2006

Addiction: Reward, motivation and stress

George F. Koob
Scripps Research Institute

Addiction: Reward, Motivation and Stress

George F. Koob, Ph.D.
Professor
Molecular and Integrative Neurosciences Department
The Scripps Research Institute
La Jolla, California

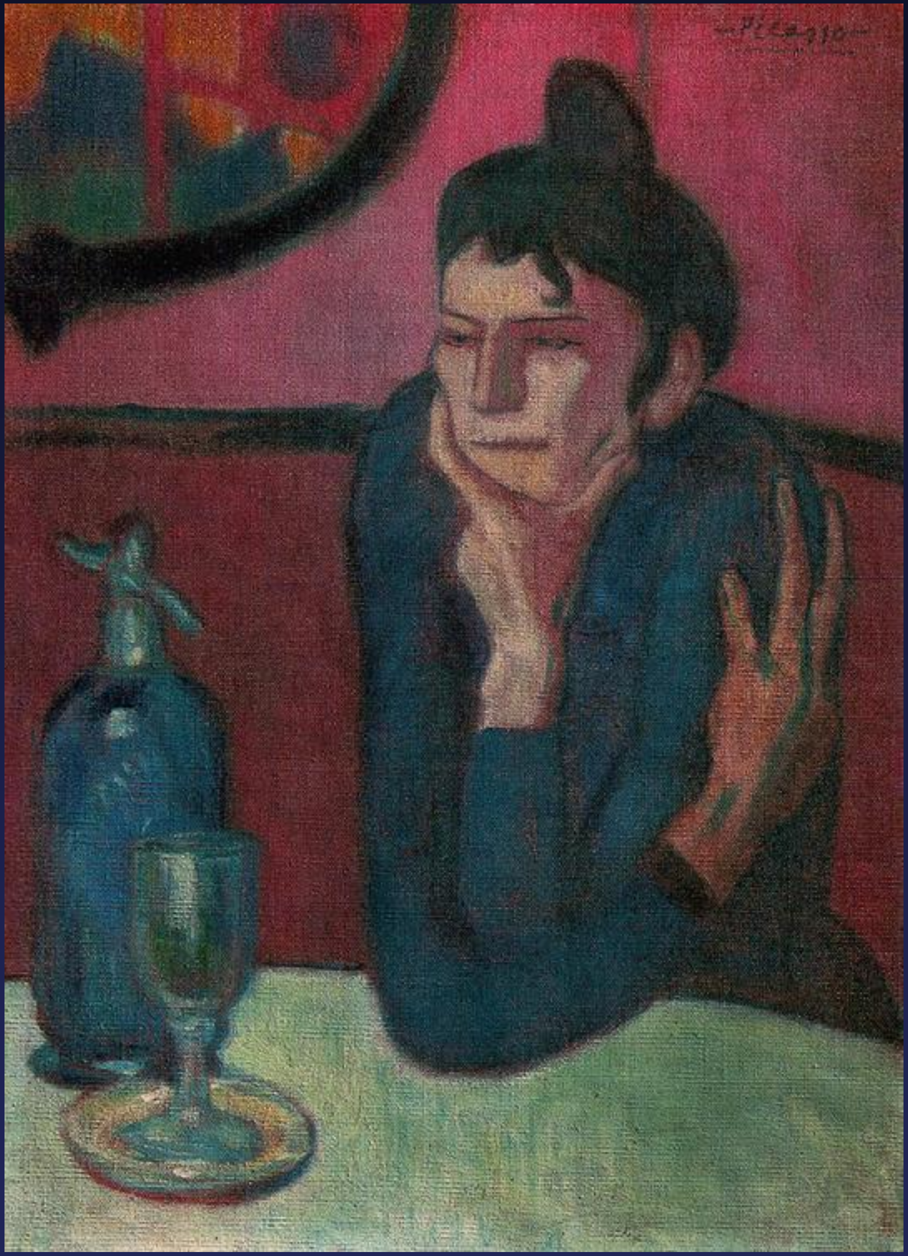
The Neurocircuitry of Drug Addiction: Neuroadaptive Mechanisms from the "Dark Side"

