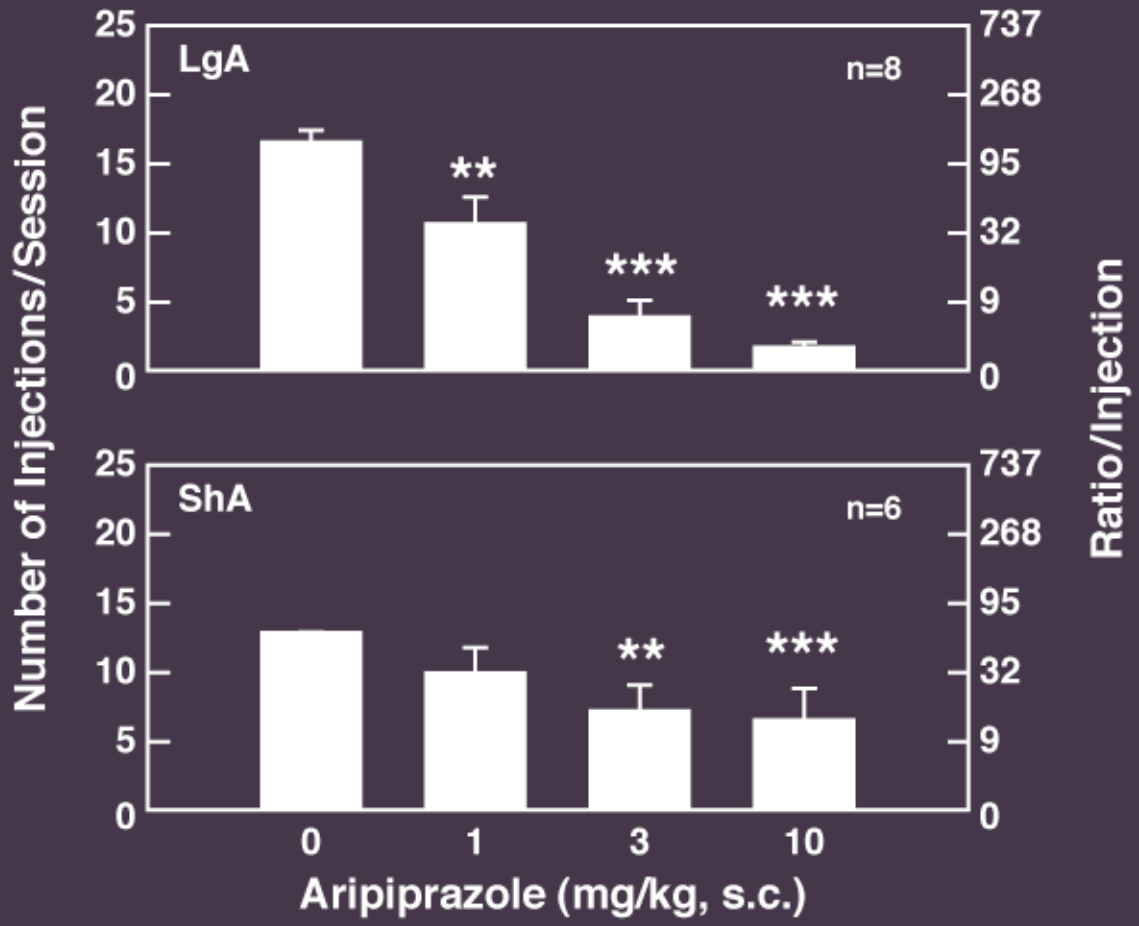
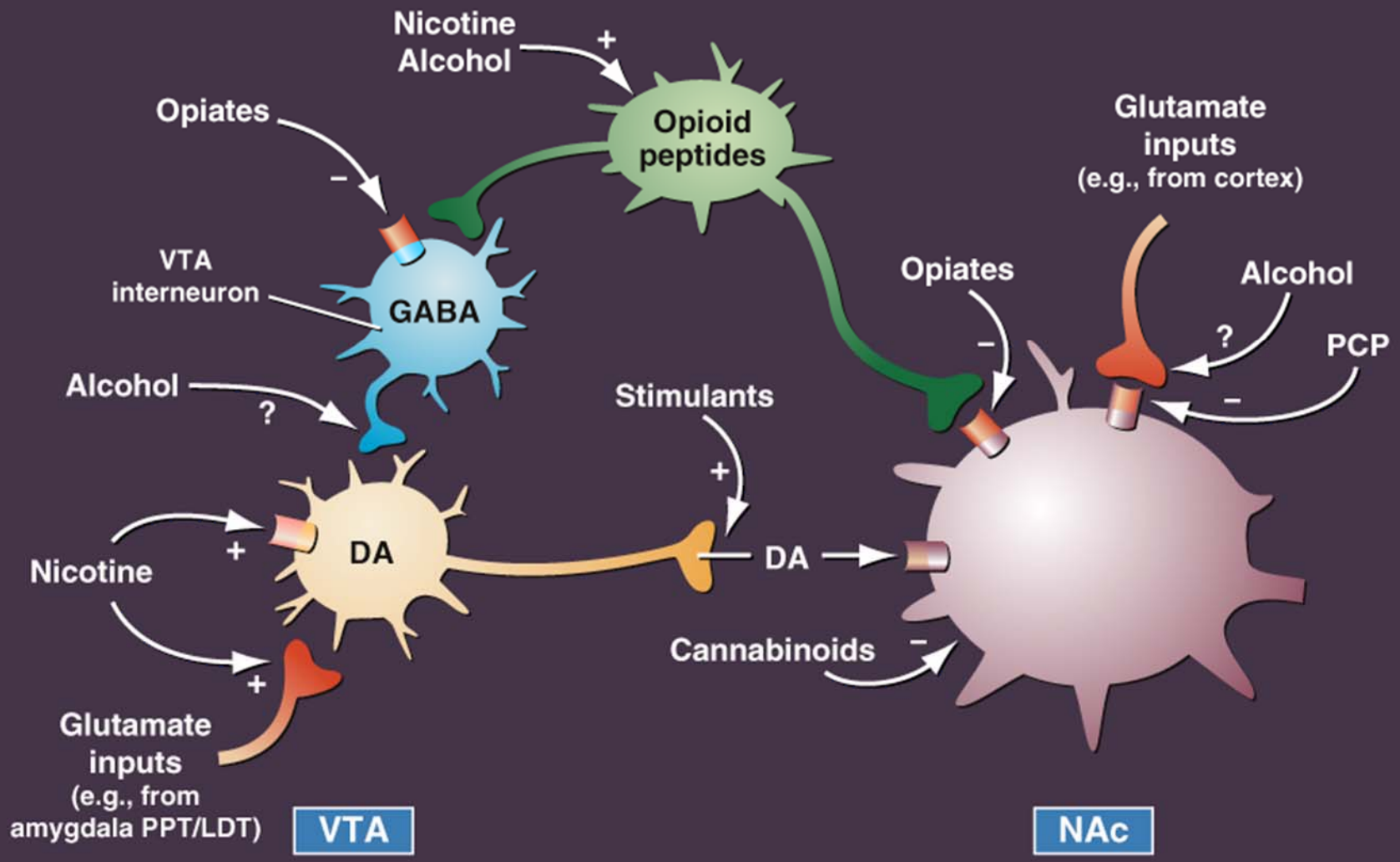
Effects of Aripiprazole on Methamphetamine Self-administration
(0.05 mg/kg/inf progressive-ratio)



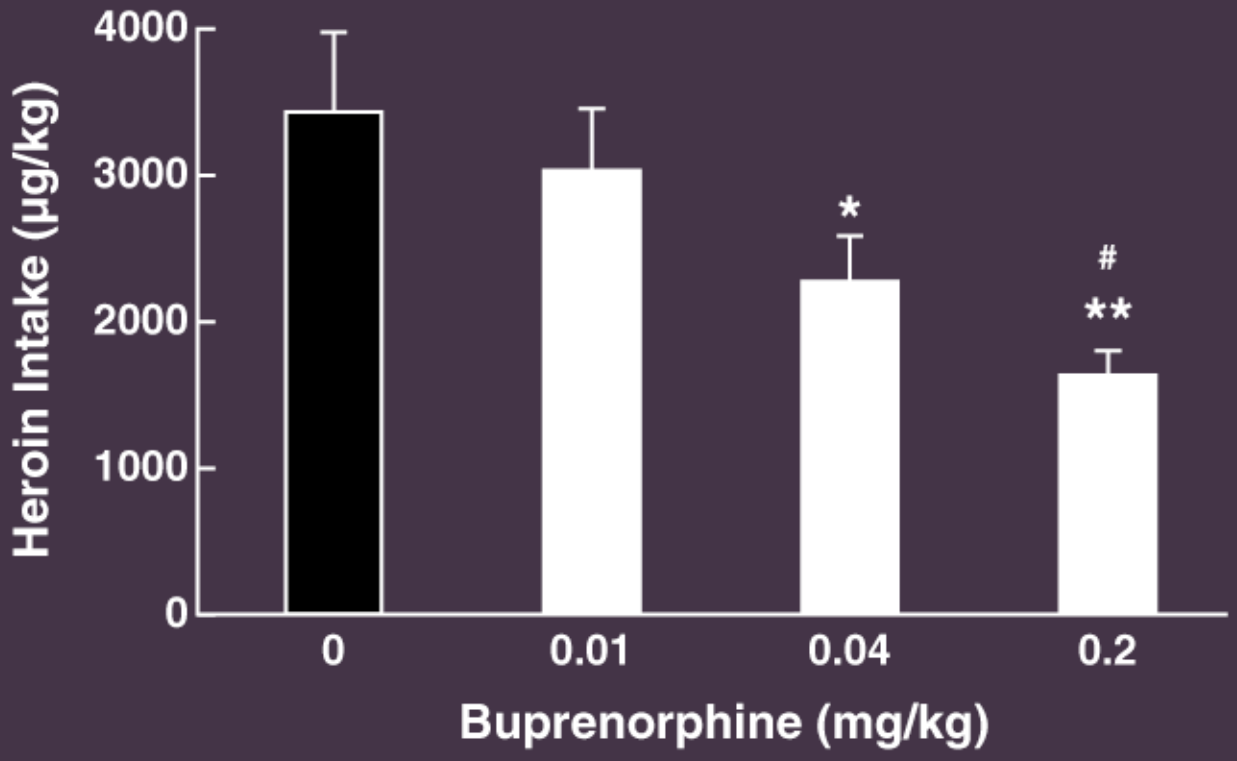
Adapted from: Wee S, Wang Z, Woolverton WL, Pulvirenti L and Koob GF, Neuropsychopharmacology, 2007, 32:2238-2247.

Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens



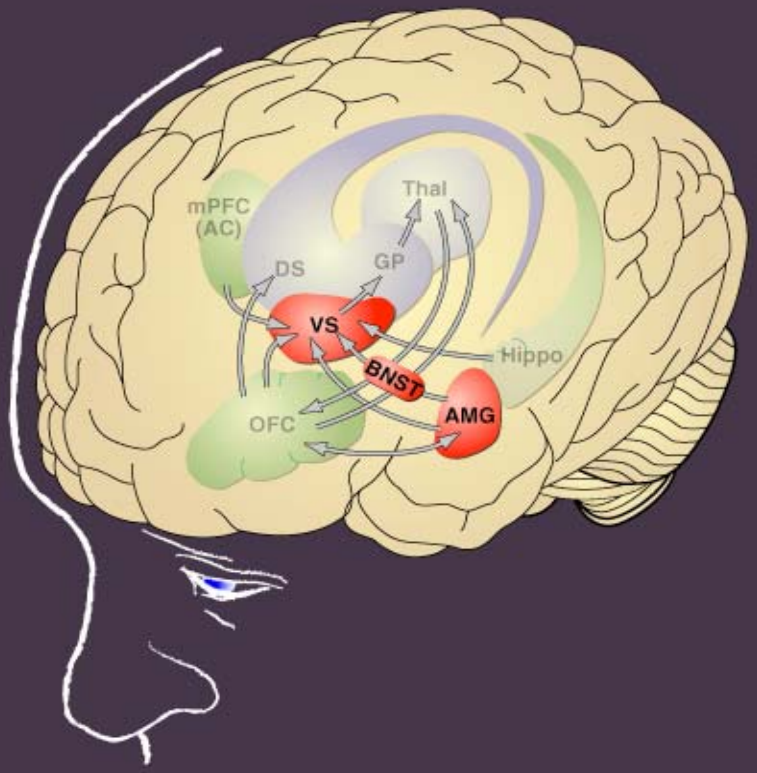
From: Nestler EJ, Nat Neurosci, 2005, 8:1445-1449.

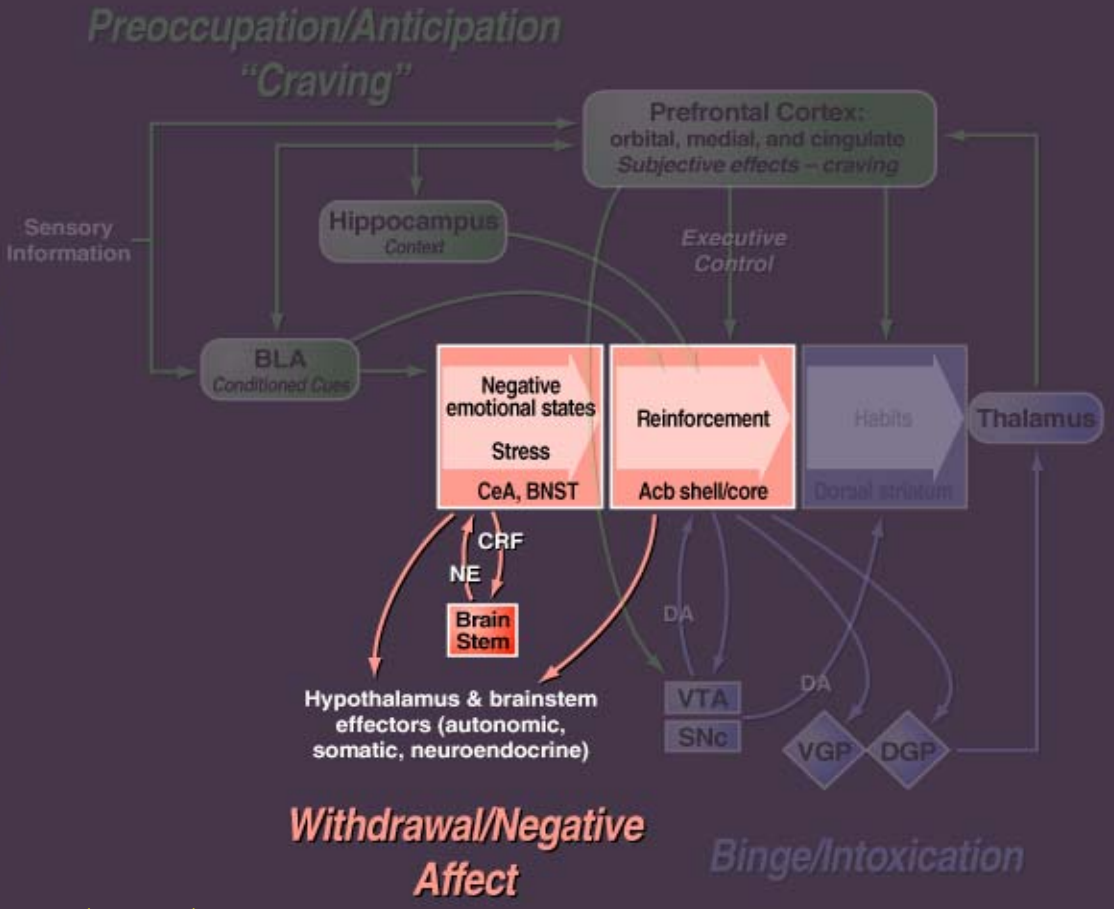
Effect of Partial Opioid Agonist Buprenorphine on Heroin Self-Administration in Rats



From: Chen SA, O'Dell L, Hoefer M, Greenwell TN, Zorrilla EP and Koob GF, Neuropsychopharmacology, 2006, 31:2692-2707, 2802.

Existing and Future Medications for Addiction: Withdrawal/Negative Affect Stage





Existing medications
- methadone
- buprenorphine
- varenicline

Future targets
- GABA modulators
- CRF_1 receptors
- κ opioid antagonists

Anti-Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

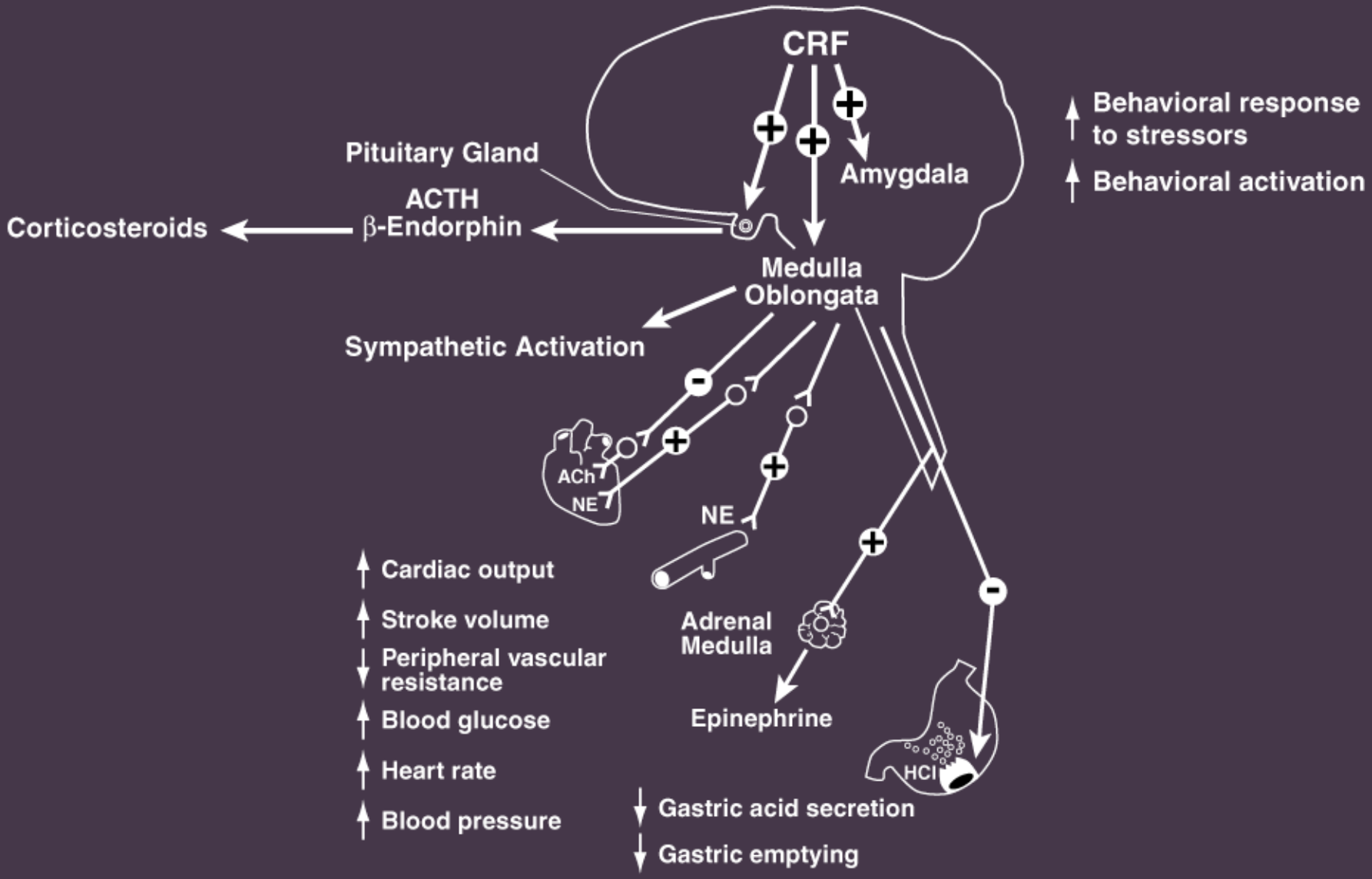
Dynorphin … “dysphoria”

