Incubation of cocaine craving: behavioral and neuronal mechanisms

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Special thanks:

The Waletzky family
SfN committee

Jane Stewart
Roy Wise

Lin Lu
Bruce Hope

Ongoing research projects

1. Stress-induced reinstatement of drug and palatable food seeking
   (Sunila Nair, Udi Ghitza)

2. Context-induced reinstatement of heroin seeking
   (Jennifer Bossert)

3. Developing a new model to assess relapse to cocaine and food seeking
   (with Abraham Zangen, Weizmann Institute, Israel)

4. Time-dependent increases in cocaine seeking after withdrawal
   (incubation of cocaine craving)

Outline

1. The clinical problem

2. Behavioral studies

3. Neurobiological studies

4. Conclusions and a brief summary of recent results on incubation of craving

5. Acknowledgements

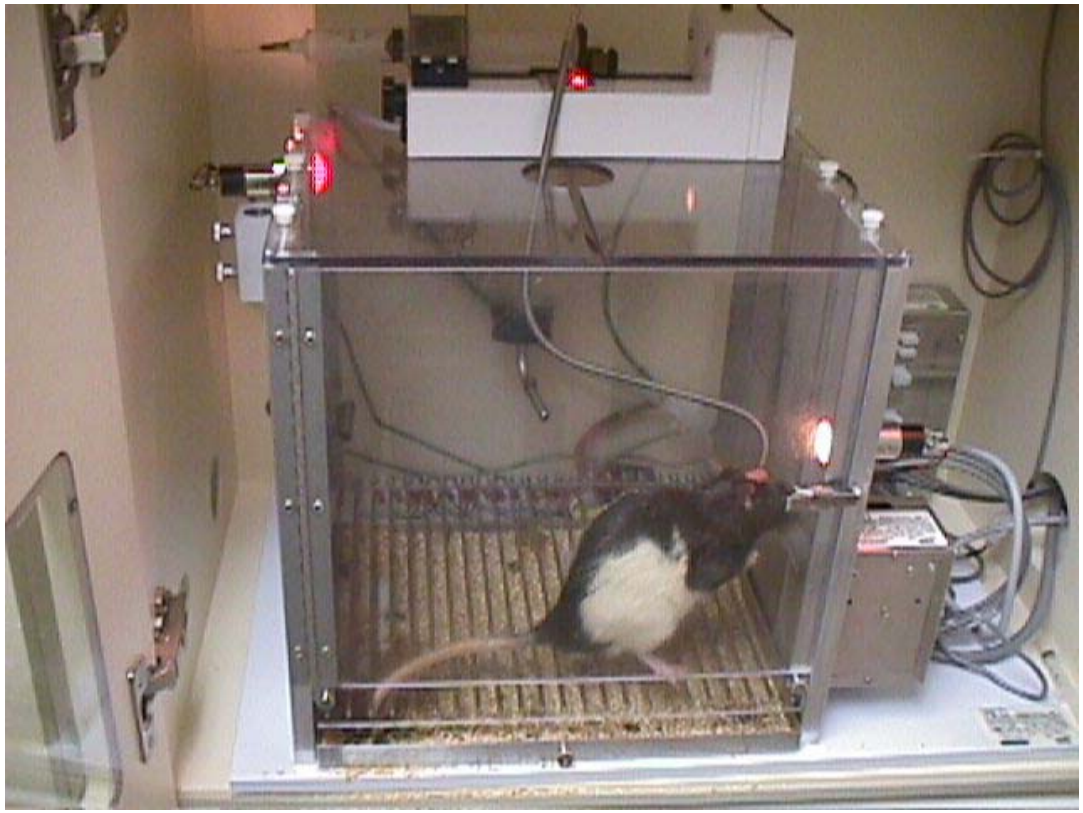
Background

The clinical problem: Relapse to cocaine use after prolonged abstinence

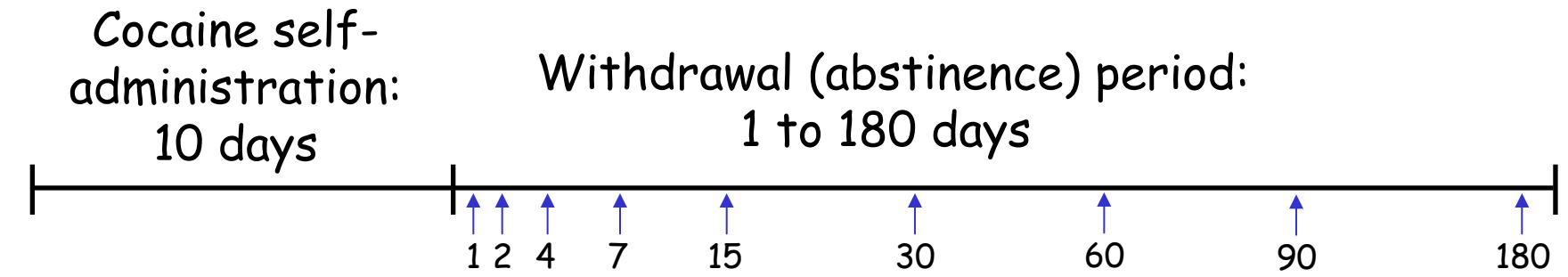
This relapse can be provoked by re-exposure to cocaine-associated cues that also induce drug craving

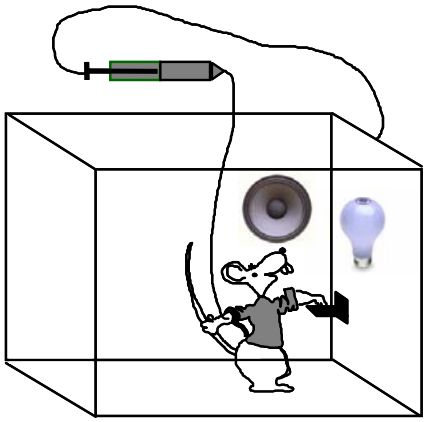
Based on anecdotal evidence, Gawin and Kleber (1986) suggested that cue-induced cocaine craving increases over the first several weeks of abstinence and remains high over extended abstinence periods

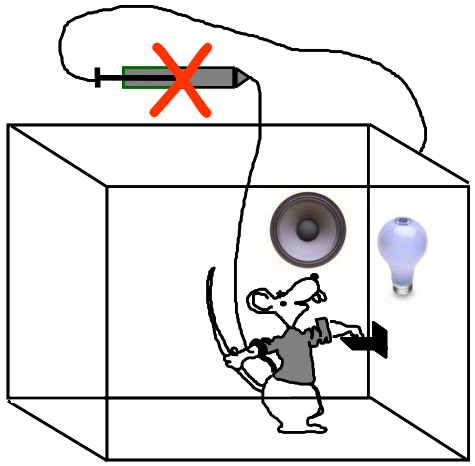
Research question: how do we study this "incubation" phenomenon in the laboratory rat?