- What is Addiction?
  1. Conceptual framework
  2. The 'dark side' of compulsivity

- Animal Models for the Motivational Effects of Dependence
  1. Brain stimulation reward
  2. Place aversion
  3. Anxiogenic-like responses in the plus maze and defensive burying tests
  4. Escalation in drug self-administration with prolonged access

- A Role for Corticotropin-Releasing Factor in Drug Addiction
  1. Cocaine
  2. Nicotine
  3. Heroin
  4. Alcohol

- Future Directions
  1. Development of CRF_1 antagonists for treatment of addiction
  2. The neurocircutry of emotional behavior



"Absinthe Drinker"
Pablo Picasso (1910)

Key Definitions

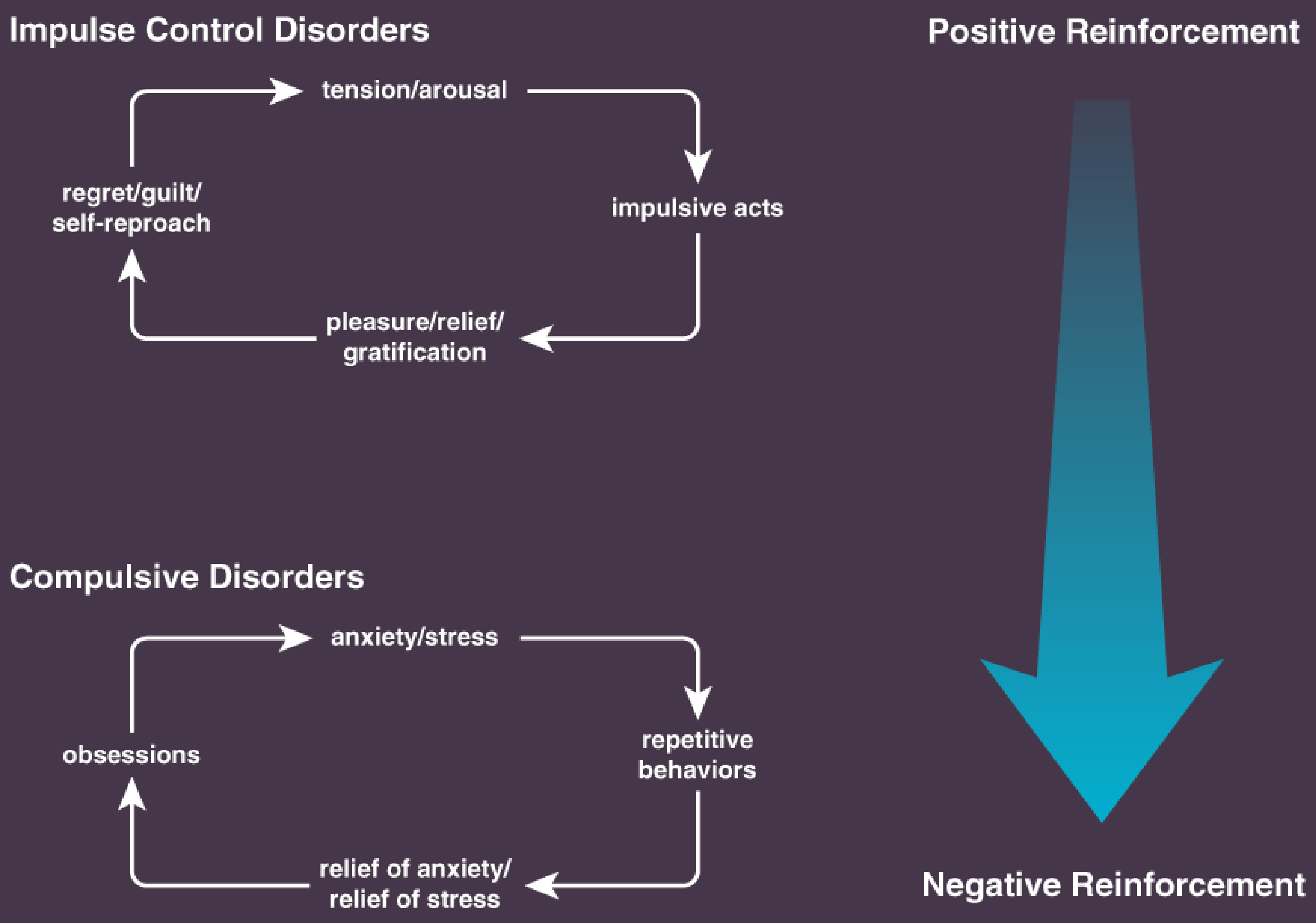
***Drug Addiction* —** Chronically relapsing disorder that is characterized by a compulsion to seek and take drug, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug is prevented (here, defined as the "dark side" of addiction)

