This is your brain on drugs…

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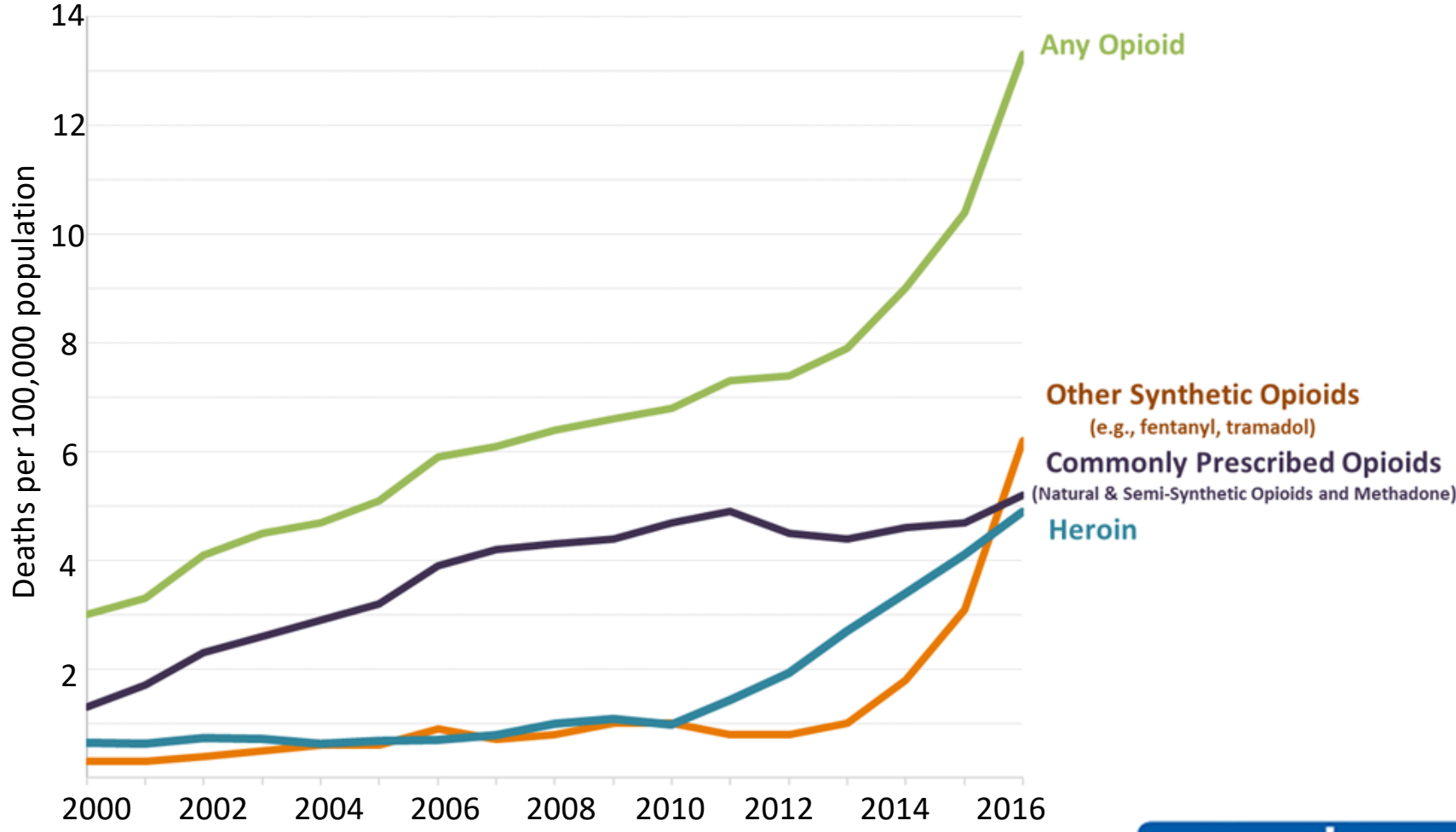
NeuroFest 2019

When I say addict….who do you see?

Overdose Death Rates Involving Opioids, by Type, United States, 2000-2016



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2017. https://wonder.cdc.gov/.

www.cdc.gov
Your Source for Credible Health Information

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?

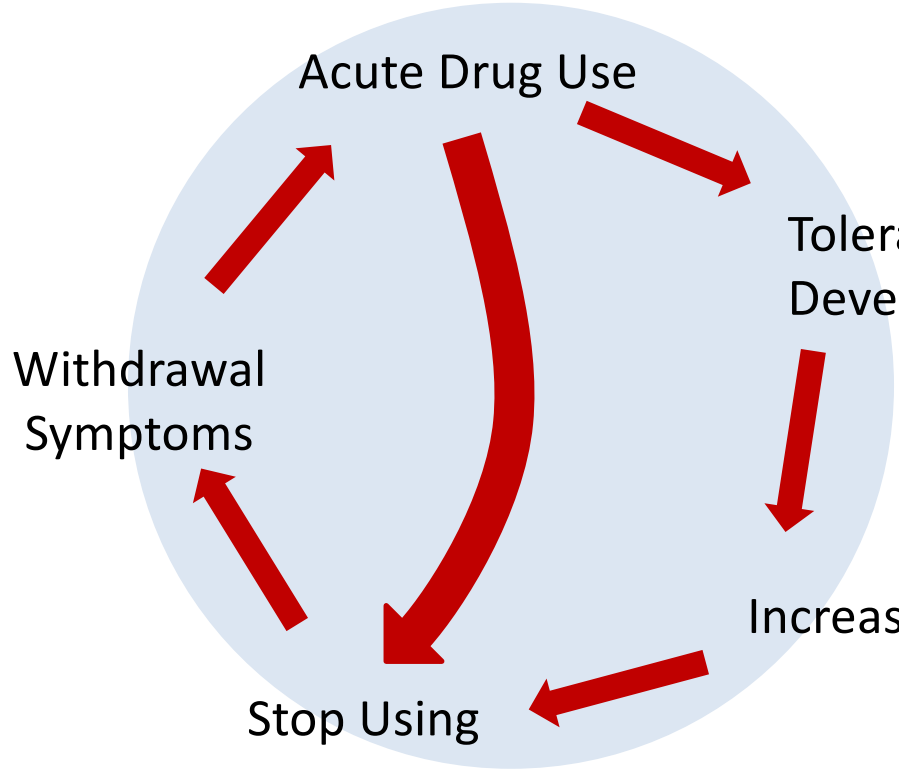
What is Addiction?