An experimental procedure to study time-dependent changes in cue-induced cocaine seeking

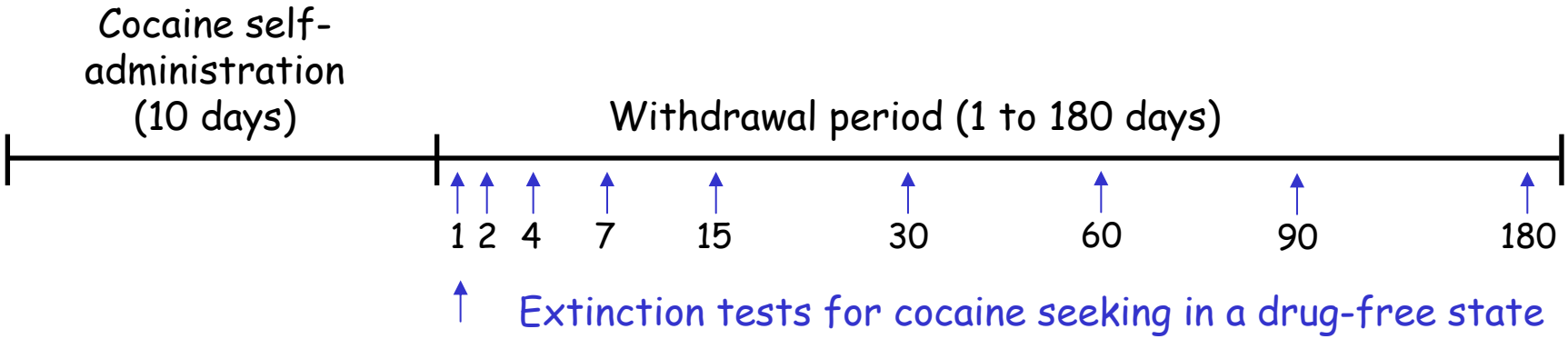


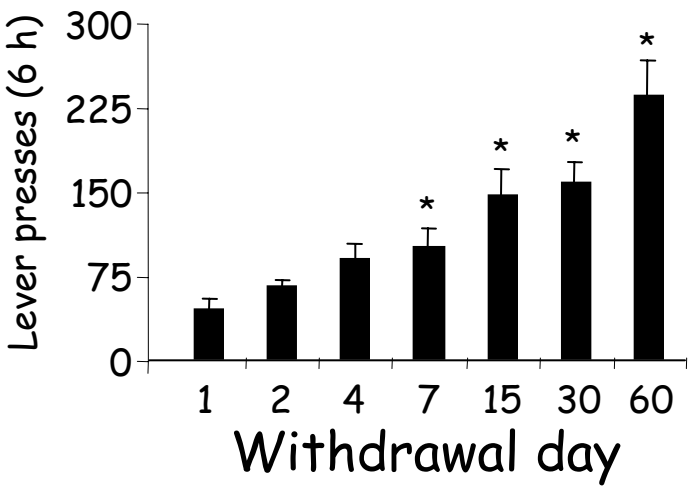




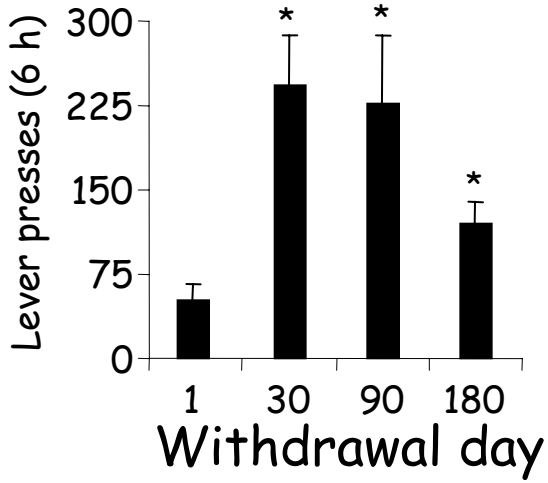
↑ Extinction tests for cocaine seeking in a drug-free state

Time-dependent increases in cue-induced cocaine seeking after withdrawal from drug self-administration





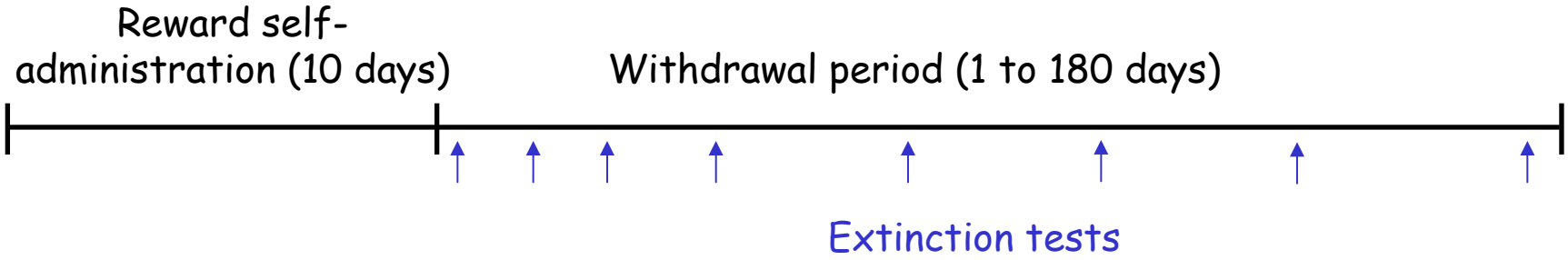
60 days in rats ~ 5-6 years in humans



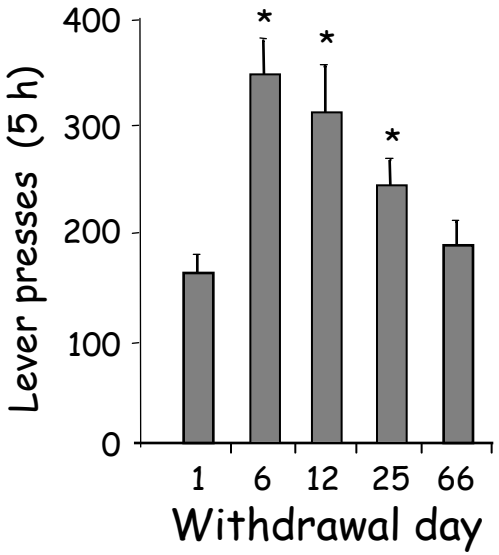
180 days in rats ~ 15-18 years in humans

Grimm et al. **Incubation of cocaine craving after withdrawal.** Nature, 2001

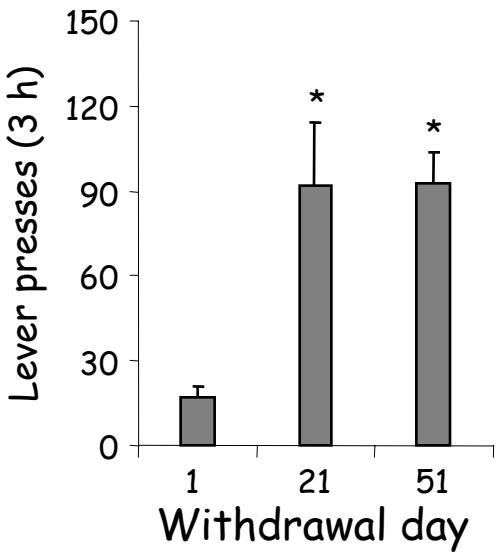
Generality of the incubation phenomenon to other drug and non-drug rewards



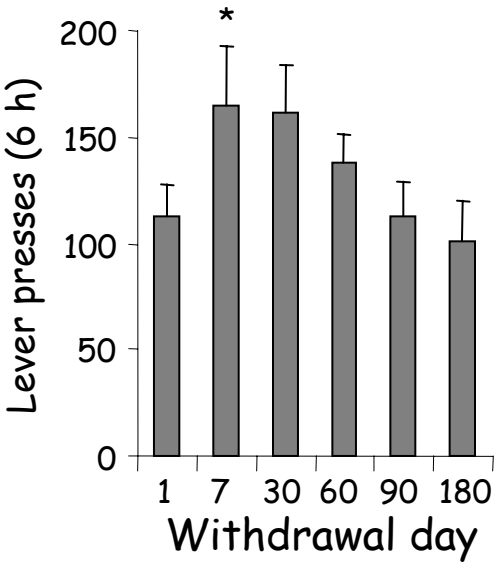
Heroin



Methamphetamine



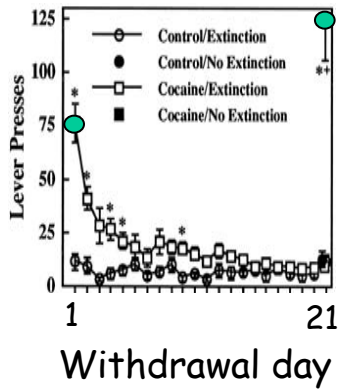
Sucrose



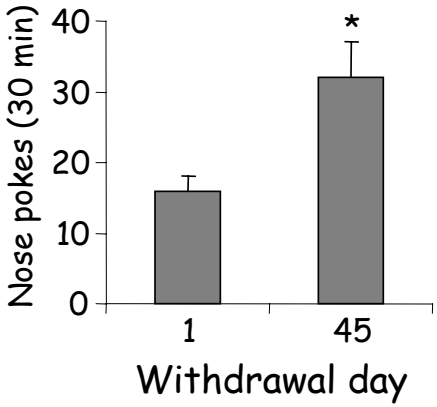
Shalev et al. Psychopharmacology, 2001
Lu et al. Neuropharmacology, 2004
Shepard et al. Biol Psychiatry, 2004