***Extended Amygdala* —** Forebrain macrostructure composed of central medial amygdala, bed nucleus of the stria terminalis, and a transition zone in the medial part of the nucleus accumbens

Corticotropin-Releasing Factor — 41 amino acid polypeptide "brain stress" neurotransmitter that controls hormonal, sympathetic, and behavioral responses to stressors

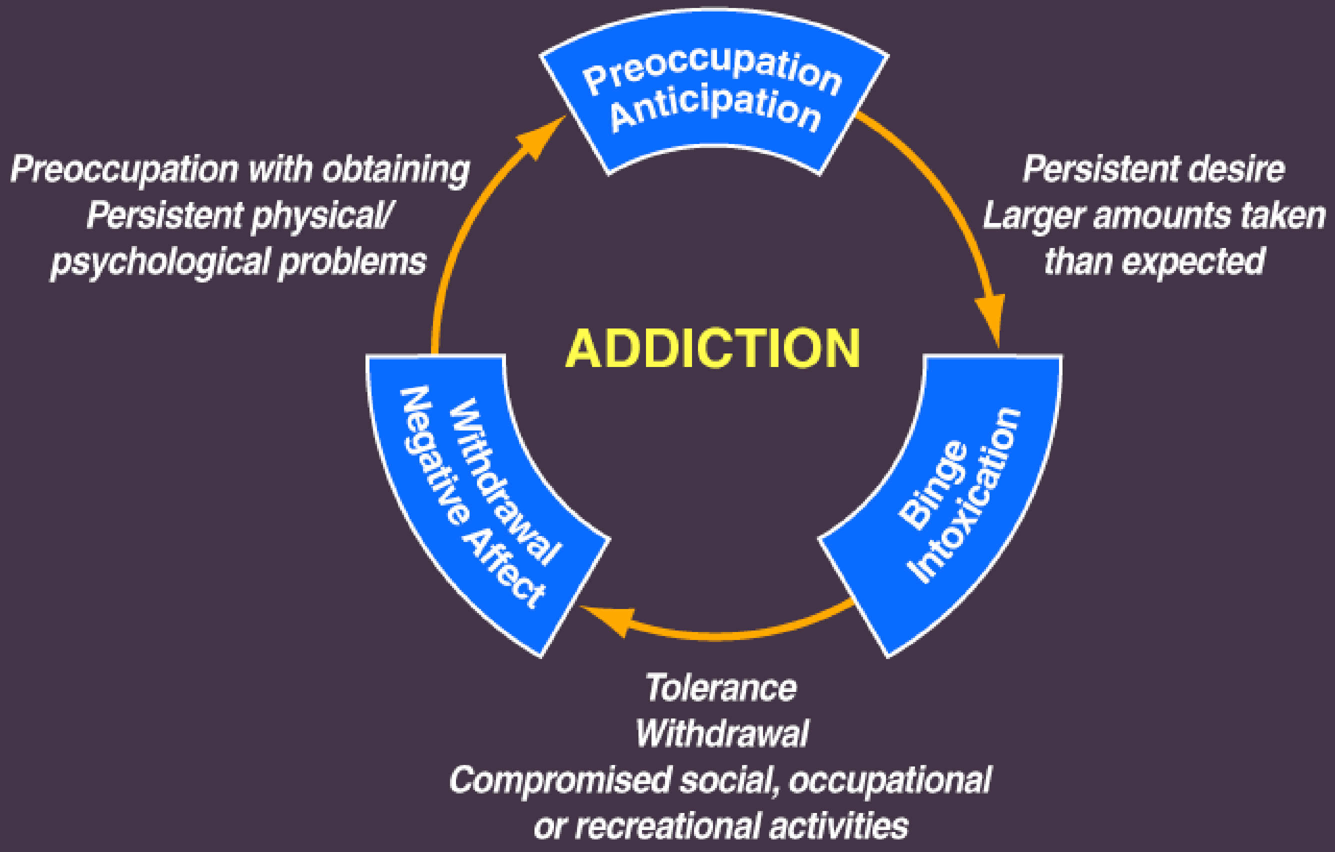
Drug Addiction