- 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

- Fever
- Chills
- Sweating
- Muscle Pain
- Vomiting
- Diarrhea
- Anxiety
- Depression
- Insomnia



"I feel bad when I'm not on my drug."

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

Big Picture Scientific Questions:

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

Why do only some people become addicted?

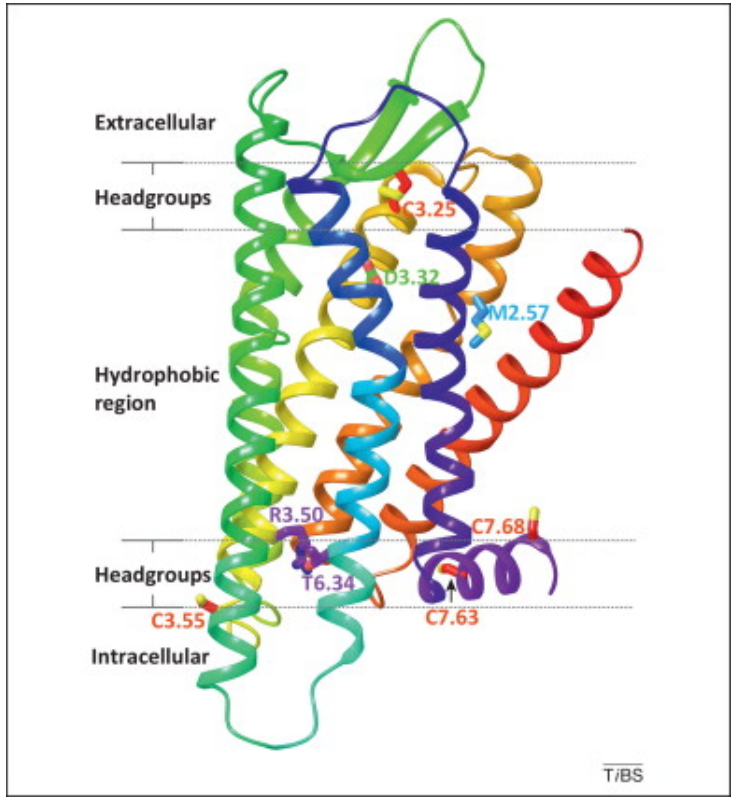
The Scientific Goals:

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

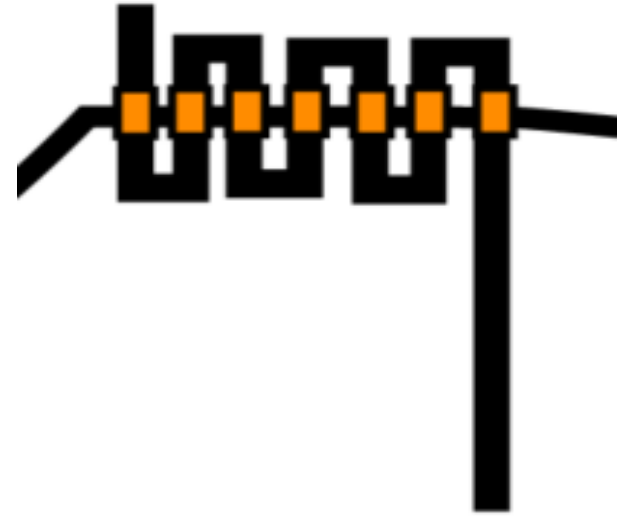
2. **Can we reverse or block the side effects with out compromising therapeutic utility?**

What are opioids; where do the work?

The "lock" is the mu opioid receptor

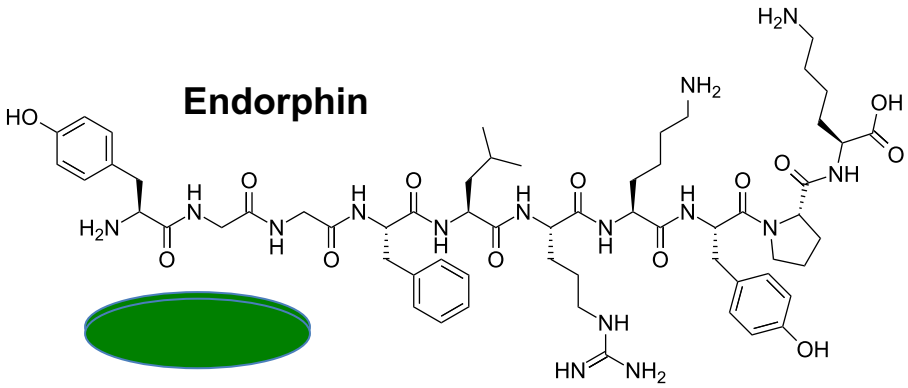


So, why isn't endorphin addictive?



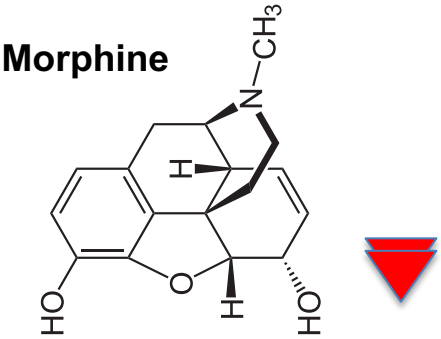
Your body's opioids ("the key") are peptides