CRF … stress

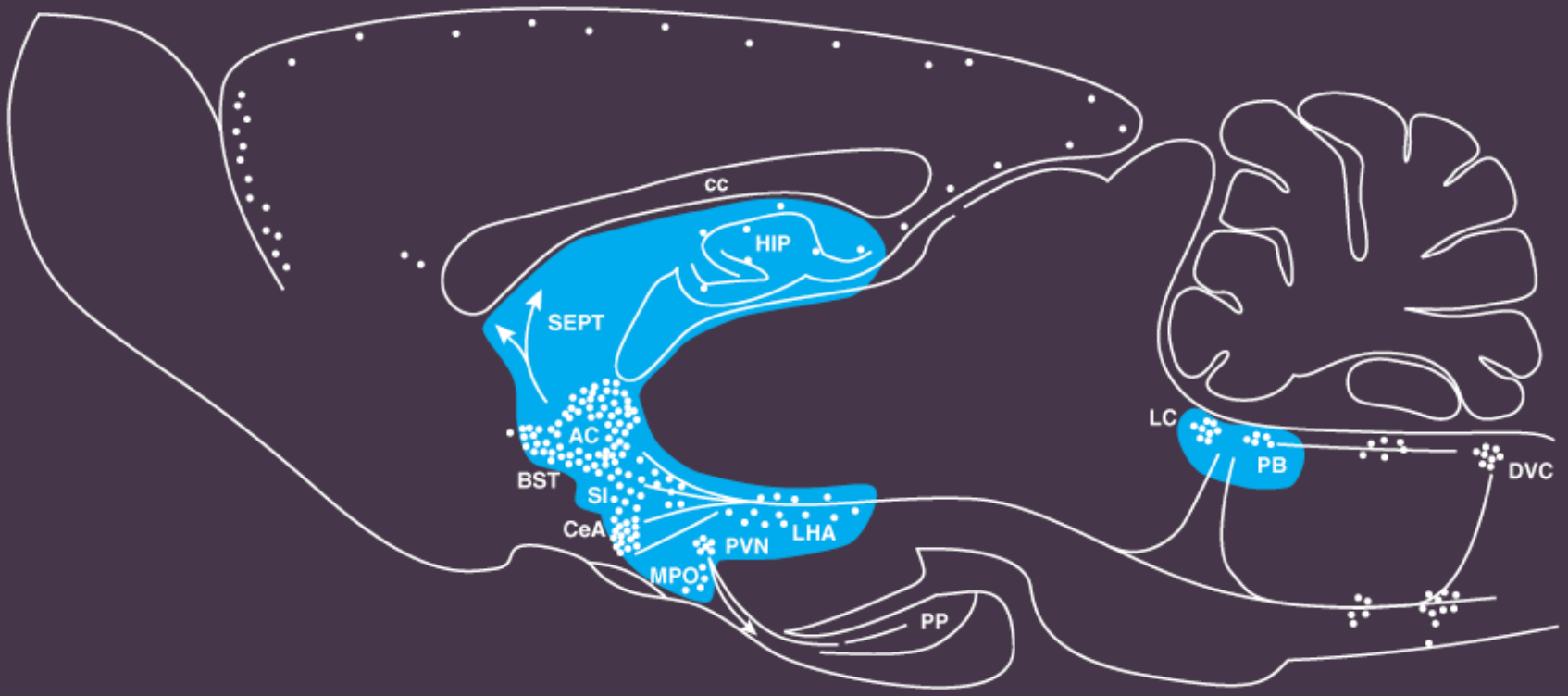
Norepinephrine … stress

NPY … anti-stress

CNS Actions of Corticotropin-Releasing Factor (CRF)



Major CRF-Immunoreactive Cell Groups and Fiber Systems in the Rat Brain

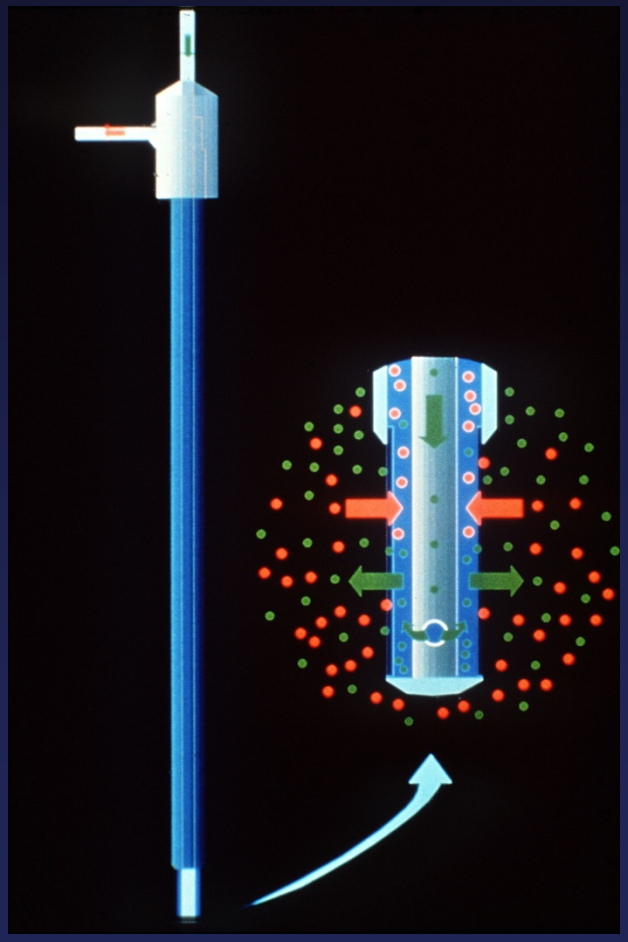


From: Swanson LW, Sawchenko PE, Rivier J and Vale W, Neuroendocrinology, 1983, 36:165-186.

CRF Produces Arousal, Stress-like Responses, and a Dysphoric, Aversive State

Paradigm	CRF Agonist	CRF Antagonist
Acoustic startle	Facilitates startle	Blocks fear-potentiated startle
Elevated plus maze	Suppresses exploration	Reverses suppression of exploration
Defensive burying	Enhances burying	Reduces burying
Fear conditioning	Induces conditioned fear	Blocks acquisition of conditioned fear
Cued electric shock	Enhances freezing	Attenuates freezing
Taste / Place Conditioning	Produces place aversion	Weakens drug-induced place aversion

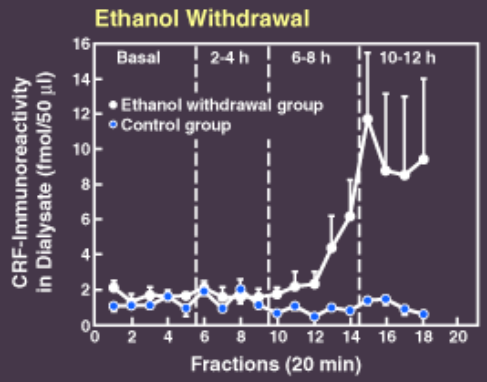
Sampling of Interstitial Neurochemicals by *in vivo* Microdialysis

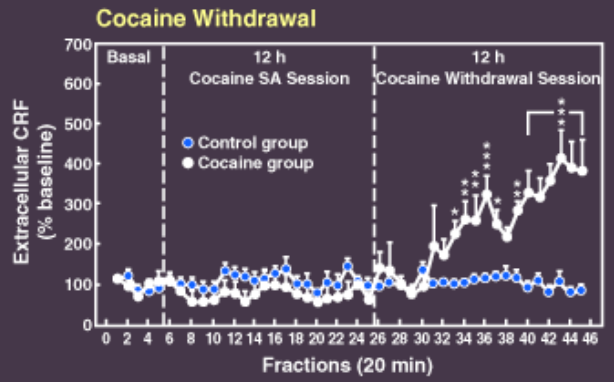


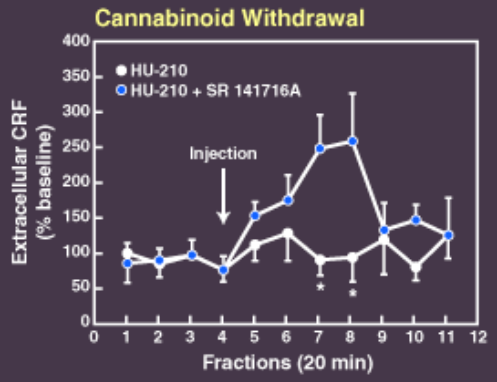
- Allows sampling of neurochemicals in conscious animals (correlate brain chemistry with behavior).
- Implanted so that semi-permeable probe tip is in specific brain region of interest.
- Substances below the membrane MW cutoff diffuse across membrane based on concentration gradient.
- Both neurochemical sampling and localized drug delivery are possible.

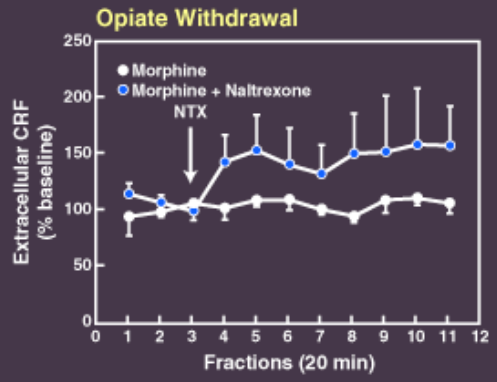
Collaborators: Dr. Friedbert Weiss, Dr. Larry Parsons, Dr. Emilio Merlo-Pich, Dr. Regina Richter

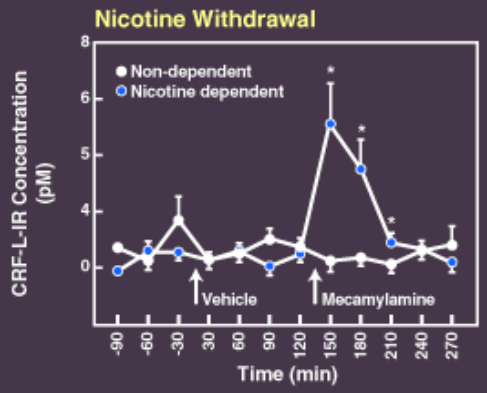
Withdrawal-induced Increases in Extracellular Levels of CRF









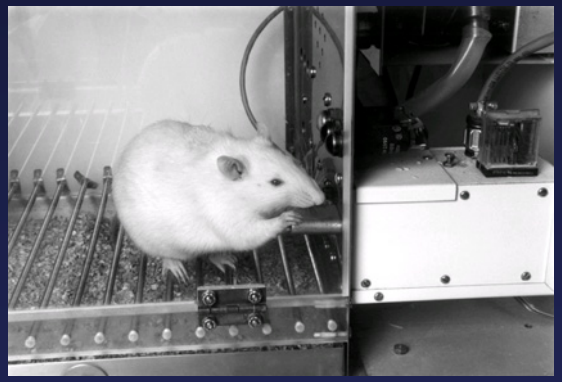


Ethanol	From: Merlo-Pich *et al.*, J Neurosci, 1995.
Cocaine	From: Richter and Weiss, Synapse, 1999.
Cannabinoid	From: Rodriguez de Fonseca *et al.*, Science, 1997.
Opiate	From: Weiss *et al.*, Ann NY Acad Sci, 2001.
Nicotine	From: George *et al.*, Proc Natl Acad Sci USA, 2007.