Drug addiction is conceptualized as a chronic relapsing syndrome that moves from an impulse control disorder involving positive reinforcement to a compulsive disorder involving negative reinforcement



From: Koob GF, Alcohol Clin Exp Res, 2003, 27:232-243.

Stages of the Addiction Cycle



Animal Models for the Motivational Components of Dependence

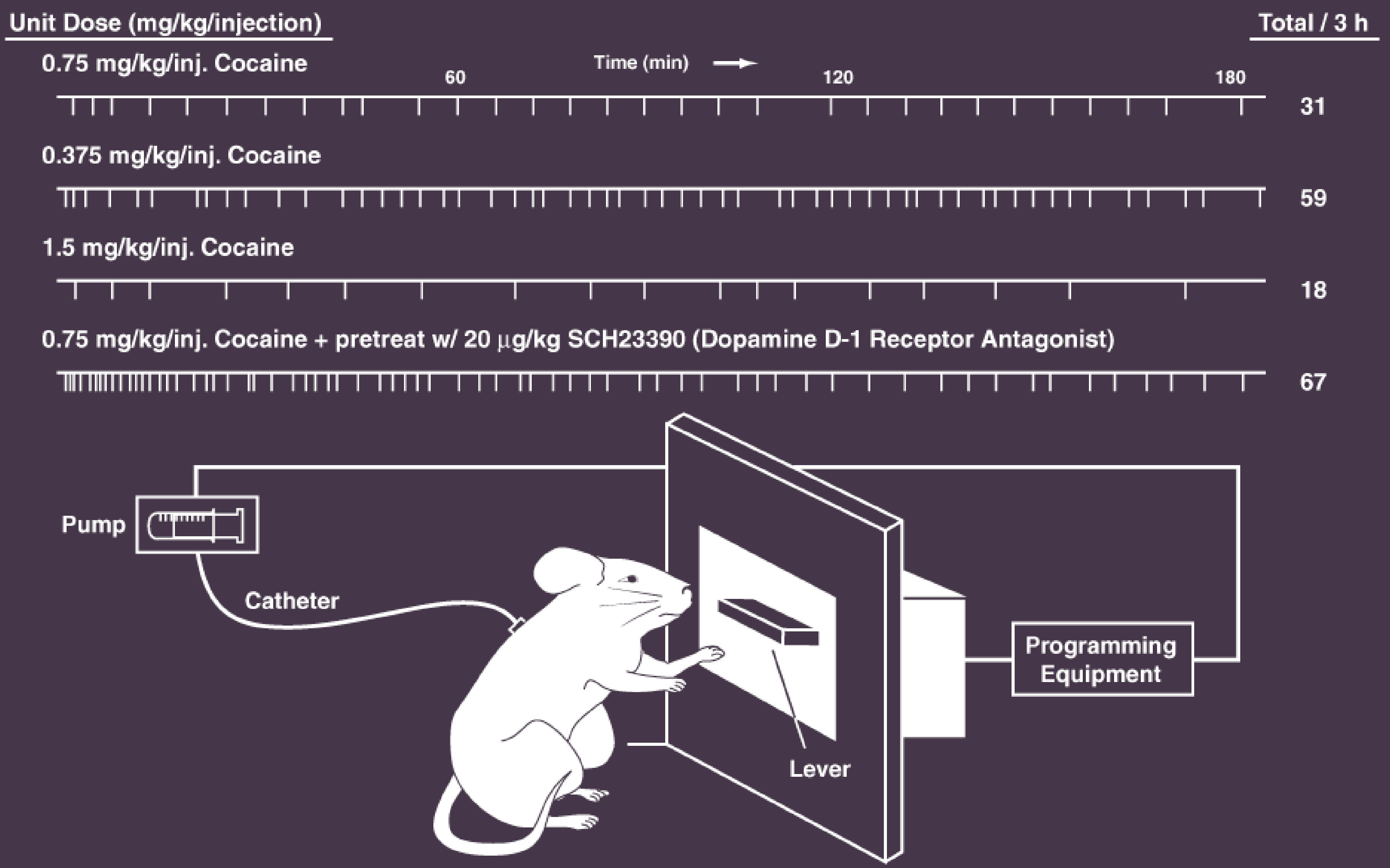
Animal Models for the Withdrawal/Negative Affect Stage