Endorphin



Nature gave us a gift that fits the lock

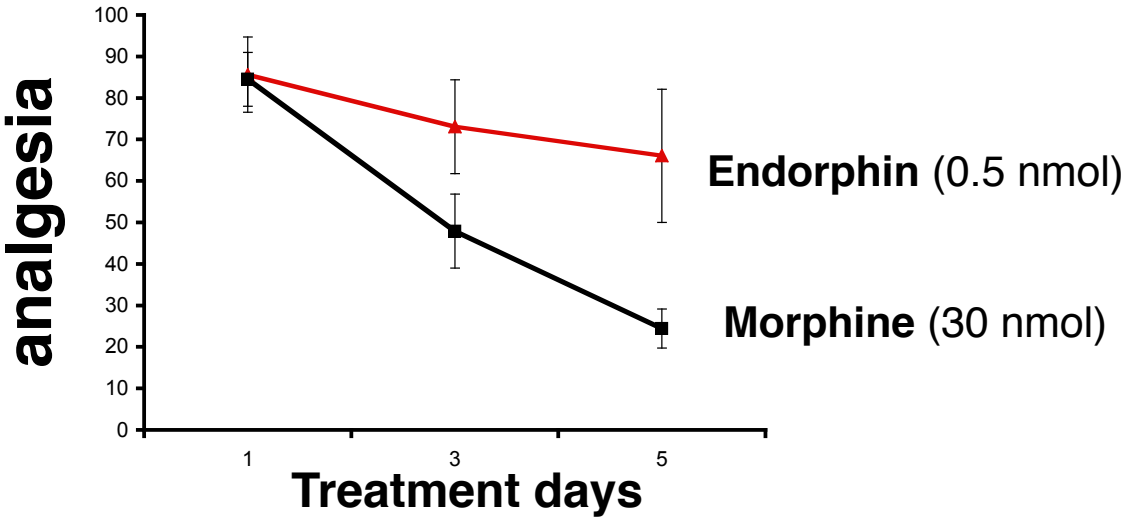
Morphine



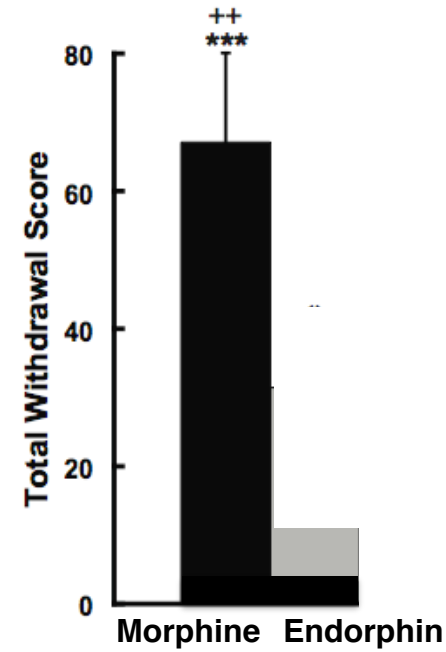
Endorphins don't produce tolerance or dependence

So, why isn't endorphin addictive?

No tolerance to Endorphin

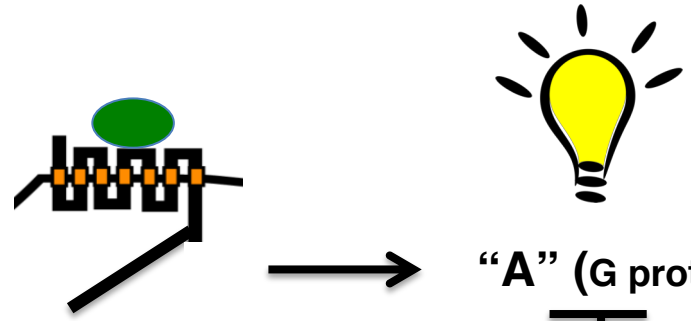


No dependence to Endorphin

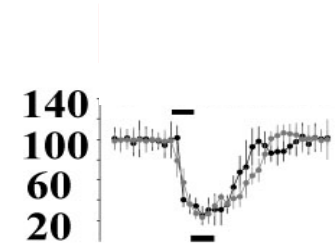


If we can figure out why endorphin isn't addictive, we can do better!

How do endorphin and morphine "signal" the mu opioid receptor?



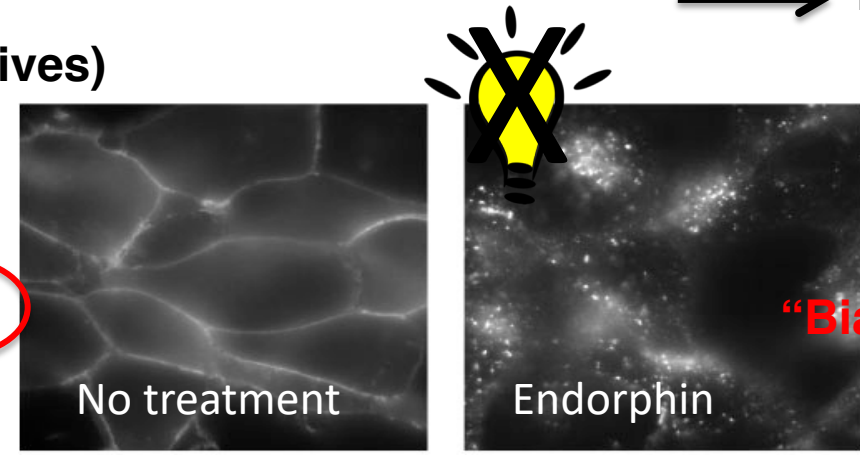
"A" (G protein)



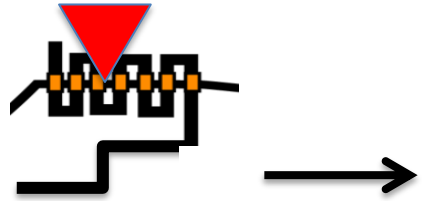
"B" (Arrestins) → Endocytosis

Endorphin
balanced or "unbiased"

Morphine (and its derivatives)
"biased"



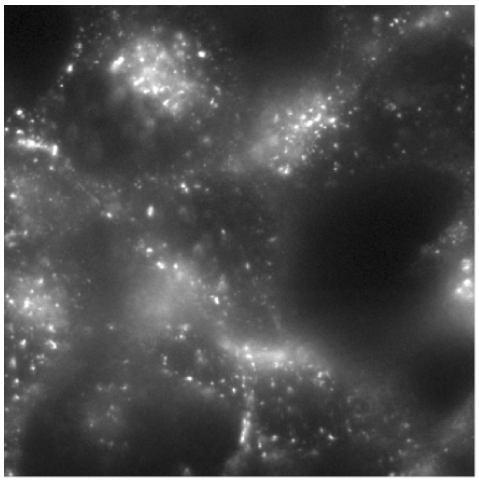
"Biased" agonist



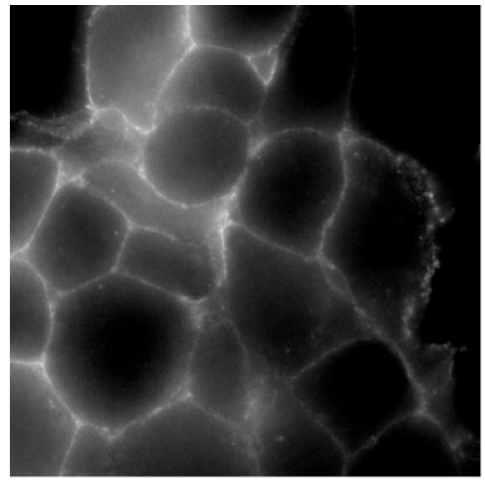
G protein

Does Bias Matter??