Rodent model of excessive drinking during withdrawal

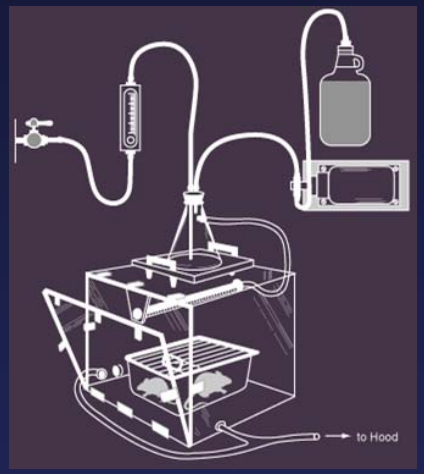
(*Roberts et al 1996, 2000; O'Dell et al 2004*)

Self-administration training → **Dependence induction** → **Withdrawal from alcohol vapors**



Sweetened solution fading used to train animals to lever press for:

10%w/v EtOH **vs** ***Water***



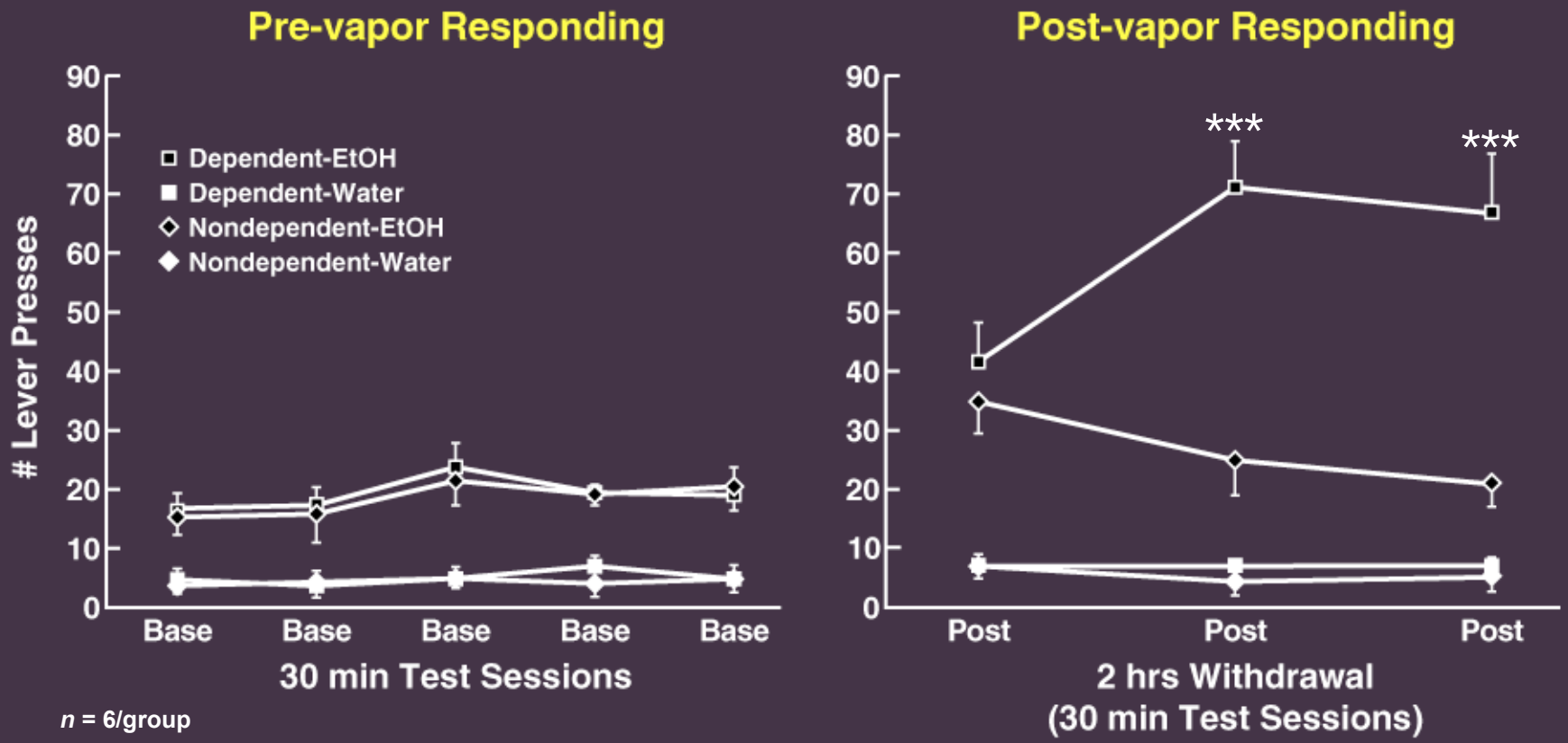
Chronic intermittent alcohol vapors (4+ wks)

Target blood alcohol levels (BALs): 0.125-.250 g%

Negative emotional state:
- Anxiety-like behavior
- Reward threshold deficits
- Increased CRF release in the extended amygdala

•Excessive drinking:
- 2-3 fold higher alcohol intake
- Increased progressive ratio breakpoints
- Relapse following prolonged abstinence

Enhanced Ethanol Self-Administration During Withdrawal in Dependent Animals

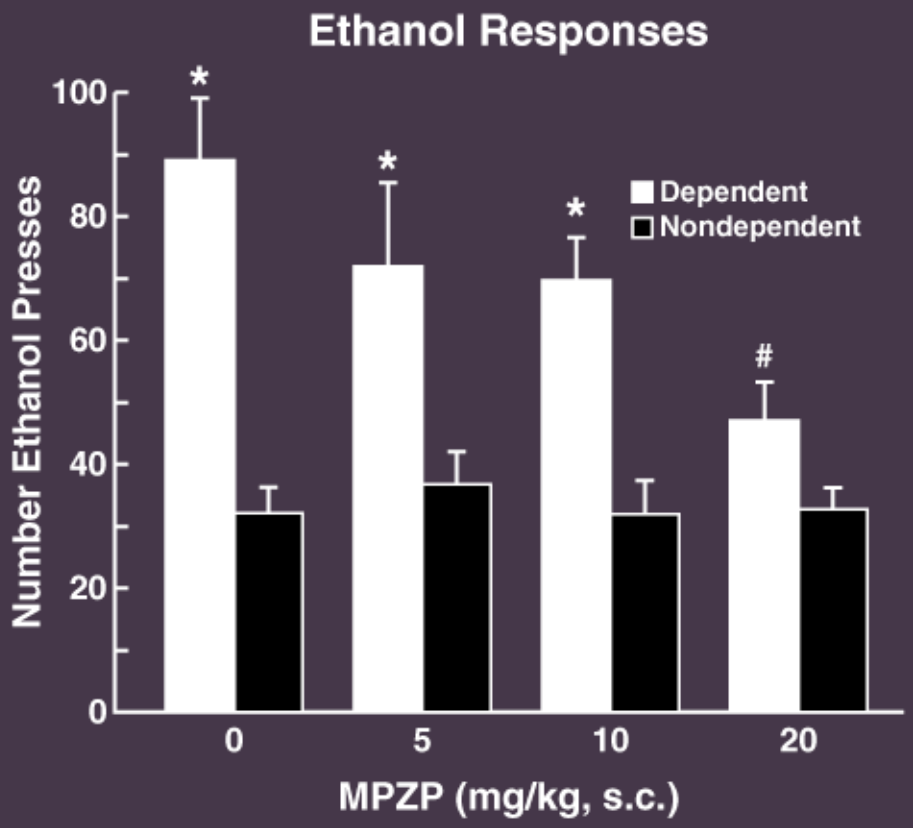


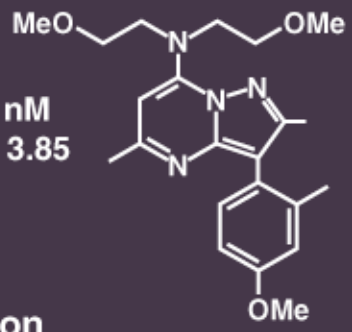
n = 6/group

*$p < 0.001$ vs. Nondependent-EtOH

From: Funk C and Koob GF, unpublished results.

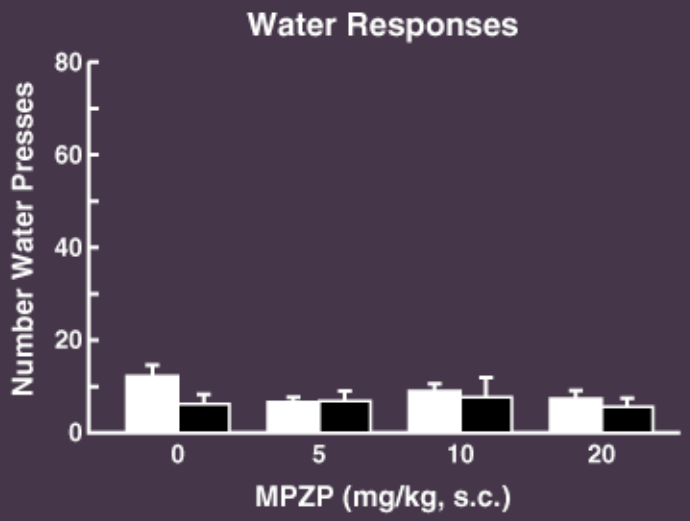
CRF_1 Specific Antagonists
MPZP





K_i = 10 nM
cLogP = 3.85

- administered s.c.
- 60 min pre-incubation
- n = 8
- HBC (20% w/v)