More evidence for incubation of reward craving

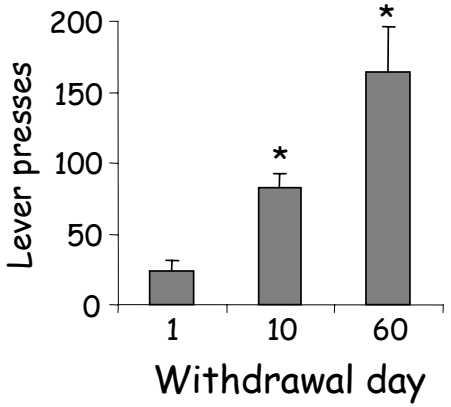
Cocaine 1
Neisewander et al. 2000



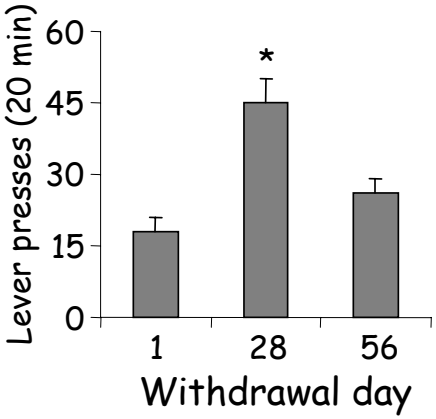
Cocaine 2
Conard, Marinelli, Wolf, 2005



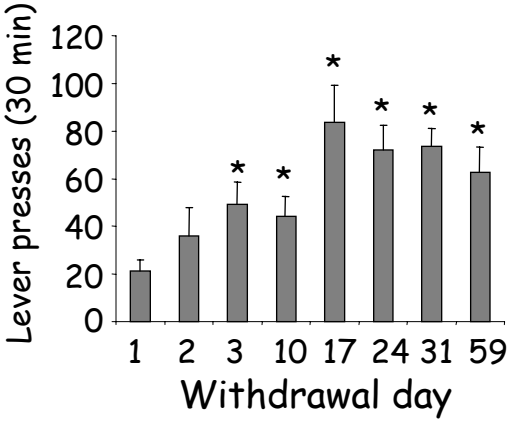
Cocaine 3
Sorge and Stewart, 2005



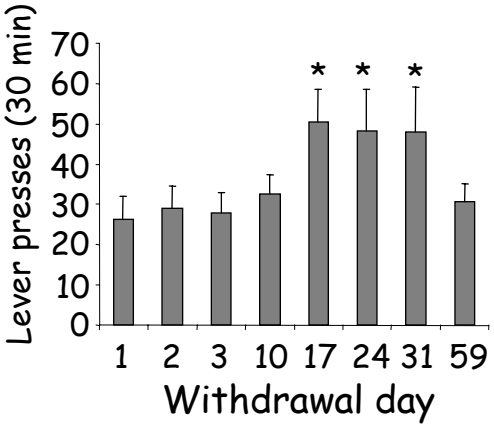
Alcohol
Bienkowski et al. 2004



Heroin
Di Ciano and Everitt 2004



Sucrose
Di Ciano and Everitt 2004



Summary of behavioral findings

Incubation of reward craving:

- Long-lasting, but not permanent
- Observed with several drugs of abuse
- Observed with non-drug reinforcers
- Not evident after acute re-exposure to cocaine priming injections

Lu L, Grimm JW, Hope BT, Shaham Y (2004) Incubation of cocaine craving after withdrawal: a review of preclinical data. Neuropharmacology 47S1: 214-227 (NIDA special issue)

The neuronal mechanisms of incubation of craving

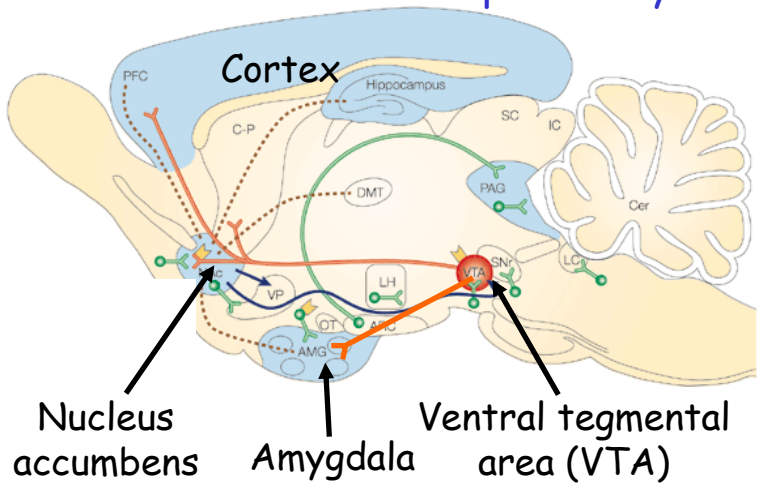
Initial molecular findings

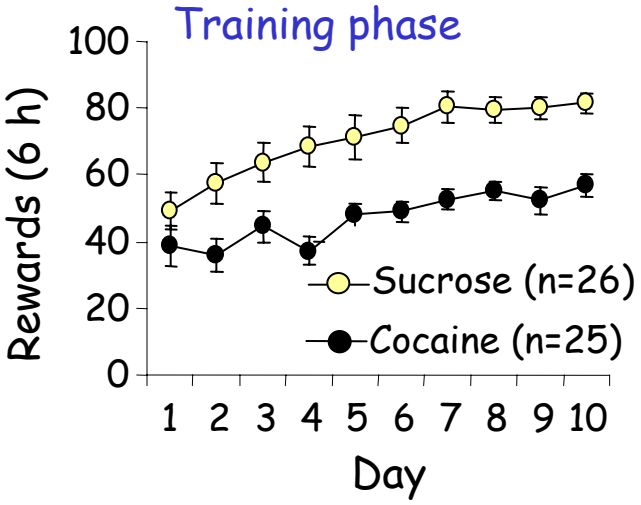
The neuroadaptation hypothesis of addiction

Chronic drug exposure causes long-lasting molecular, cellular, and neurochemical adaptations in the mesocorticolimbic dopamine system that underlie compulsive drug use and prolonged relapse vulnerability during abstinence

(Karler et al., 1989; Wolf and Khansa, 1991 ; Nestler et al. 1990; Kalivas and Stewart 1991)

The mesocorticolimbic dopamine system





Withdrawal phase

1 day
30 days
90 days

From Nestler. Nat. Rev. Neurosci. 2001

Summary of initial molecular findings

Incubation of cocaine craving:

Associated with increases in peptide levels of brain-derived neurotrophic factor (BDNF) in VTA, accumbens and amygdala

Not associated with increases in protein levels of AMPA and NMDA glutamate receptor subunits in VTA, accumbens and amygdala

Not associated with increases in protein levels of cyclin-dependent kinase 5 (cdk5) and tyrosine hydroxylase (TH) in VTA and accumbens

Not associated with increases in the activity of cAMP-dependent protein kinase (PKA) and adenylate cyclase (AC) in VTA and accumbens