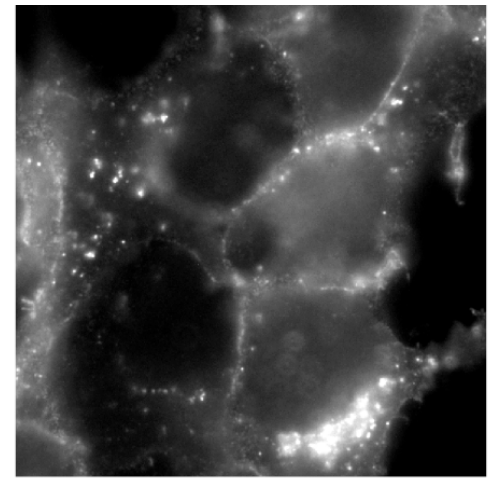
Balanced is better?



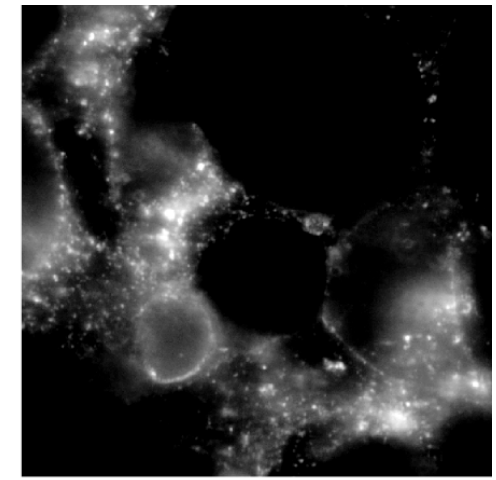
Endorphin



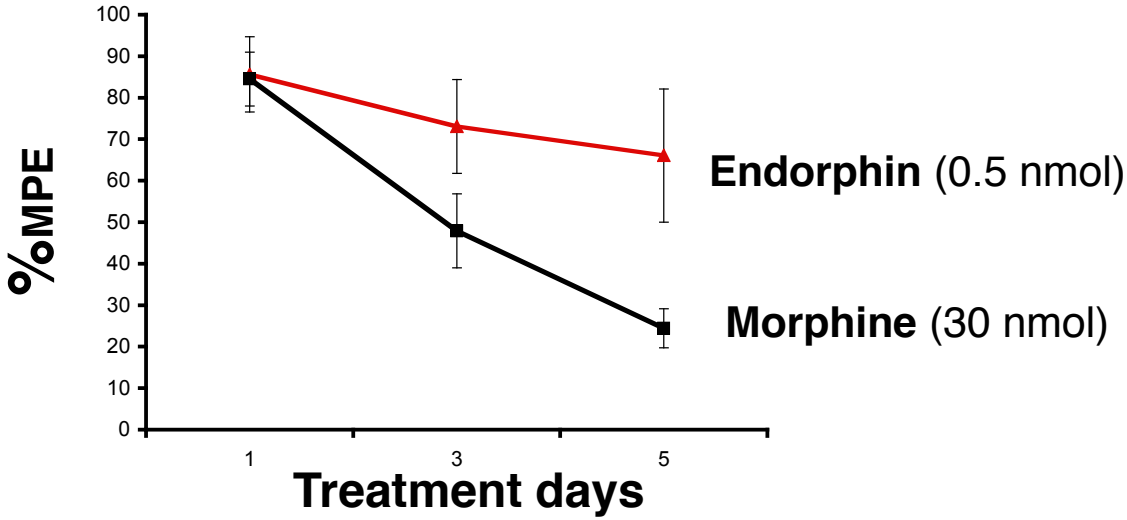
Morphine

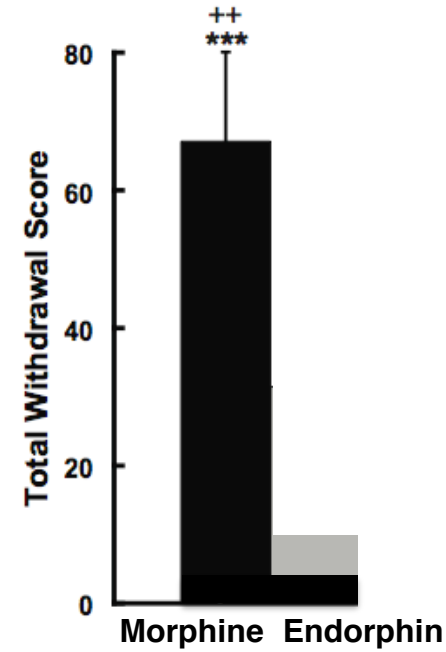


Enkephalin

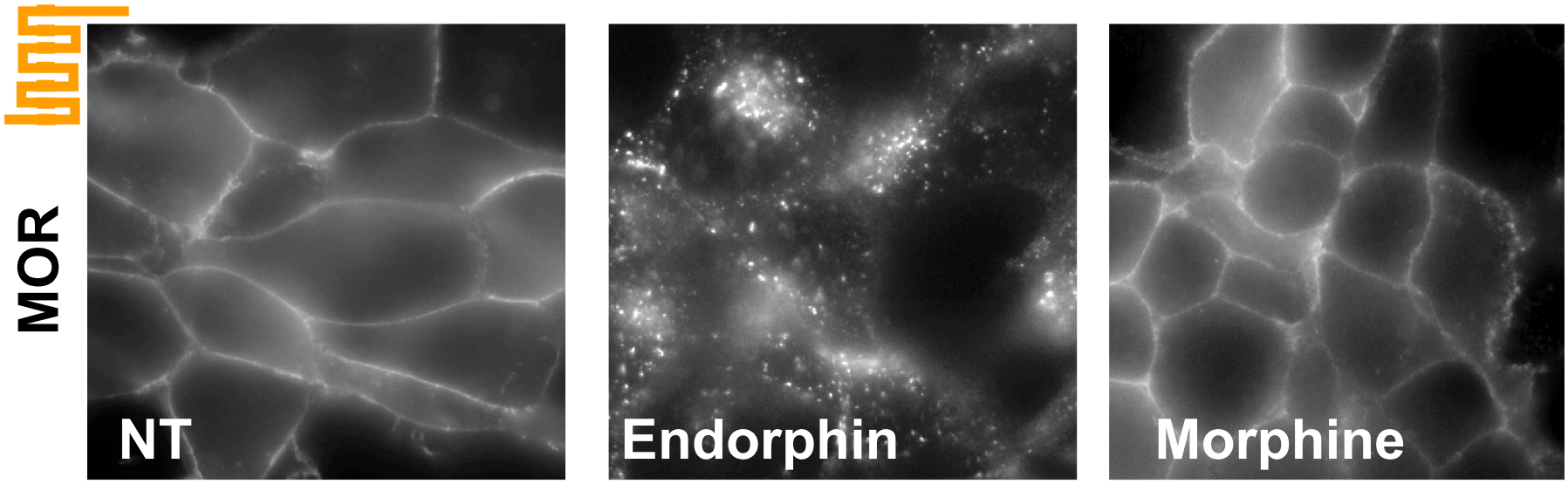