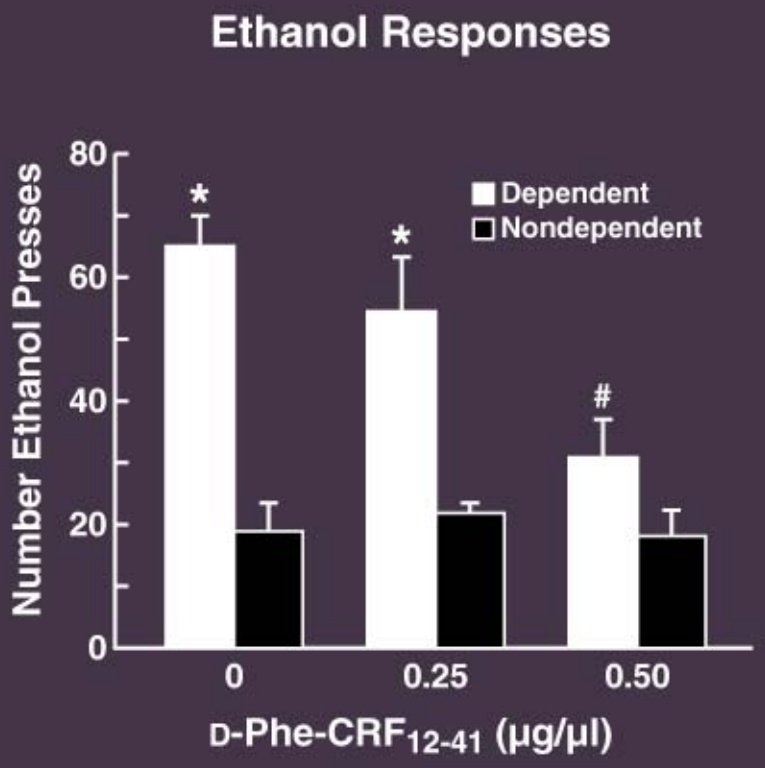


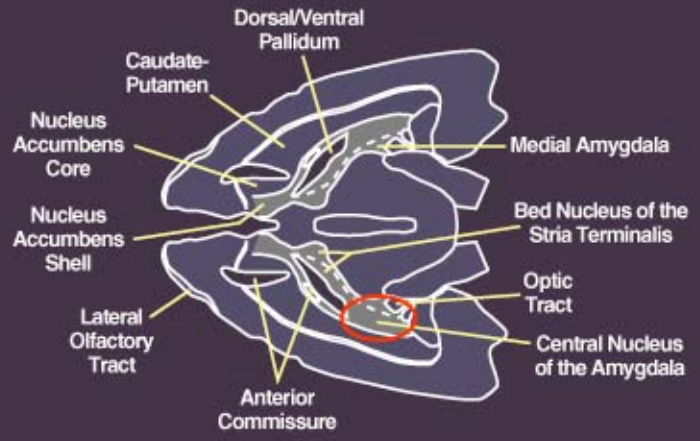
* $p < 0.001$ vs. same-dose, nondependent group

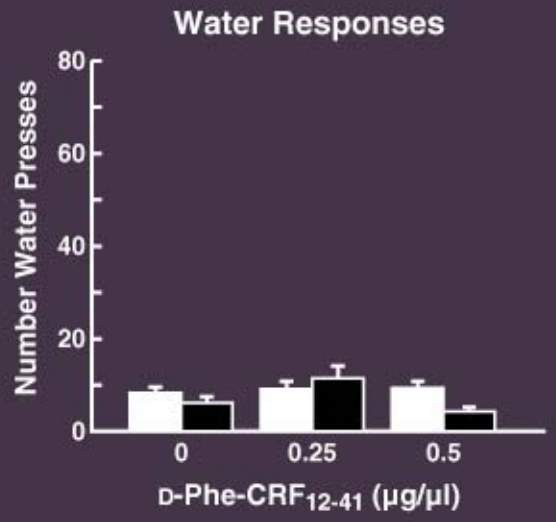
\# $p = 0.002$ vs. dependent, vehicle group

From: Richardson HN, Zhao Y, Fekete EM, Funk CK, Wirsching P, Janda KD, Zorrilla EP and Koob GF, Pharmacol Biochem Behav, 2008, 88:497-510.

Effect of CRF Antagonist D-Phe-CRF$_{12-41}$ – Central Nucleus of the Amygdala –







* $p < 0.001$ vs. same-dose, nondependent group

\# $p < 0.001$ vs. dependent, vehicle group

From: Funk C, O'Dell LE and Koob GF, J Neurosci, 2006, 26:11324-11332.

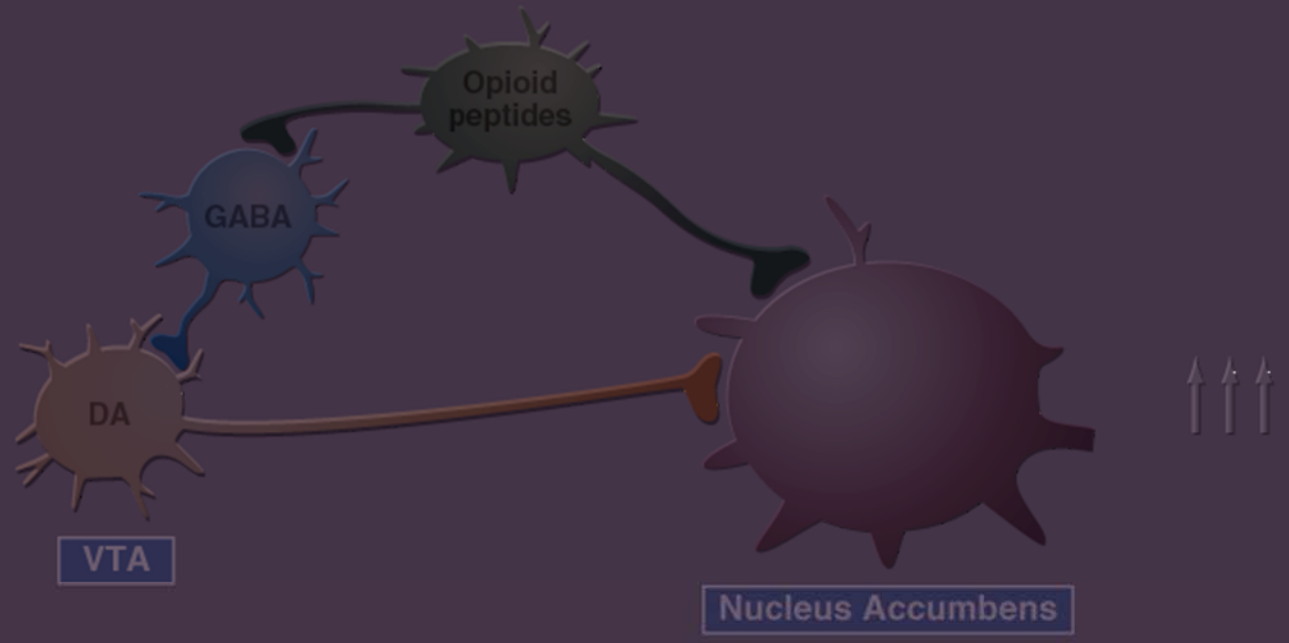
Role of Corticotropin-releasing Factor in Dependence

Drug	CRF antagonist effects on withdrawal-induced anxiety-like responses	Withdrawal-induced changes in extracellular CRF in CeA	CRF antagonist effects on dependence-induced increases in self-administration	CRF antagonist reversal of stress-induced reinstatement
Cocaine	↓	↑	↓	↓
Opioids	↓*	↑	↓	↓
Ethanol	↓	↑	↓	↓
Nicotine	↓	↑	↓	↓
Δ^9-tetrahydrocannabinol	↓	↑	nt	nt

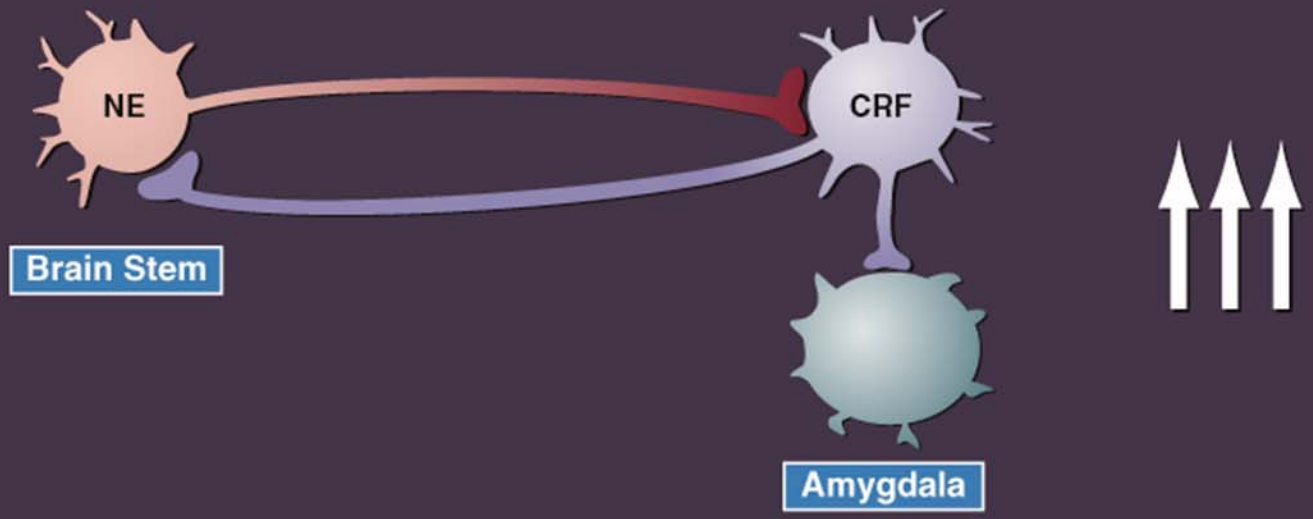
* = aversive effects with place conditioning. nt = not tested. CeA = central nucleus of the amygdala.