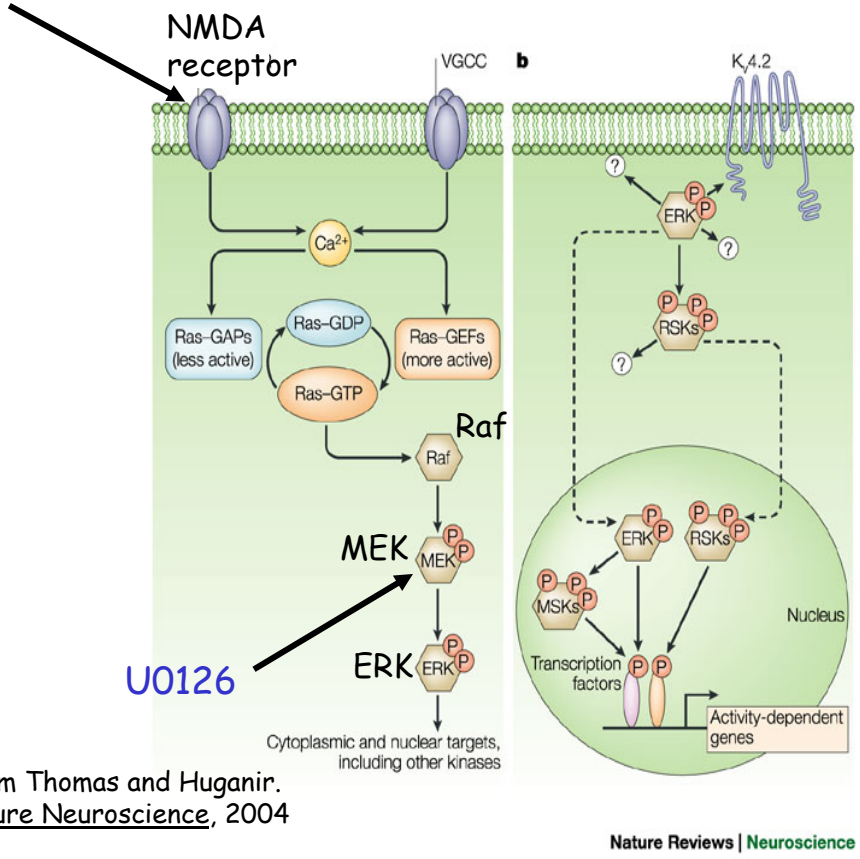
Grimm et al. J Neurosci 2003
Lu et al. J Neurochem 2003, 2005
Lu et al. J Neurosci 2004

Role of central amygdala ERK in incubation of cocaine craving

Lin Lu

Collaborator: Bruce Hope

NMDA/AP-5



From Thomas and Huganir. Nature Neuroscience, 2004

ERK
(extracellular signal-regulated kinase)

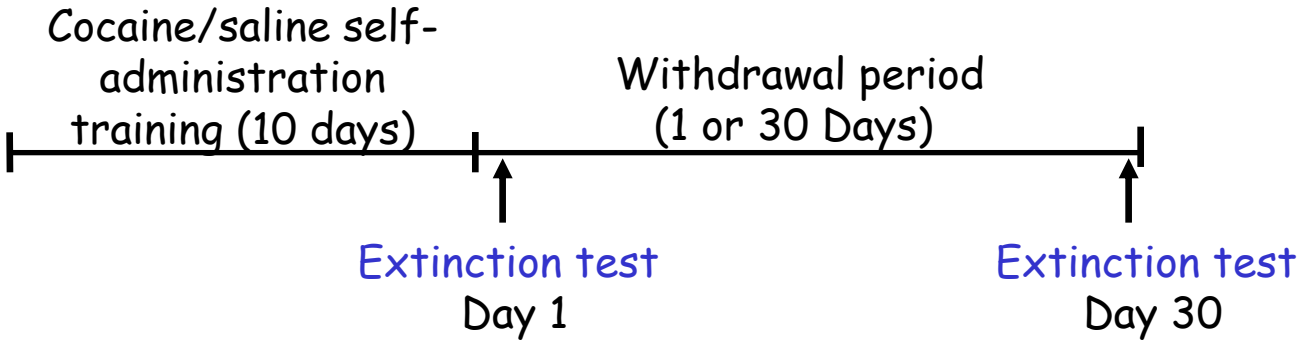
A key regulator of synaptic plasticity and learning and memory (Sweatt 2001)

Amygdala ERK is involved in conditioned fear responses (Schaffe et al. 2000)

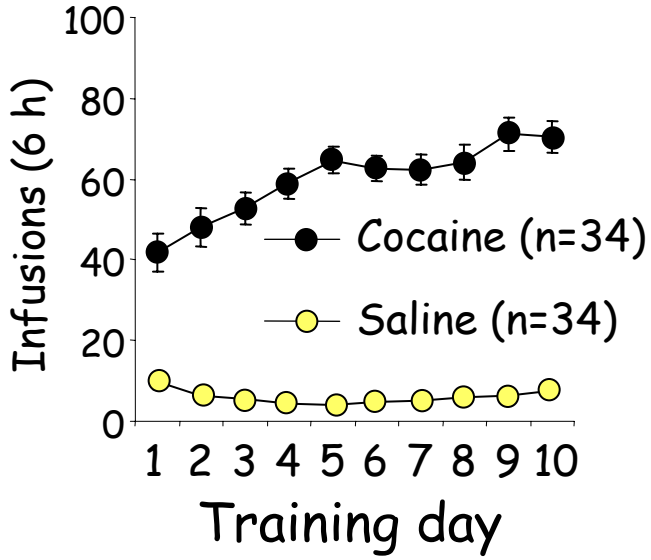
Mesolimbic ERK is activated by cocaine (Licata and Pierce 2003; Valjent et al. 2000)

The human amygdala is activated by cocaine cues (Grant et al. 1996; Childress et al. 1999)

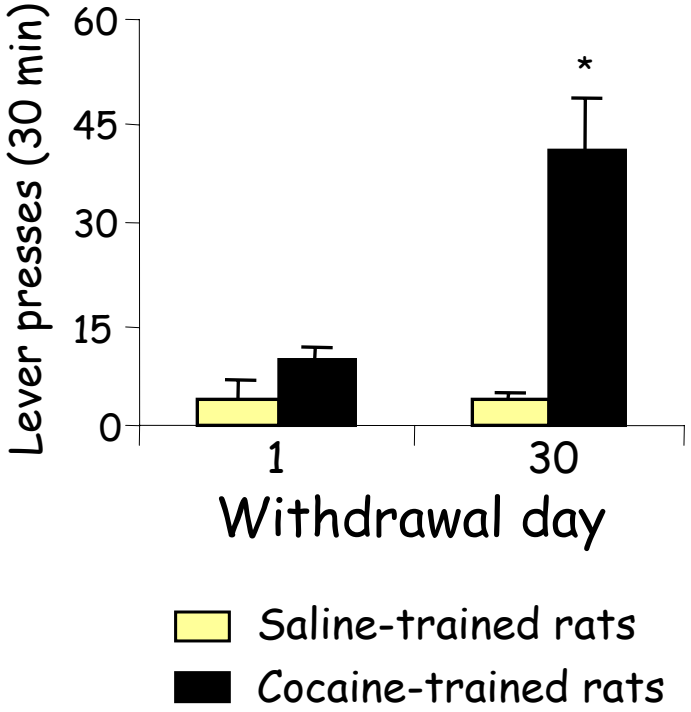
Behavioral data: Training and extinction tests