Methadone

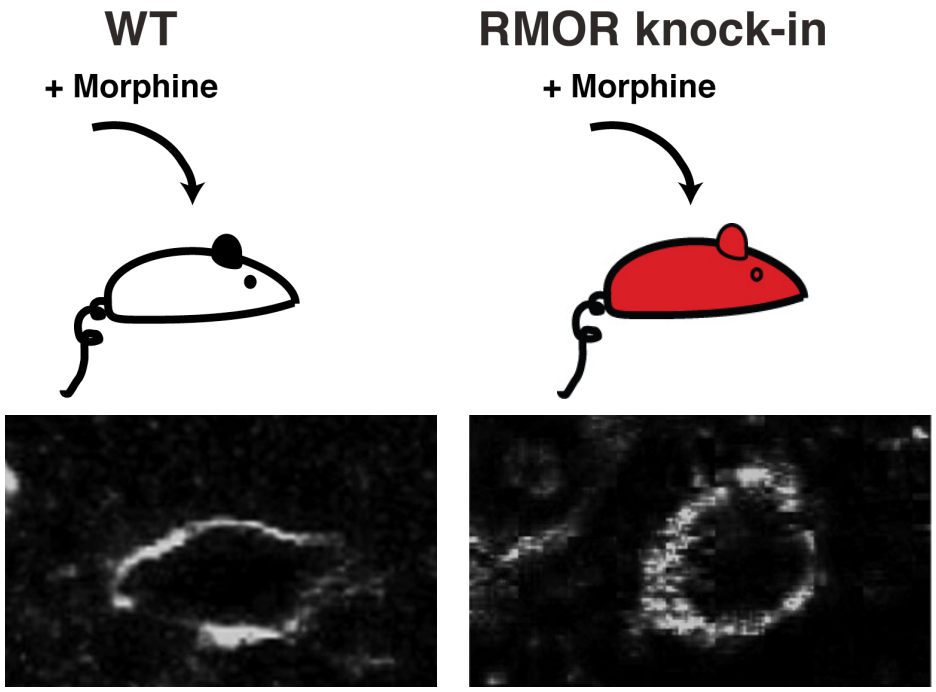




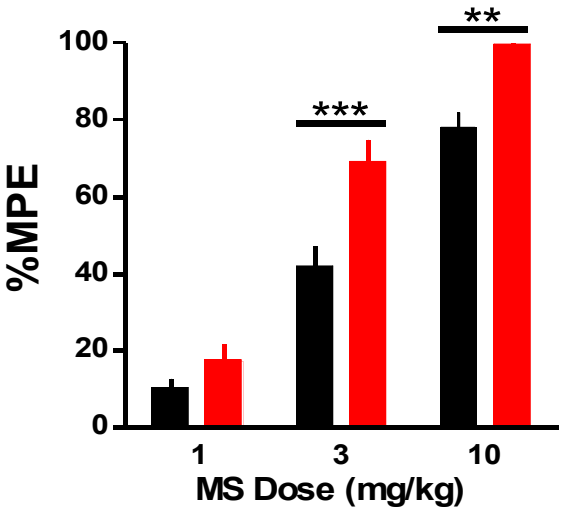
We converted morphine into endorphin!

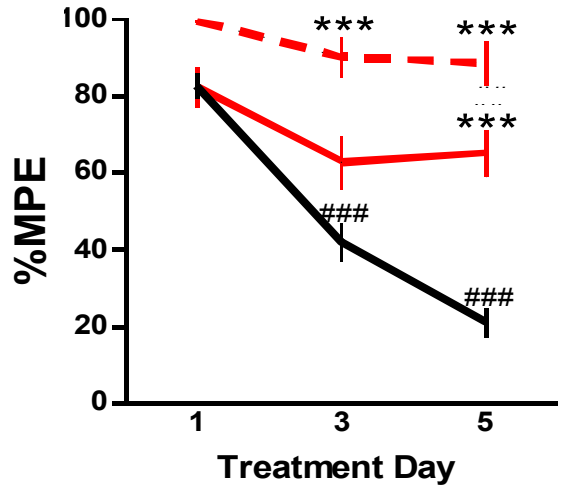


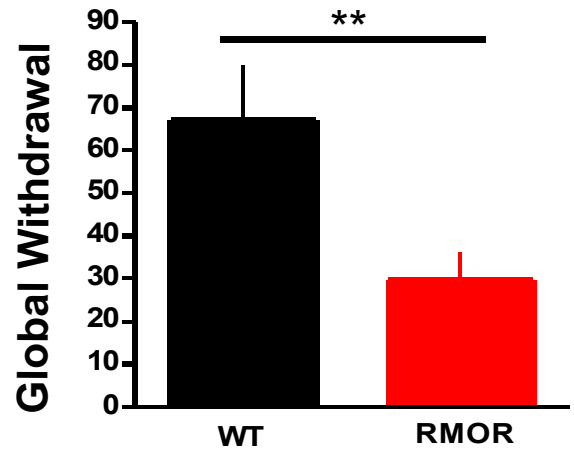
Now I'm balanced…what happens?