Dependent

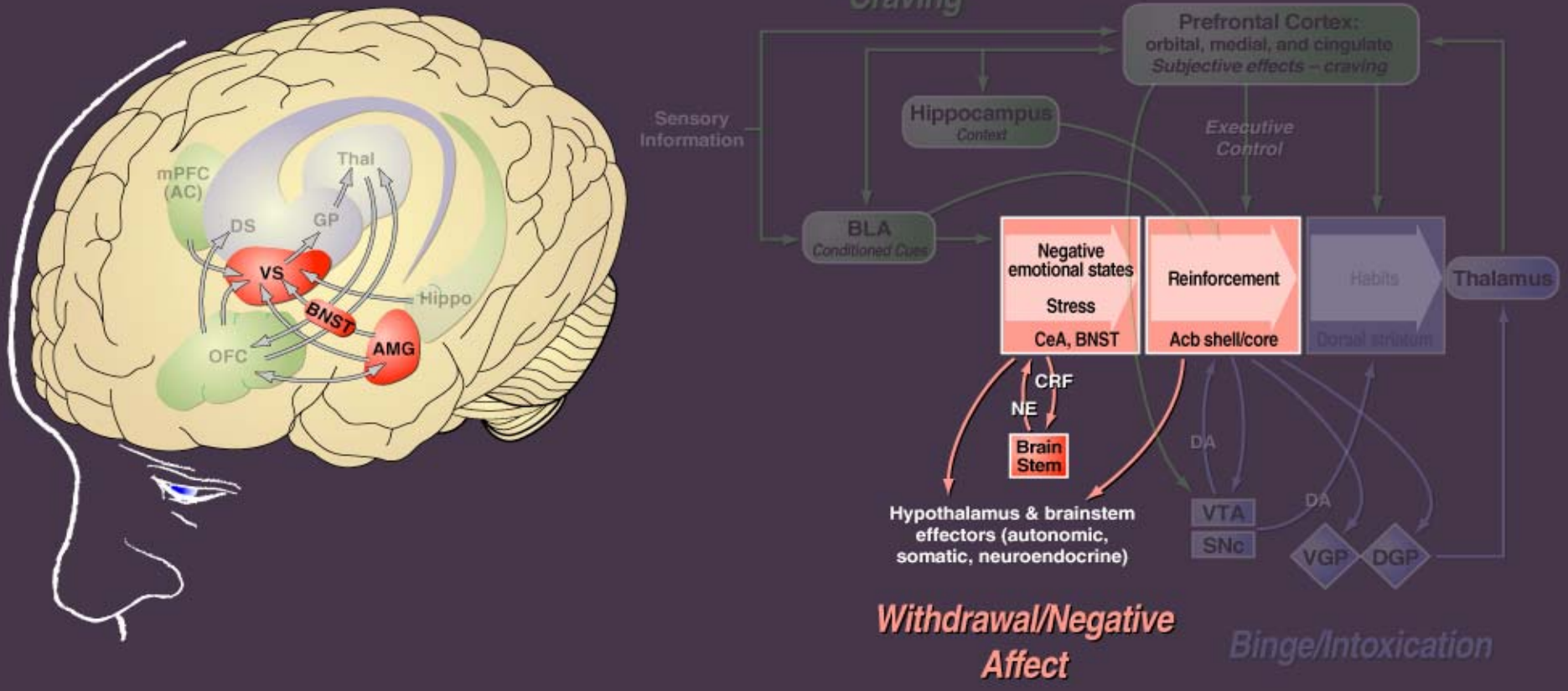
Positive Reinforcement



Negative Reinforcement



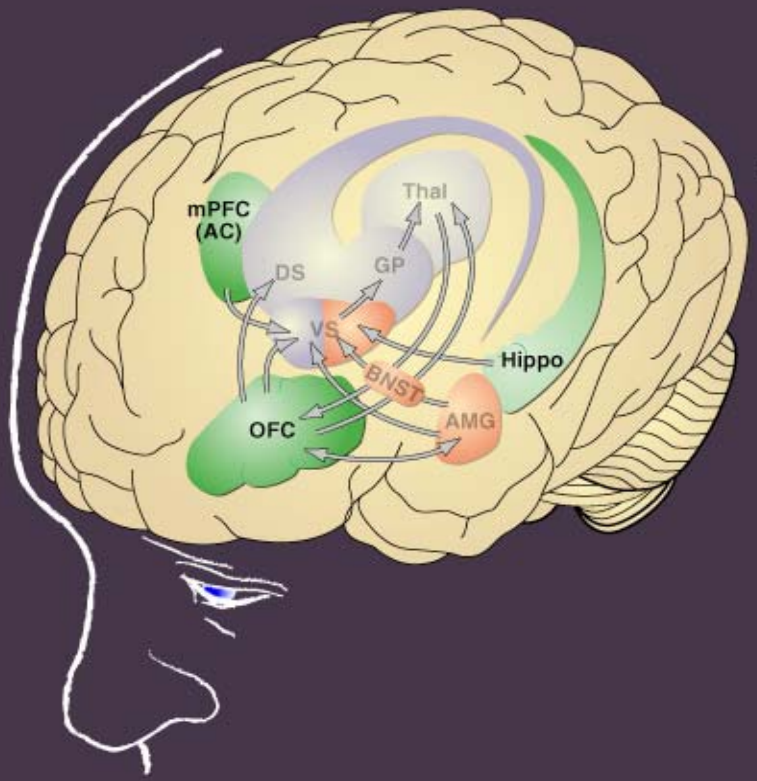
Existing and Future Medications for Addiction: Withdrawal/Negative Affect Stage

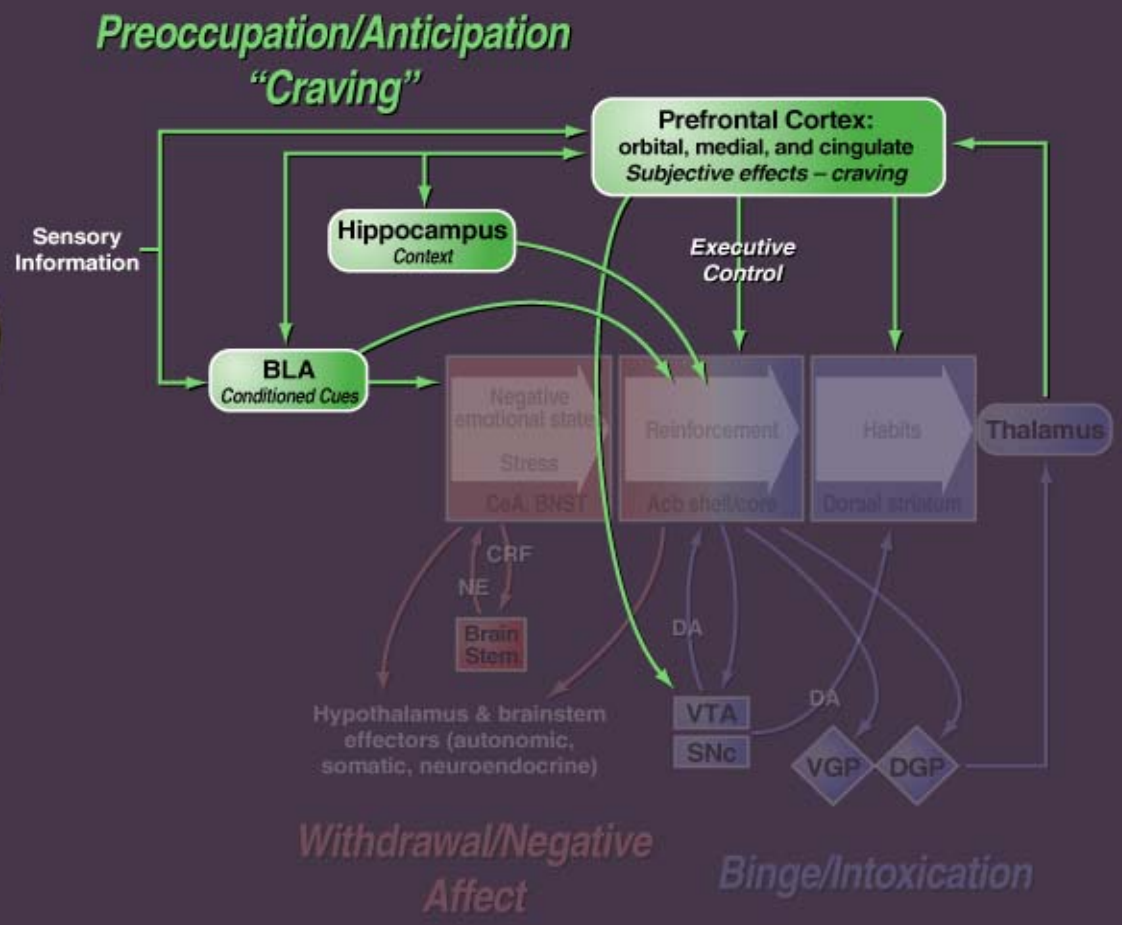


Existing medications
- methadone
- buprenorphine
- varenicline

Future targets
- GABA modulators
- CRF_1 receptors
- κ opioid antagonists

Existing and Future Medications for Addiction: Preoccupation/Anticipation "Craving" Stage





Existing medications
acamprosate
buproprion

Future targets
- homeostatic resetters (GABA modulators)
- stress reducers (CRF_1 antagonists)
- habit reducers (glutamate modulators)

Craving-Type 1

- “Craving”- induced by stimuli that have been paired with ethanol self-administration such as environmental cues

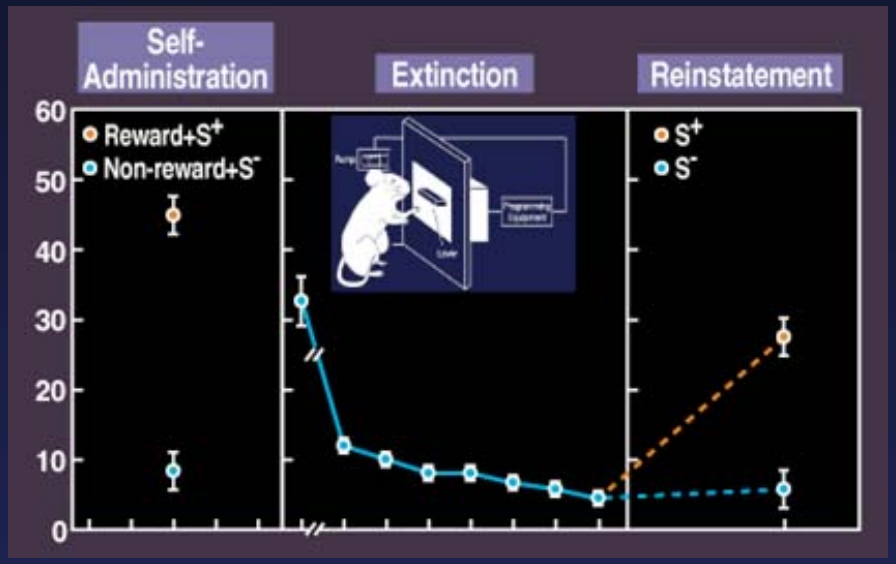
- An animal model of craving- type 1 is cue induced reinstatement where a cue previously paired with access to ethanol reinstates responding for a lever that has been extinguished.