Training

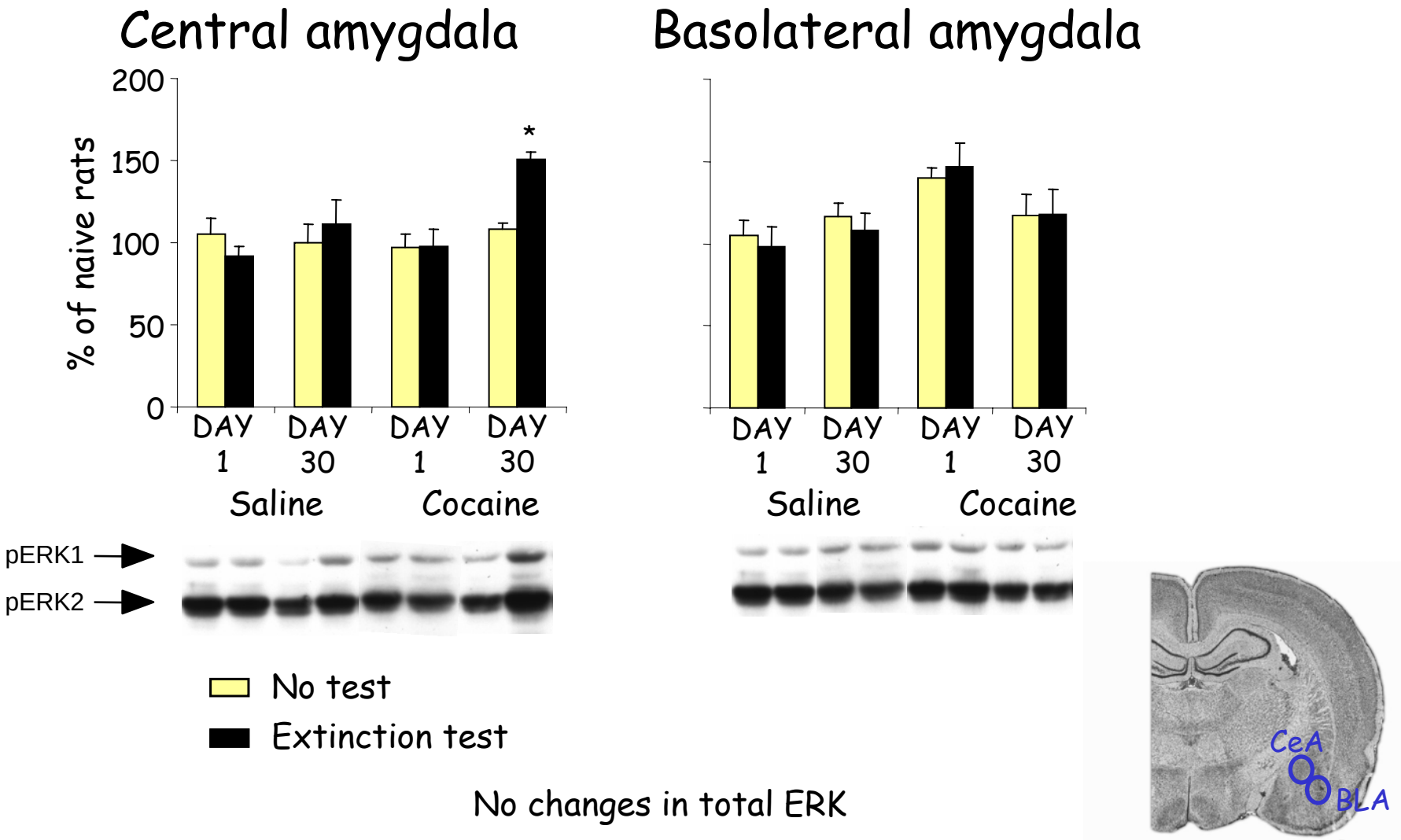


Extinction test



Lu, Hope et al. Nature Neuroscience, 2005

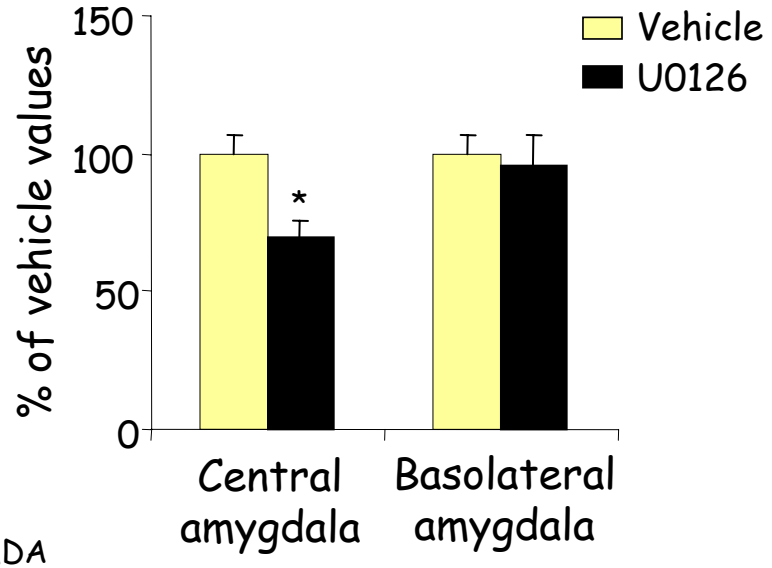
Exposure to cocaine cues increases ERK phosphorylation in the central amygdala after 30 days of withdrawal



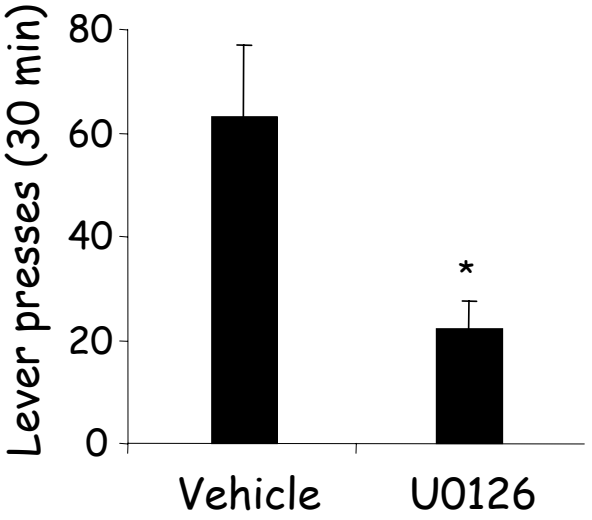
No changes in total ERK

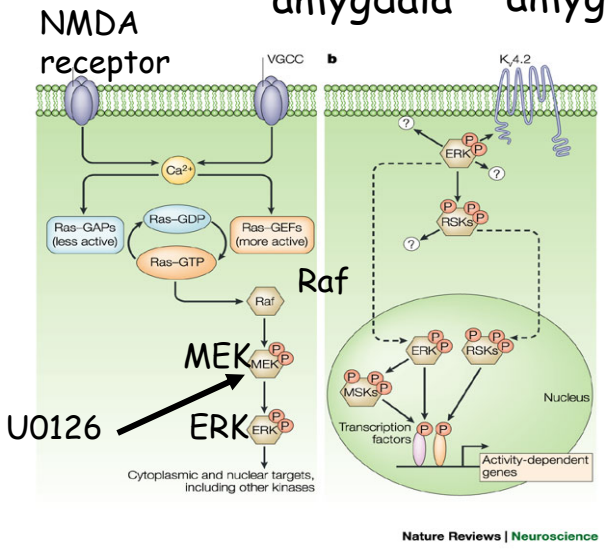
Inhibition of ERK phosphorylation in the central amygdala attenuates cocaine seeking after 30 days of withdrawal