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







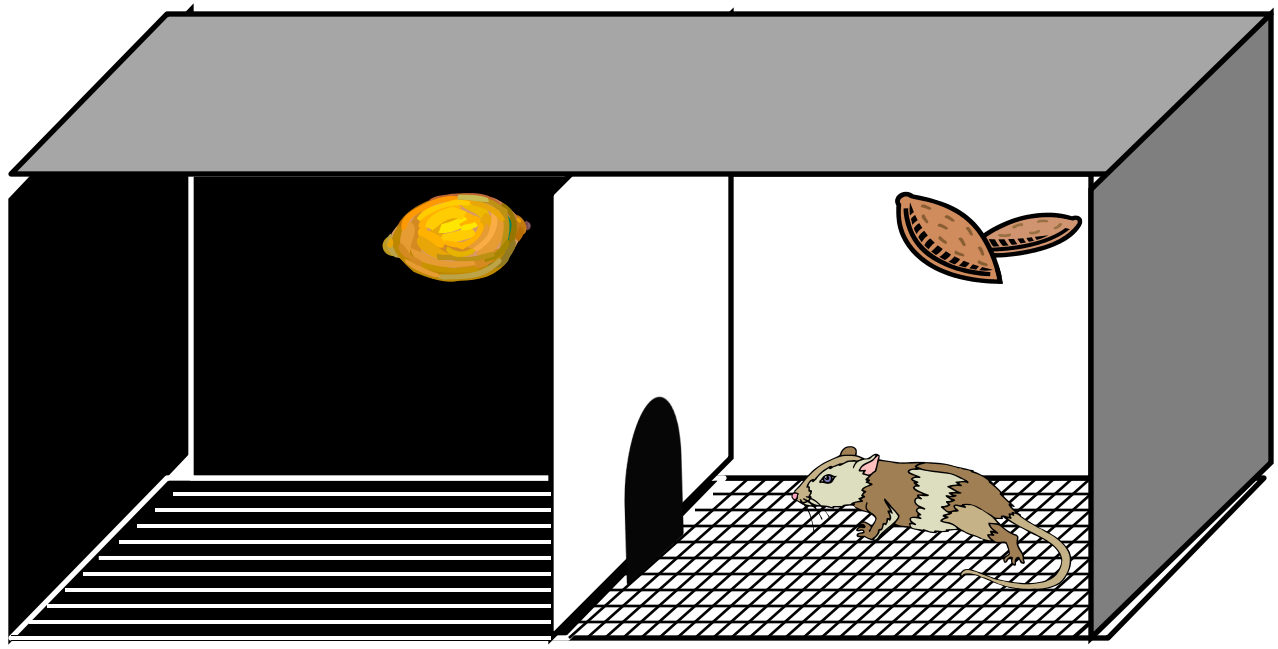
Kim et al. Curr. Biol, 2008

So what about “addiction”

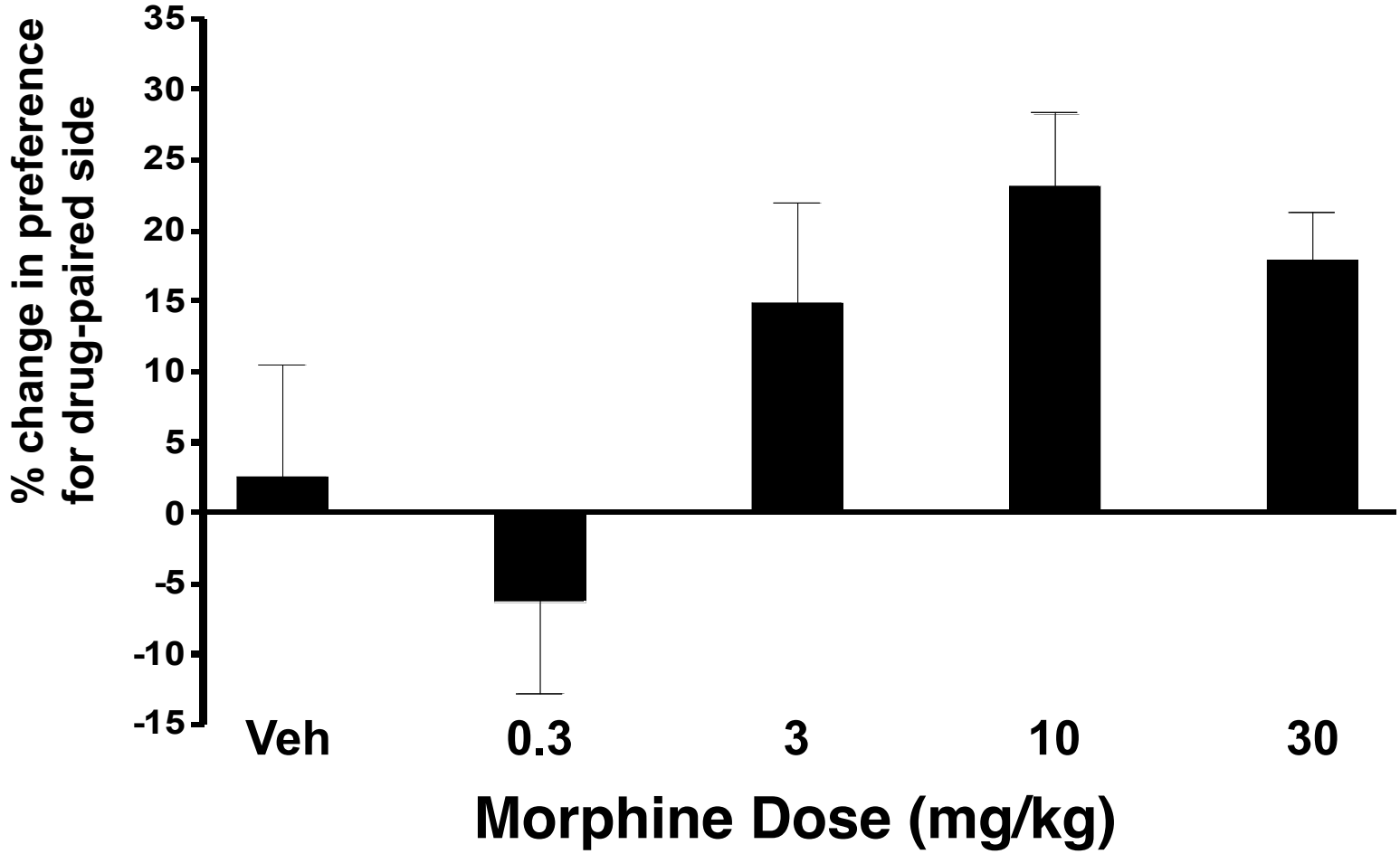
Do you like it?