1. **Brain stimulation reward**
2. **Place aversion**
3. **Anxiogenic-like responses in elevated plus maze and defensive burying**

Animal Models for the Transition to Addiction

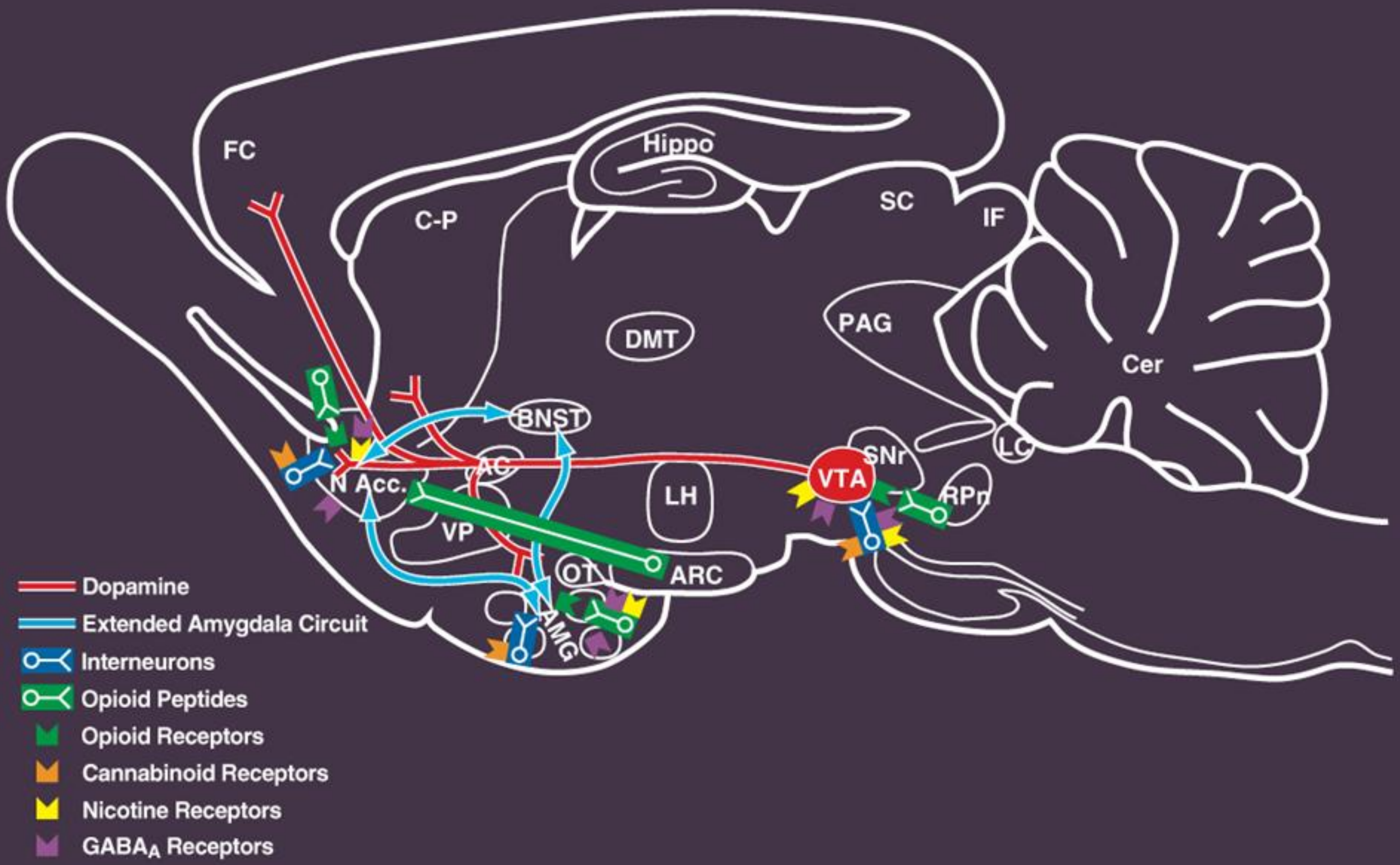
1. **Drug taking in selected lines of drug preferring animals**
2. **Withdrawal-induced drug taking**
3. **Escalation in drug self-administration with prolonged access**
4. **Drug taking despite aversive consequences**