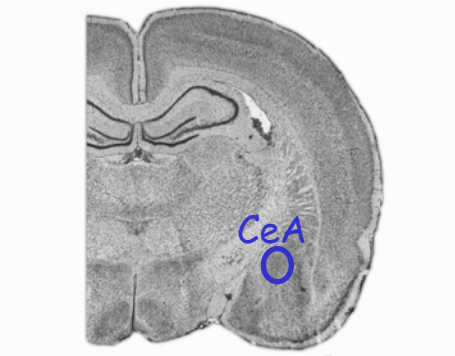
Phosphorylated ERK



Extinction responding

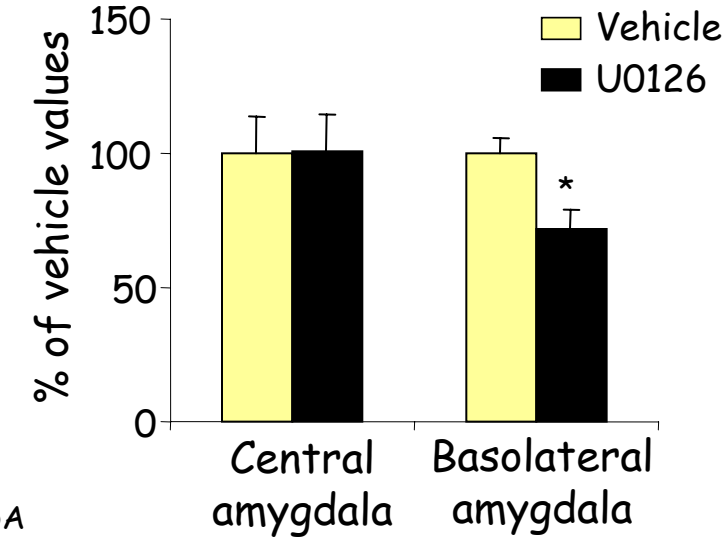




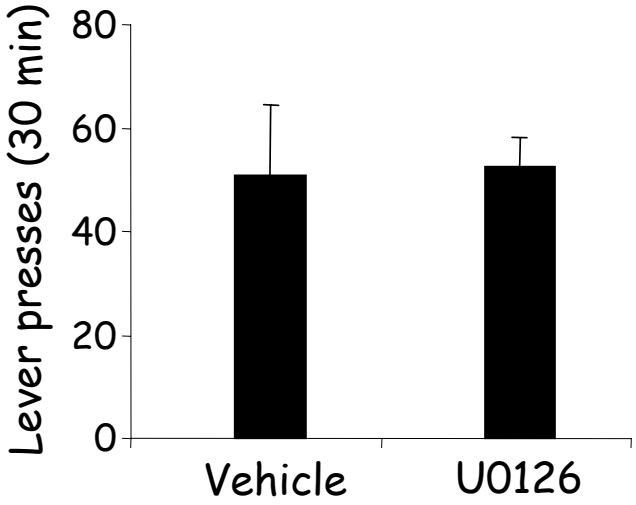


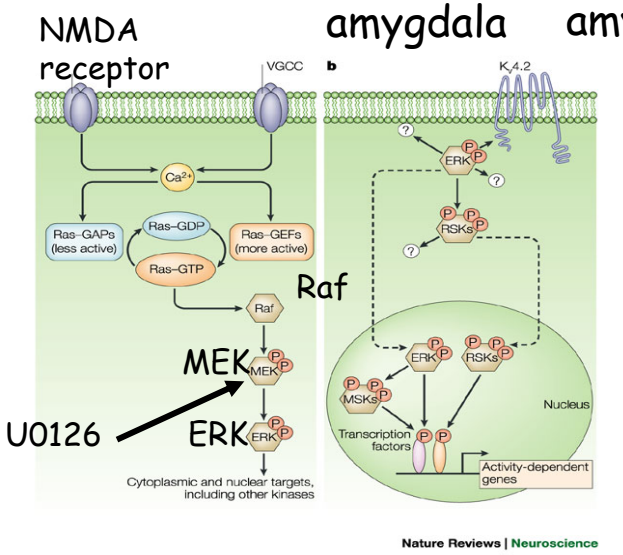
Inhibition of ERK phosphorylation in the basolateral amygdala has no effect on cocaine seeking after 30 days of withdrawal

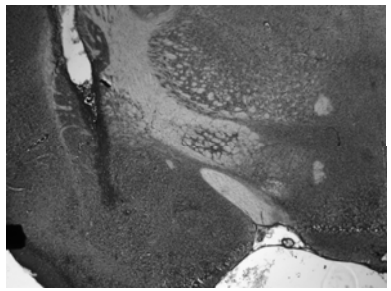
Phosphorylated ERK

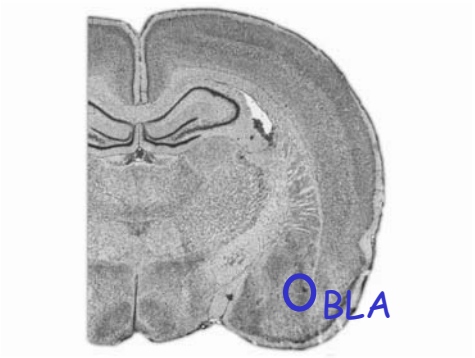


Extinction responding



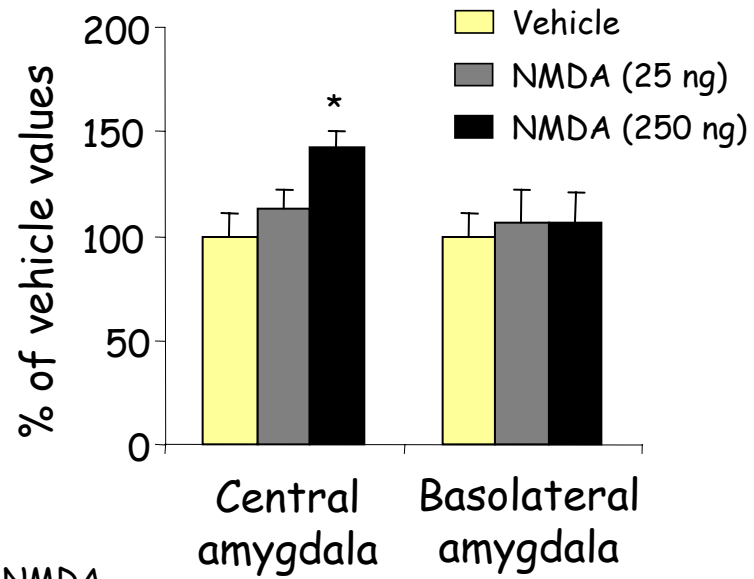




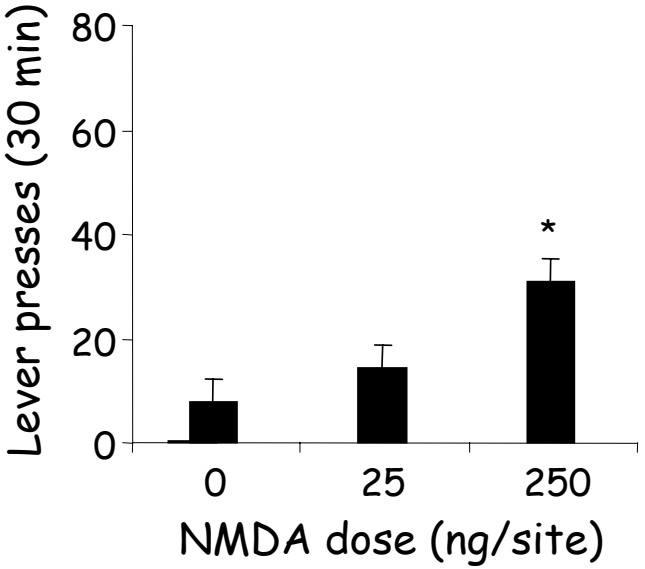


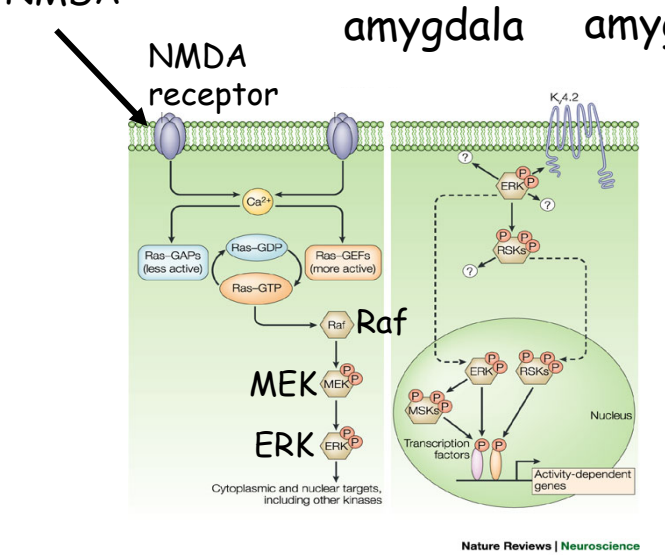
Induction of ERK phosphorylation in the central amygdala restores cocaine seeking after 1 day of withdrawal