Do you hate withdrawal?

Conditioned Place Preference/Aversion



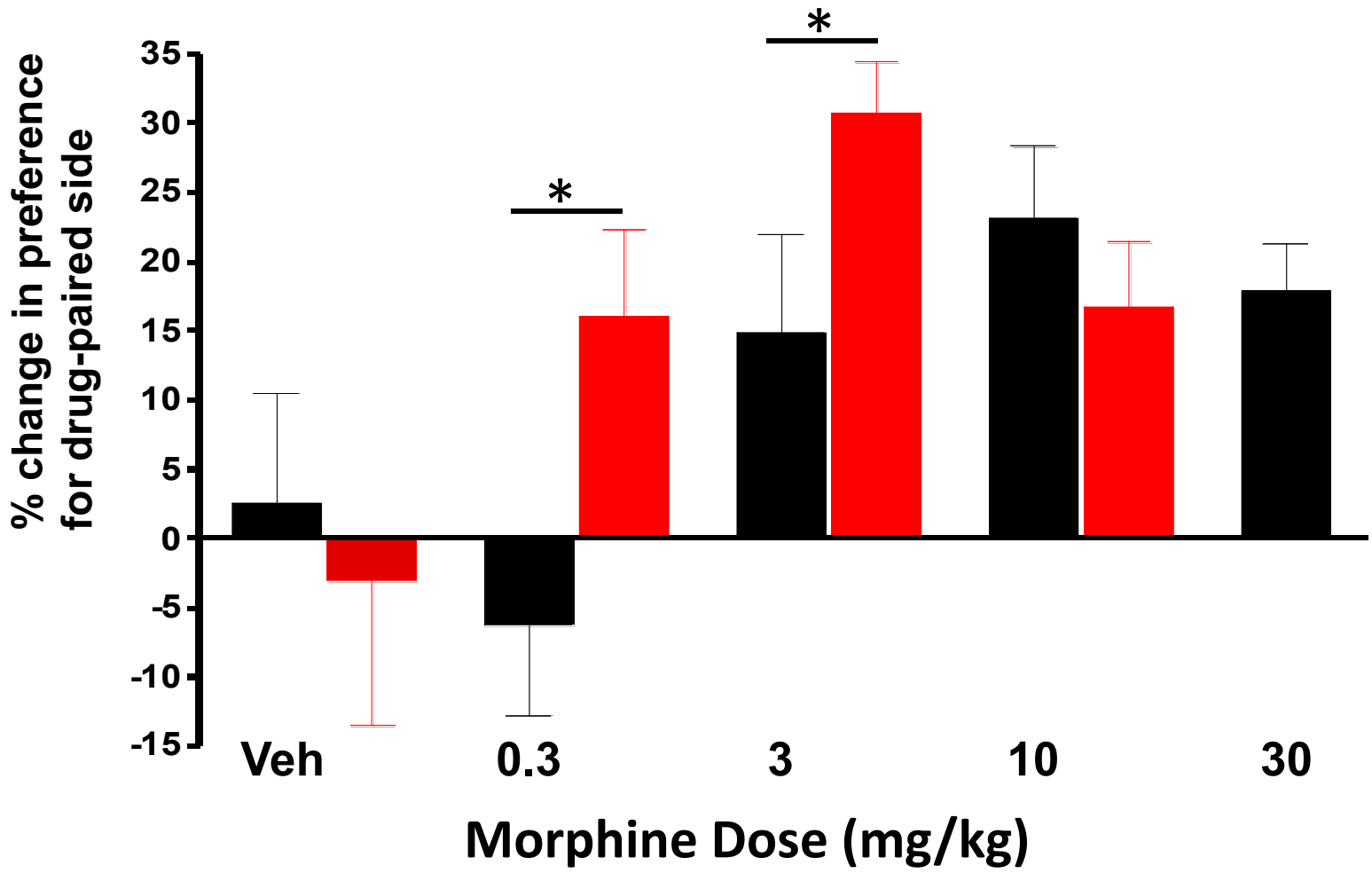
Wild type mice: Yes, I like it



Berger and Whistler, EMM 2011

Wild type mice: Yes, I like it

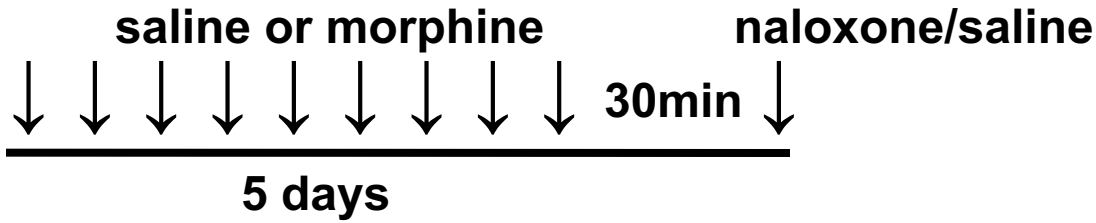
RMOR mice: I like it more

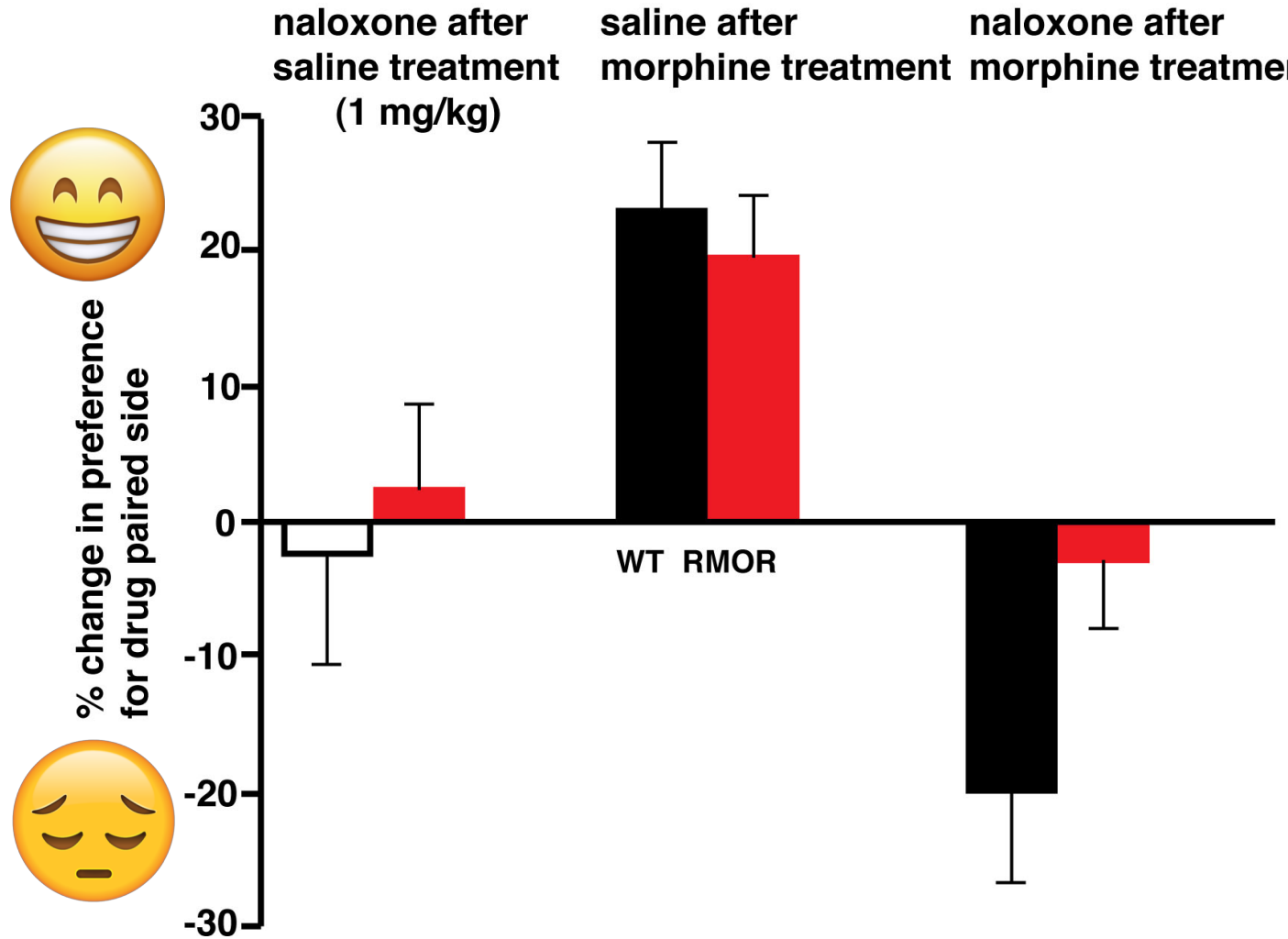


RMOR mice show enhanced morphine reward

Berger and Whistler, EMM 2011

Do you Hate Withdrawal?





Berger and Whistler, EMM 2011