- Neurobiological substrates include glutamatergic projections from medial prefrontal cortex and basolateral amygdala to nucleus accumbens

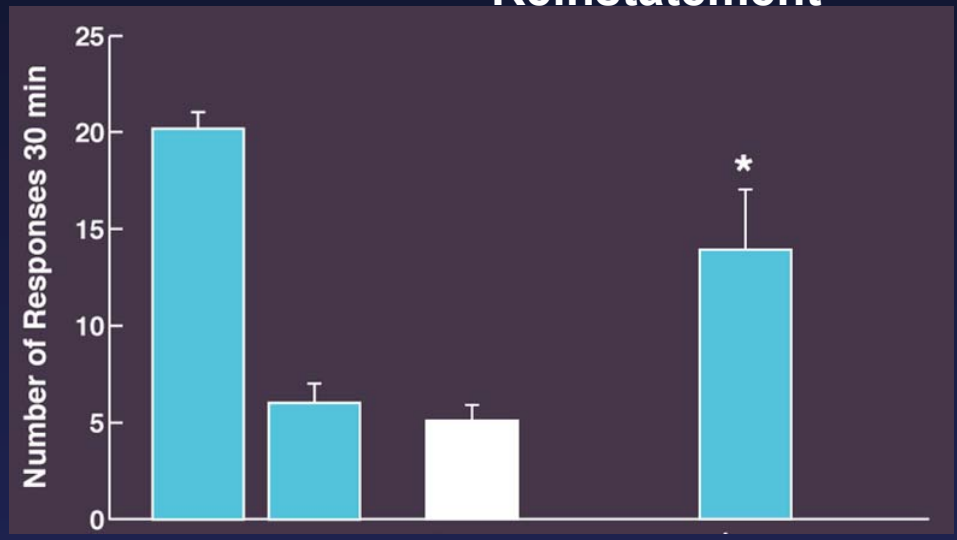
Craving-Type 2

- State of protracted abstinence in alcoholics weeks after acute withdrawal.
- Conceptualized as a state change characterized by anxiety and dysphoria or a residual negative affective state that combines with Craving-Type 1 situations to produce relapse to excessive drinking
- Animal models of Craving-Type 2 include stress-induced reinstatement, or increased drinking in animals after a prolonged deprivation (Alcohol Deprivation Effect)
- Neurobiological substrates include residual activation of brain stress systems including corticotropin releasing factor and norepinephrine in the extended amygdala

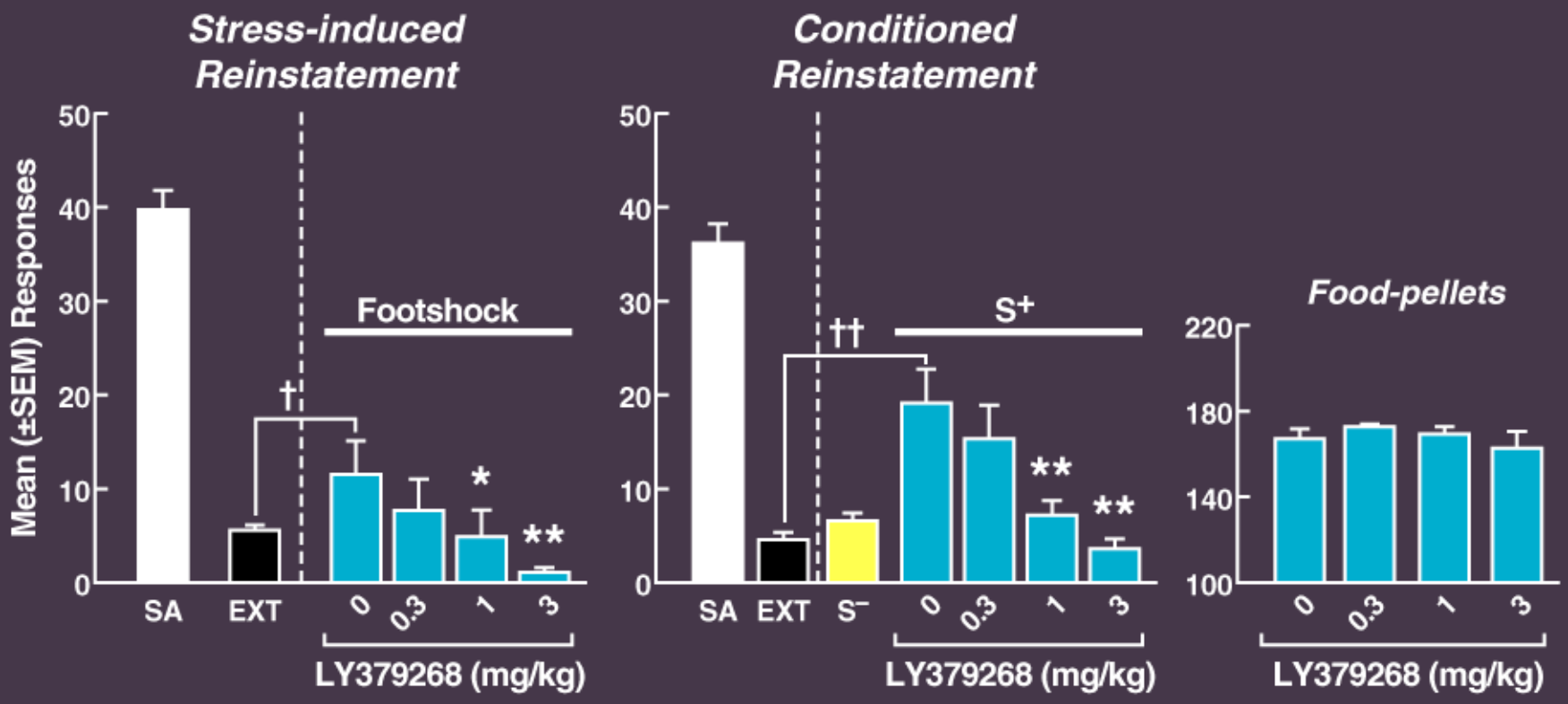
Neurobiological Effects of Exposure to Drug-Associated Contextual Stimuli



Daily Sessions of Self-Administration

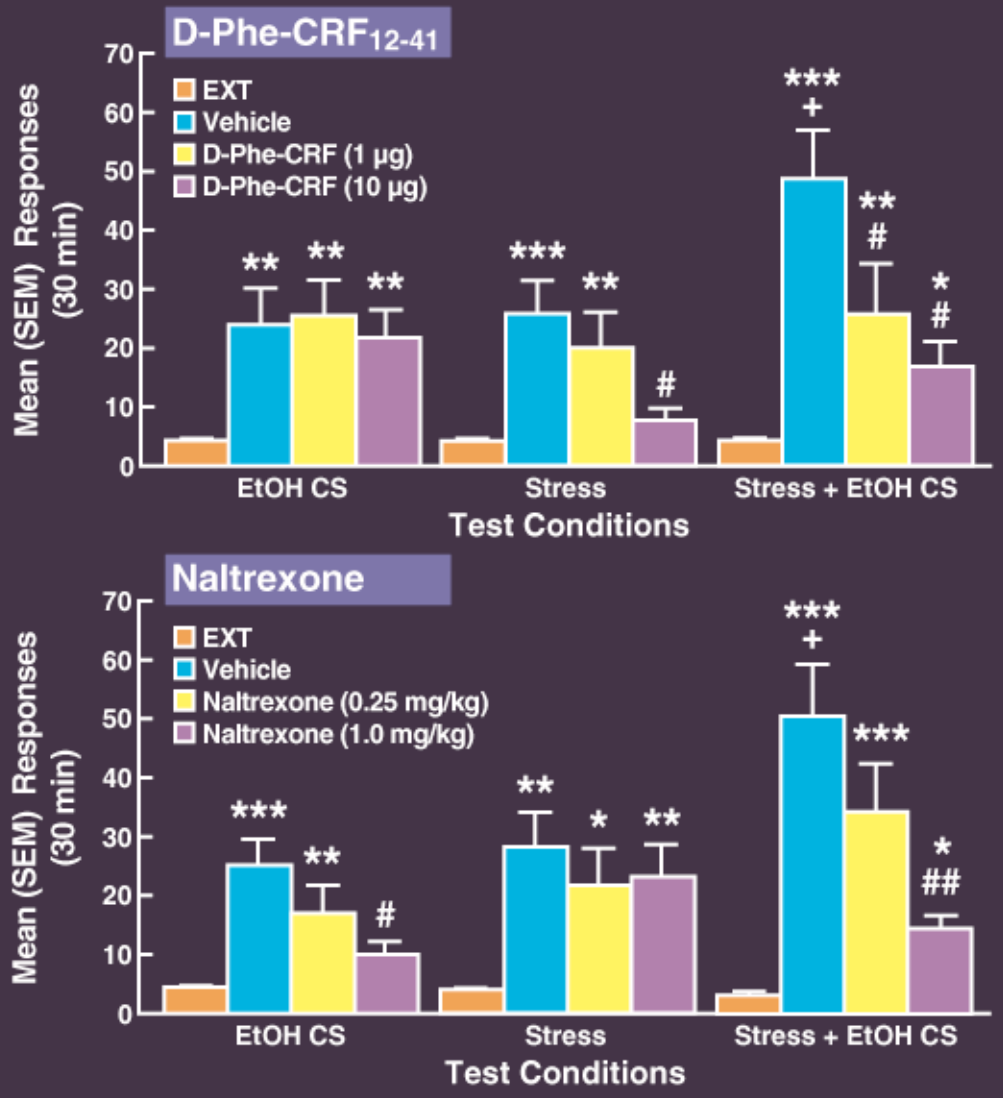


Effects of $mGlu_{2/3}$ Agonist LY379268 on Stress- and Cue-induced Reinstatement of Ethanol-seeking Behavior in Rats



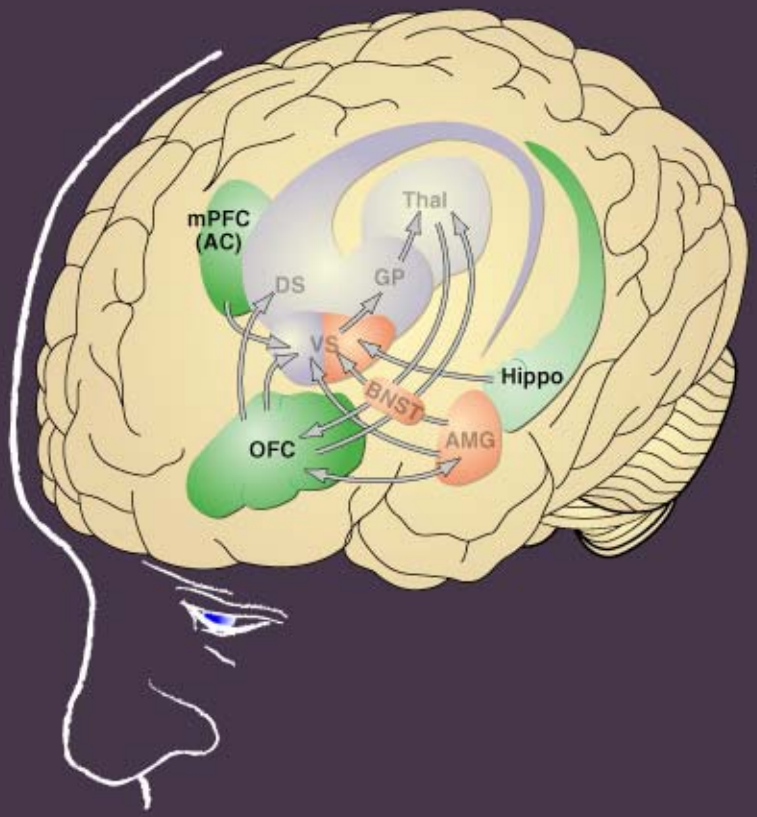
From: Zhao Y, Dayas CV, Aujla H, Baptista MAS, Martin-Fardon R and Weiss F, J Neurosci, 2006, 26:9967-9974.