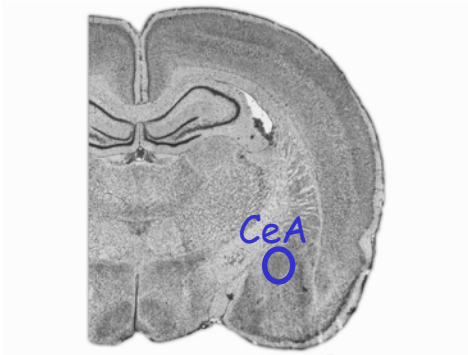
Phosphorylated ERK



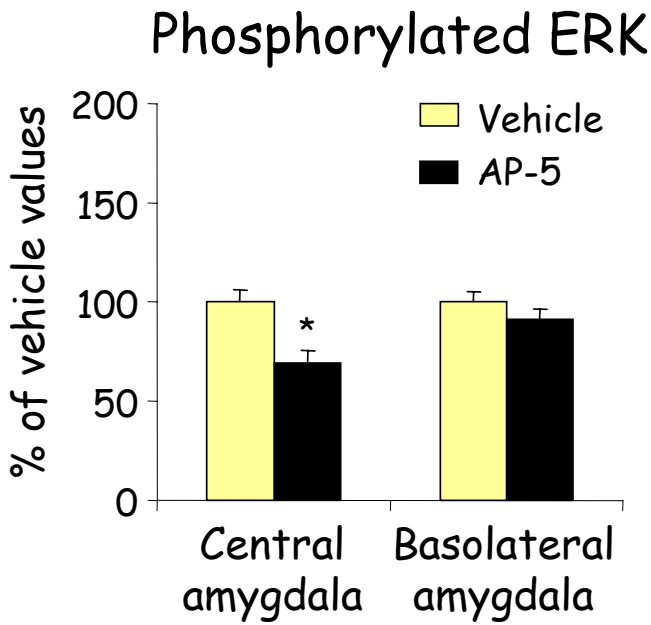
Extinction responding

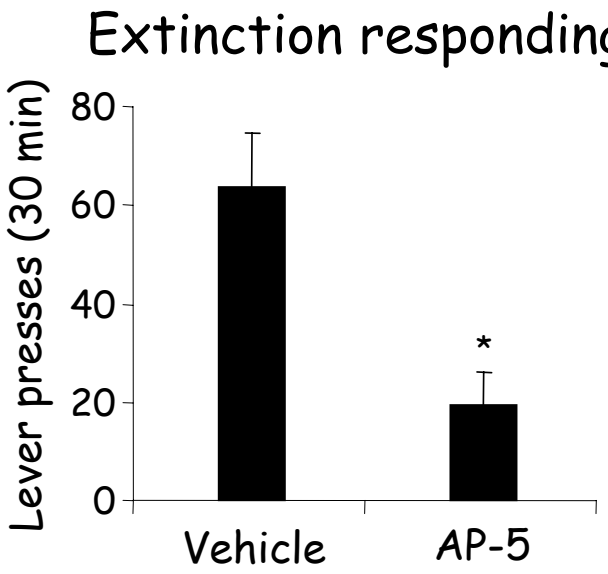


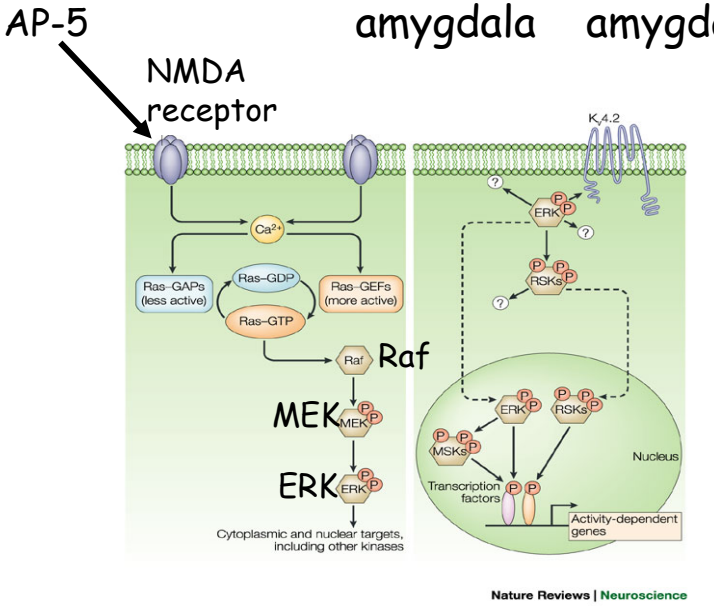


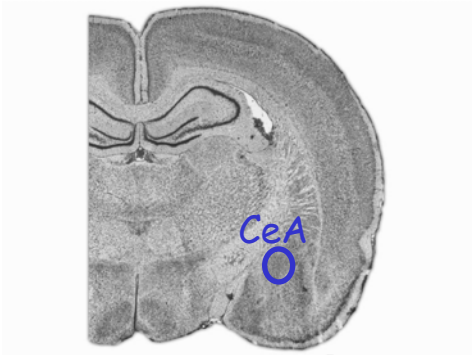


Blockade of NMDA receptors in the central amygdala attenuates cocaine seeking after 30 days of withdrawal