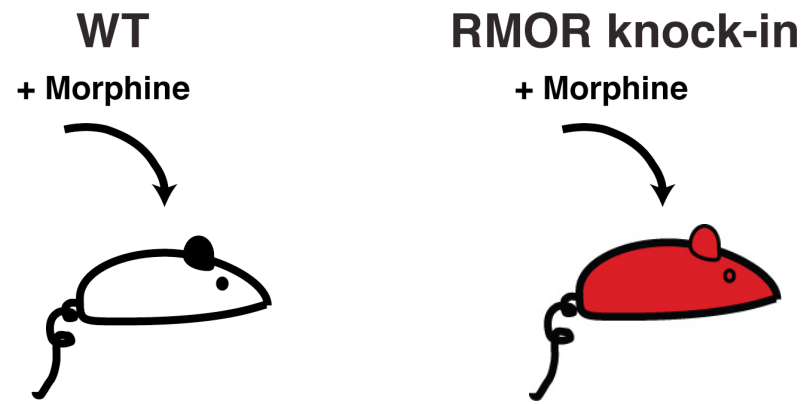
1. Can we find new drug like molecules that look like endorphin?

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!

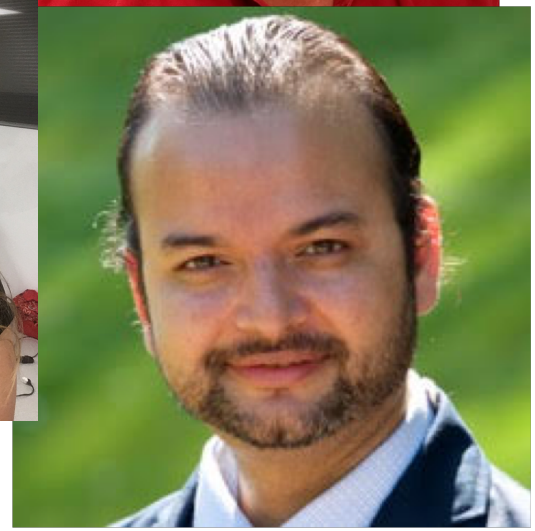
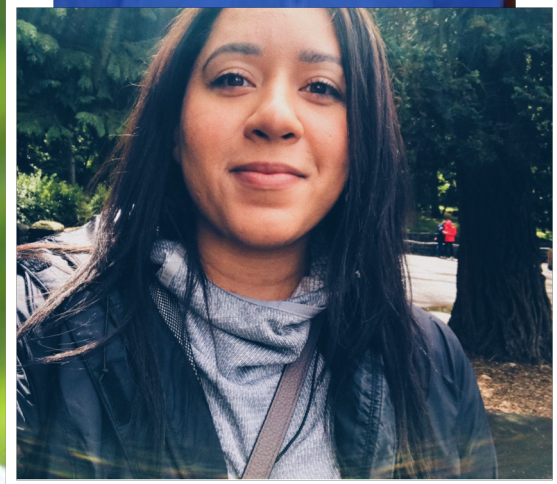


Great analgesia, no tolerance or dependence

Thanks to My Team



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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…..