Cocaine Self-Administration

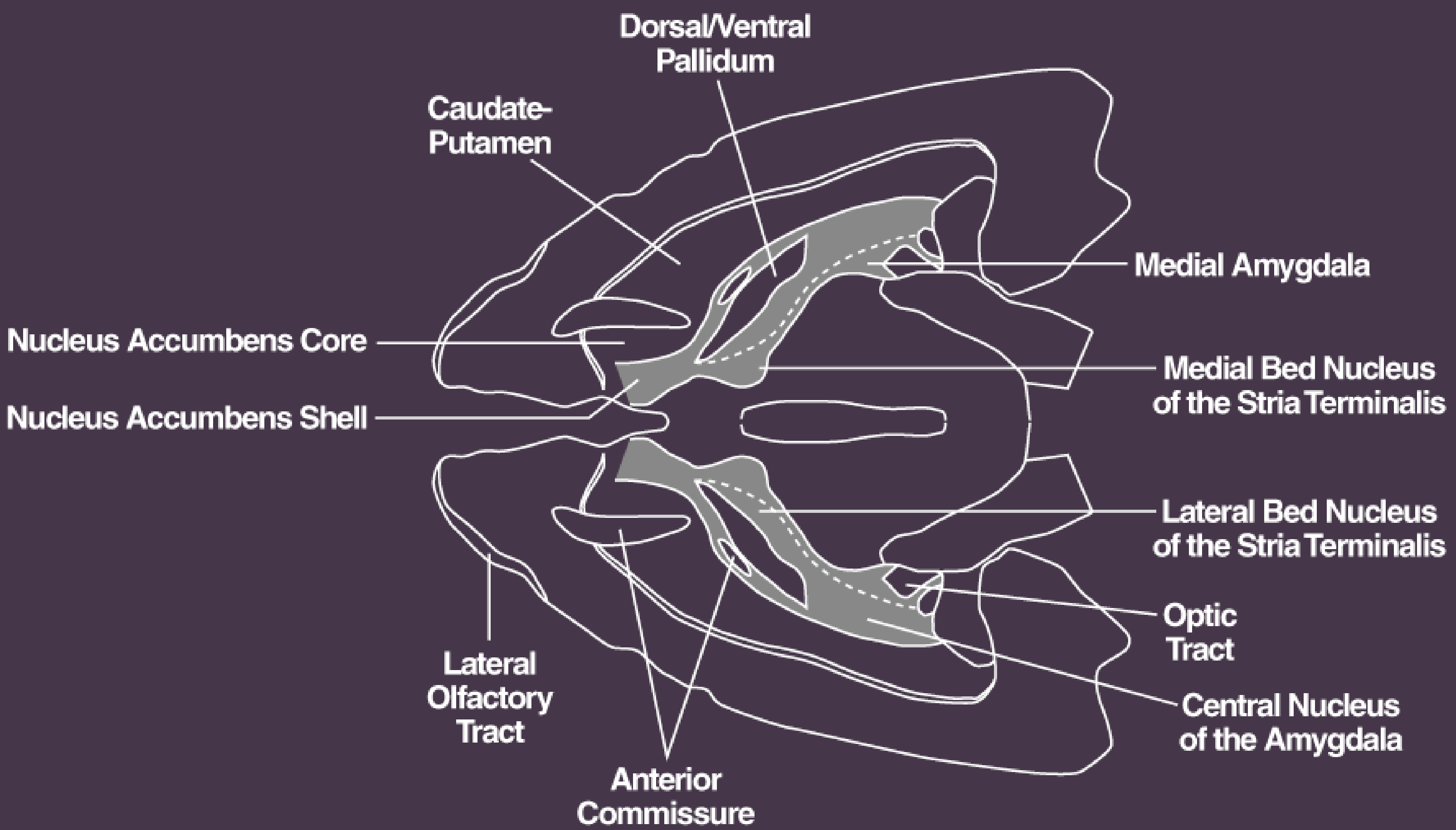


From: Caine SB, Lintz R and Koob GF. in Sahgal A (ed) Behavioural Neuroscience: A Practical Approach, vol. 2, IRL Press, Oxford, 1993, pp. 117-143.