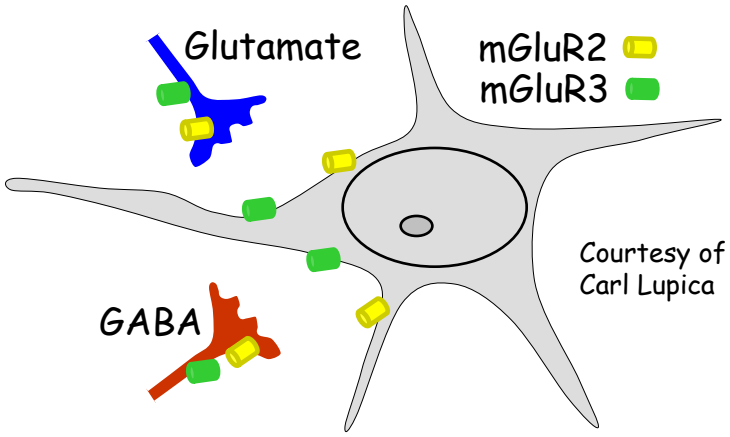




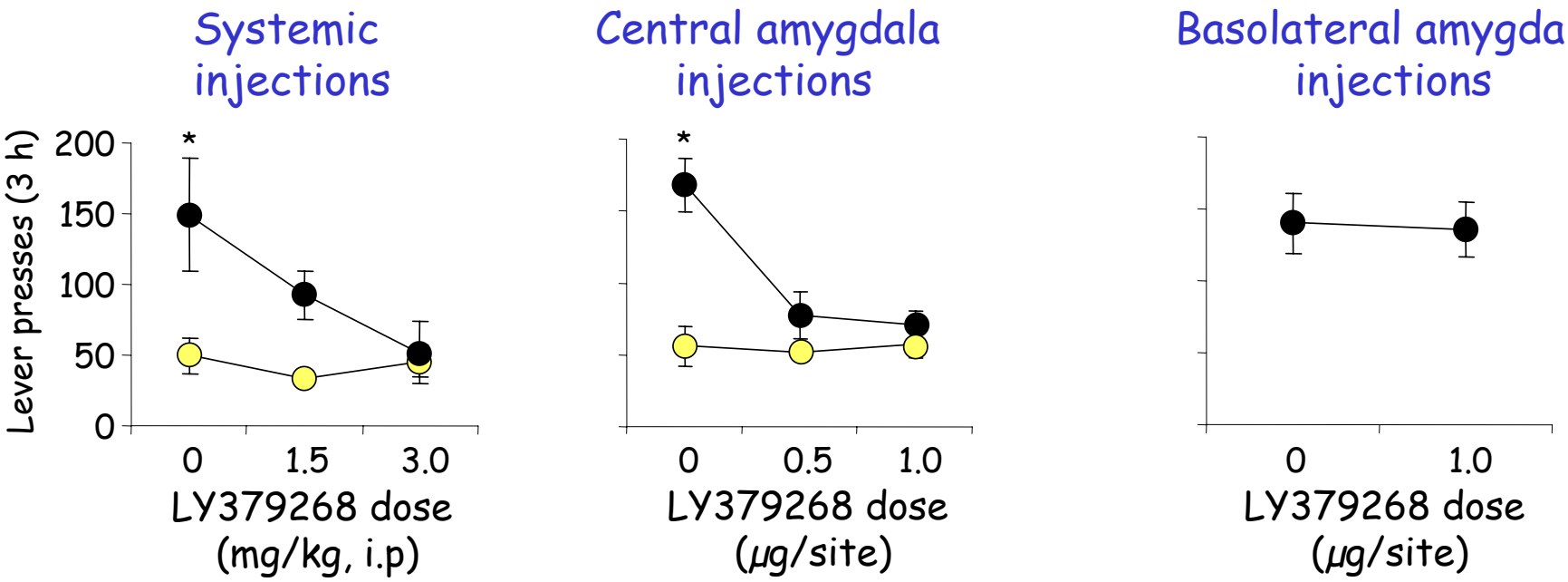


More evidence for a role of central amygdala glutamate in incubation of craving

LY379268: a selective agonist of $mGluR_{2/3}$ receptors that decreases evoked glutamate release



Day 21 withdrawal
Day 3 withdrawal



Lu et al. Biological Psychiatry 2006

Conclusions

Incubation of reward craving is a general phenomenon that occurs with both drug and non-drug rewards

Time-dependent increases in the responsiveness of central amygdala ERK and glutamate to cocaine cues mediate the incubation of craving

Implications for treatment

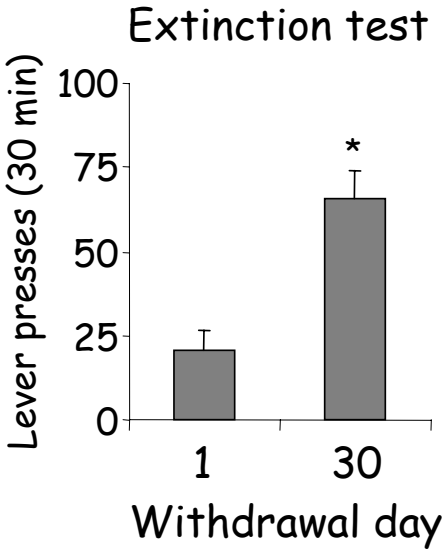
Drug addicts may be very vulnerable to relapse at time periods that are far beyond the acute drug withdrawal phase

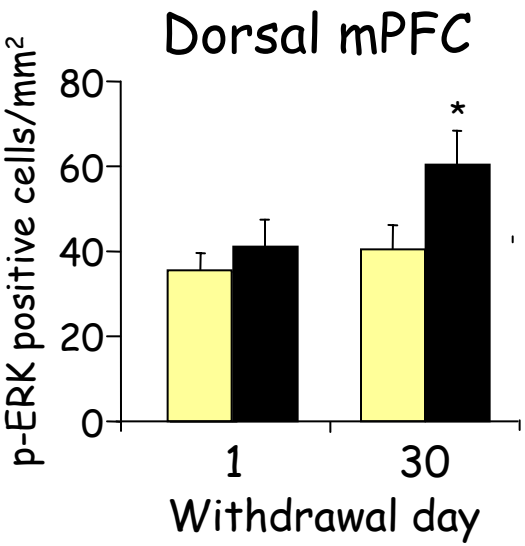
Time away from drug (e.g., incarceration) is not a good method for relapse prevention

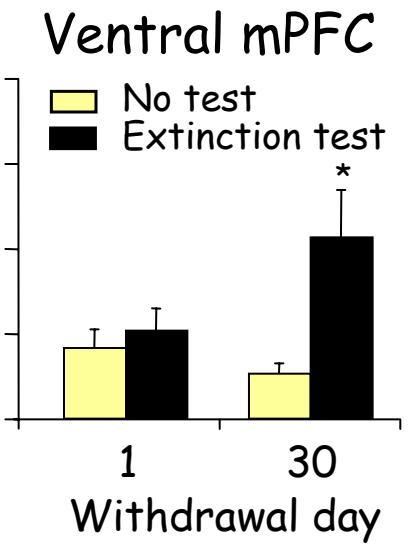
Our studies suggest that $mGluR_{2/3}$ agonists should be considered in the treatment of relapse to cocaine and other drugs

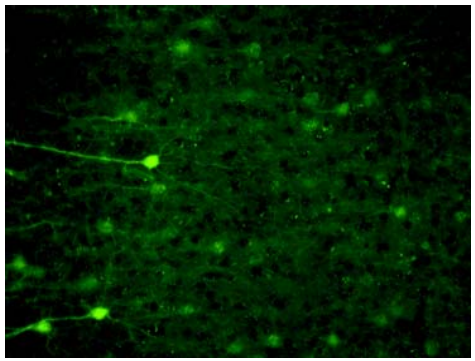
An update on incubation of cocaine craving (1)

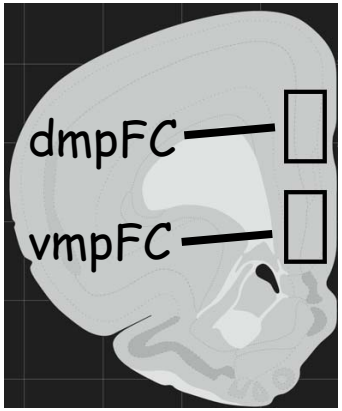
Exposure to cocaine cues increases ERK phosphorylation in the medial prefrontal cortex after 30 days of withdrawal









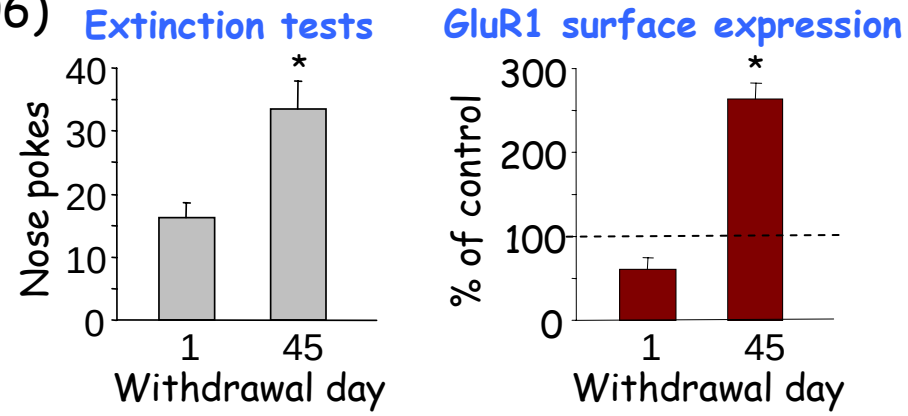


Koya, Uejima et al. SFN 2006

An update on incubation of cocaine craving (2)

Incubation of cocaine craving:

- Enhanced in GluR1 knockout mice (Mead et al. Neuropsychopharmacol. 2006)
- Attenuated by inhibition of protein synthesis in the amygdala following cue exposure during early withdrawal (Lee et al. J. Neurosci. 2006)
- Associated with increases in neuronal activity in the accumbens (Hollander & Carelli. Neuropsychopharmacol. 2006)
- Associated with greater total production and surface expression of GluR1 in the accumbens (Conrad et al. SFN 2006)



Incubation of cocaine craving in humans:

Incubation of cocaine relapse during a disulfiram clinical trial (Kosten et al. CPDD 2005).

"In support of human 'incubation', only 3% of cocaine dependent subjects who stopped cocaine use for at least 2 weeks relapsed before week 4, and relapse peaked after 6.6 weeks of abstinence"

Acknowledgments

- Present post-doctoral fellows: Jennifer Bossert, Sunila Nair
- Present students: Jamie Uejima, Gabriela Poles, Sam Golden
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