morphine (and its derivatives): “biased”

No treatment

Endorphin

“Biased” agonist

Does Bias Matter??
Opioid (ICV) Tolerance Development

Treatment days

Endorphin | Morphine | Enkephalin | Methadone

Endorphin (0.5 nmol) | Morphine (30 nmol)

Balanced is better?
We converted morphine into endorphin!
Now I’m balanced…what happens?

WT + Morphine

RMOR knock-in + Morphine

Analgesia --improved
Tolerance --reduced
Dependence --reduced

So what about “addiction”

Do you like it?
Do you hate withdrawal?

Conditioned Place Preference/Aversion
Wild type mice: Yes, I like it

% change in preference for drug-paired side

Morphine Dose (mg/kg)

Berger and Whistler, EMM 2011
Wild type mice: Yes, I like it

RMOR mice: I like it more

RMOR mice show enhanced morphine reward

Berger and Whistler, EMM 2011
Do you Hate Withdrawal?

5 days

saline or morphine

naloxone/saline

30min

naloxone after saline treatment (1 mg/kg)

saline after morphine treatment

naloxone after morphine treatment

% change in preference for drug paired side

WT RMOR

Berger and Whistler, EMM 2011
1. Can we find new drug like molecules that look like endorphin?

   We are looking for/optimizing compounds like this
   And nobody else is!

2. What are the changes in the brain specific to “addiction”?

   The mutant mice are the perfect tool to do this!

   WT + Morphine

   RMOR knock-in + Morphine

   Great analgesia, no tolerance or dependence
Thanks to My Team

Funded by NIH: R01 DA019958, R01 DA015232, R01 AA020401, R01DA037963, R01MH107932, R21 DA031574, R21 MH096058, R21DA043816, R21AA023231, U01TW008160
And Private Foundations: NARSAD, ABMRF, Novo Nordisk
I am a **scientist** driven by solving **“mysteries”**

Why do we get addicted to morphine but not endorphin?

Why does it take 6 weeks for my anti-depressant to become effective?

How does one medication control both my manic and depressant states?

Why does an adversity-filled early life predispose you to mental disorders?

Why do dementia patients become addicted (think gambling, alcohol)?
Behavior boxes with all the bells and whistles…..