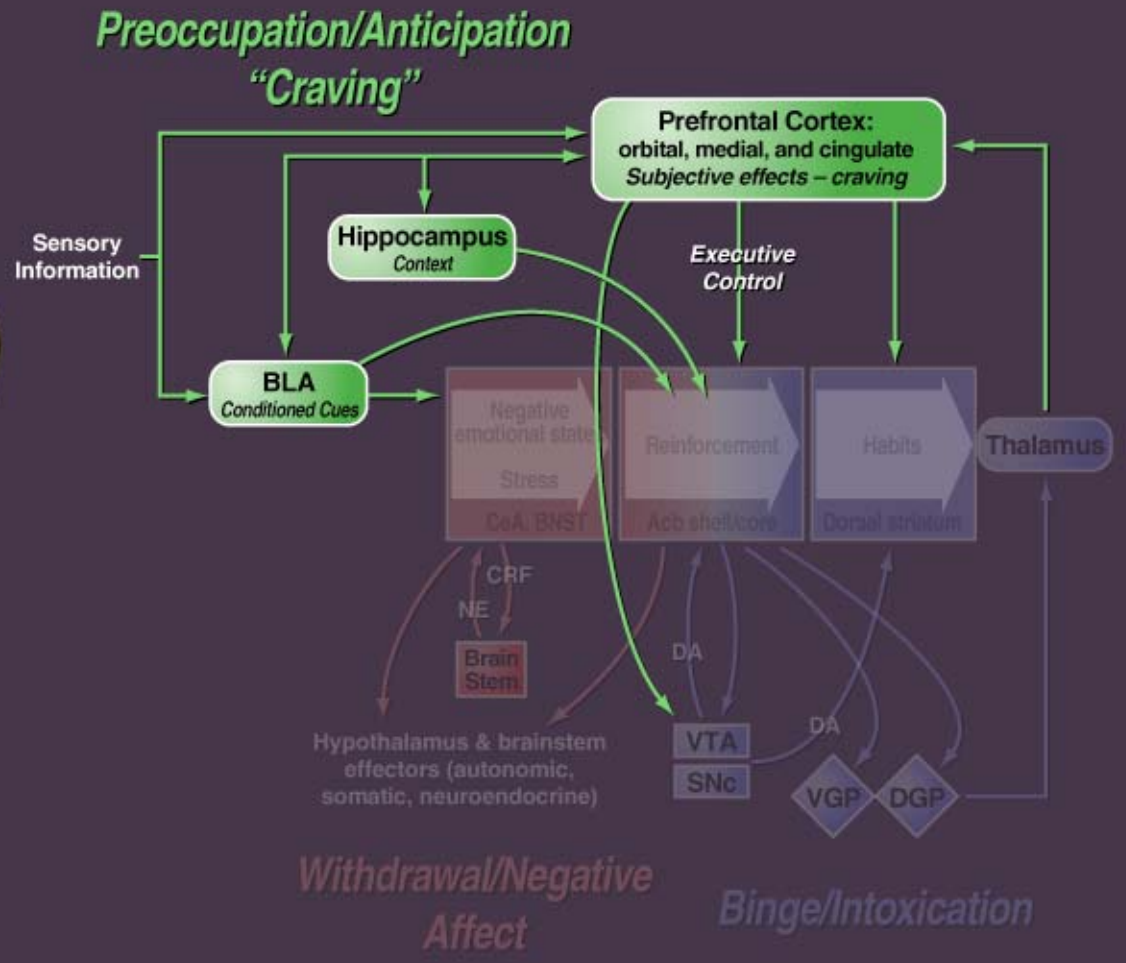
Effects of D-Phe-CRF$_{12-41}$ and Naltrexone on Stress- and Cue-Induced Reinstatement of Ethanol-Seeking



From: Liu X and Weiss F, J Neurosci, 2002, 22:7856-7861.

Existing and Future Medications for Addiction: Preoccupation/Anticipation "Craving" Stage





Existing medications
acamprosate
buproprion

Future targets
- homeostatic resetters (GABA modulators)
- stress reducers (CRF_1 antagonists)
- habit reducers (glutamate modulators)

Key Findings and Conclusions

Addiction — **loss of control over drug intake and compulsive drug taking driven by elements of impulsivity and compulsivity that are mediated by separate but overlapping neurocircuitry**

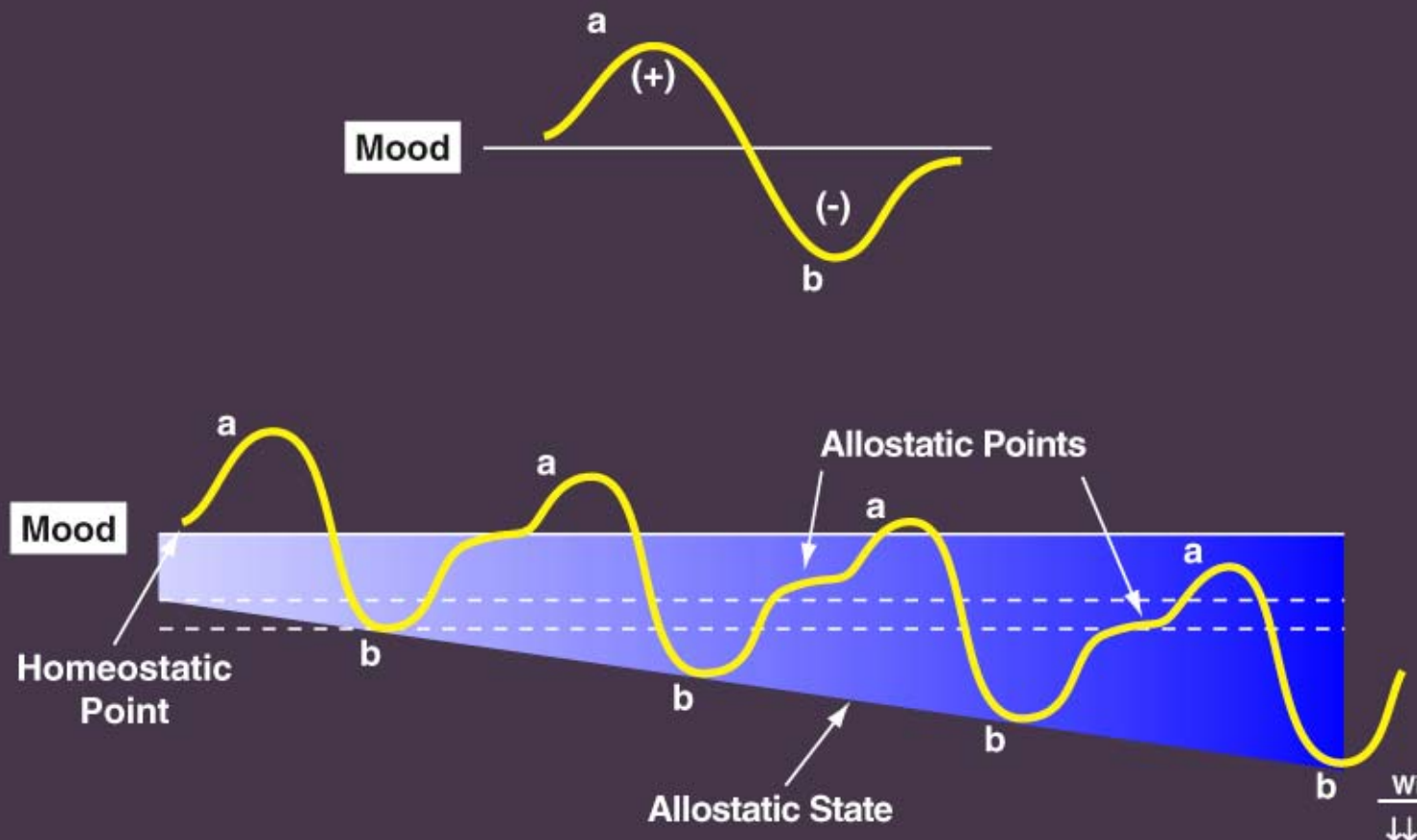
Acute rewarding effects of drugs of abuse — **are mediated by neurochemical elements such as dopamine and opioid peptides in the nucleus accumbens and amygdala**

Acute withdrawal from all major drugs of abuse — **produces increases in reward thresholds, increases in anxiety-like responses and increases in CRF in the amygdala that are of motivational significance**

Compulsive drug use associated with dependence— **is mediated by not only loss of function of reward systems but recruitment of brain stress systems such as corticotropin releasing factor, norepinephrine and dynorphin in the extended amygdala**

Brain-arousal stress systems in the extended amygdala--- **may be key components of not only for the negative emotional states that drive dependence on drugs of abuse but also may overlap with the negative emotional components of other psychopathologies**

Allostatic View of Neurotransmitter Adaptation During the Transition from Drug Use to Addiction



Within-System

↓↓↓ Dopamine, serotonin, GABA, opioid peptides

Between-System

↑↑↑ CRF, norepinephrine, dynorphin

↓↓↓ NPY

Modified from: Koob GF and Le Moal M, Neuropsychopharmacology, 2001, 24:97-129.

Neurobiology of Drug Addiction
Koob Laboratory

Postdoctoral Fellows

Nick Gilpin

Sunmee Wee

Laura Orio

Kaushik Misra

Scott Edwards

Candice Contet

Cindy Funk

Brendan Walker

Tom Greenwell

Sandy Ghozland

Chitra Mandyam

Dong Ji

Research Assistants

Bob Lintz

Richard Schroeder

Elena Crawford

Molly Brennan

Maury Cole

Tess Kimber

Yanabel Grant

TSRI Chemists

Kim Janda

Tobin Dickerson

Ed Roberts

Administrative Assistants

Lisa Maturin

Mellany Santos

Marisa Gallego

Staff Scientists

Olivier George

Bob Purdy

Heather Richardson

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(Senior Research Assistant)

Janet Hightower

(TSRI Biomedical Graphics)

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National Institute on Alcohol Abuse and Alcoholism

National Institute on Drug Abuse

National Institute of Diabetes and Digestive and Kidney Diseases