Neurochemical Circuitry in Drug Reward

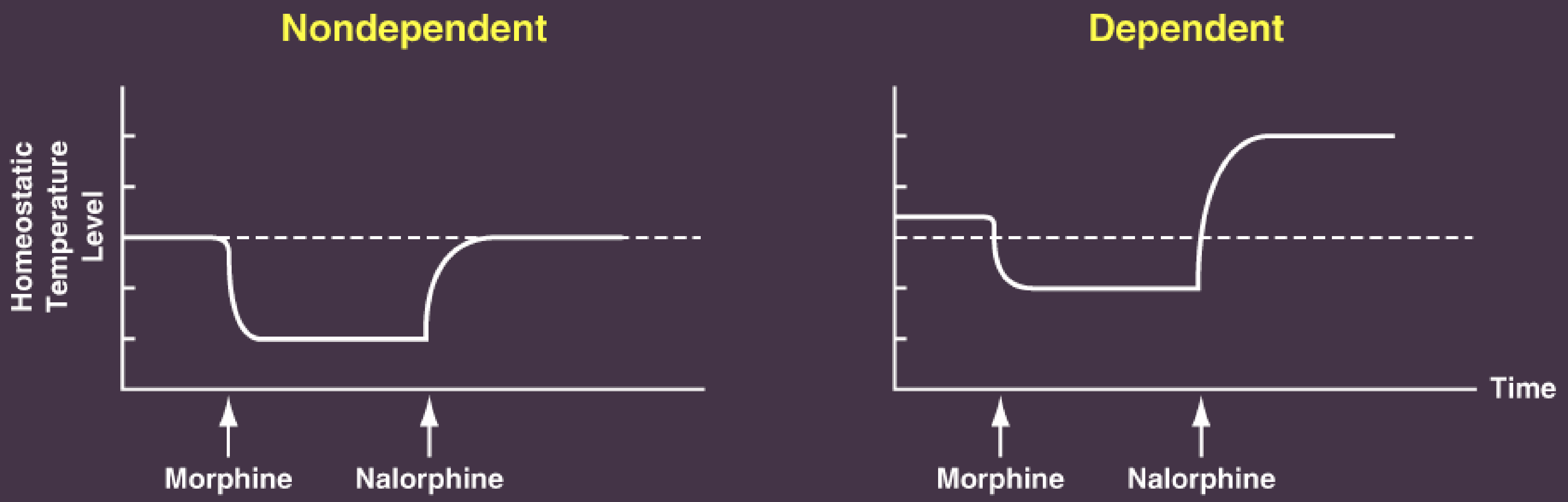


Potential Substrates in the Extended Amygdala for the Motivational Effects of Drug Dependence



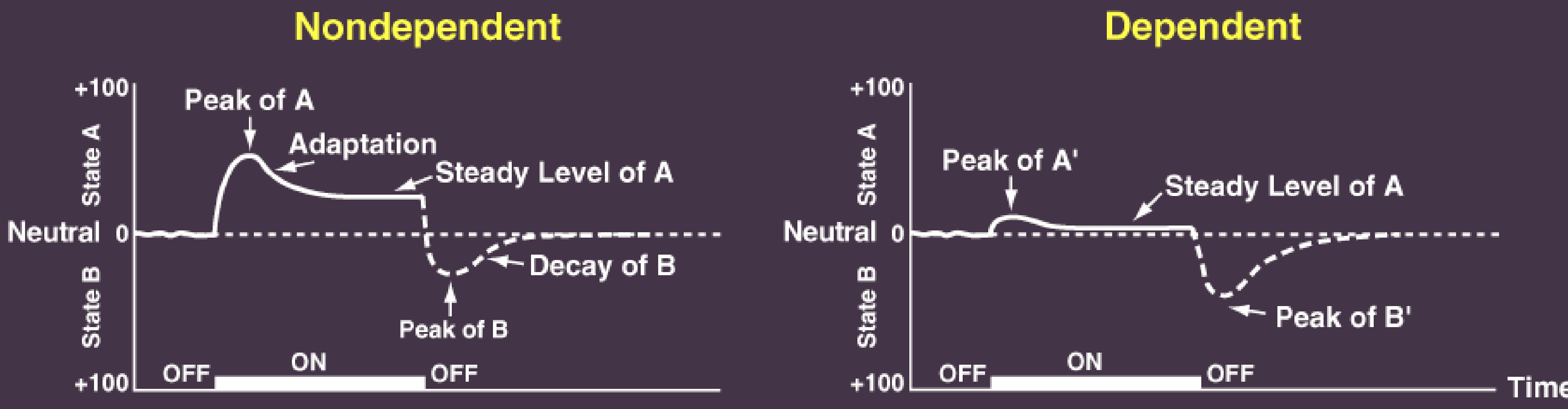
Modified from: Heimer L and Alheid G, Piecing together the puzzle of basal forebrain anatomy. In: Napier TC, Kalivas PW and Hanin I (Eds), The Basal Forebrain: Anatomy to Function (series title: Advances in Experimental Medicine and Biology, Vol. 295), Plenum Press, New York, 1991, pp. 1-42.

Equilibrium State for a Homeostatic Regulatory System in a Nondependent and Dependent Organism



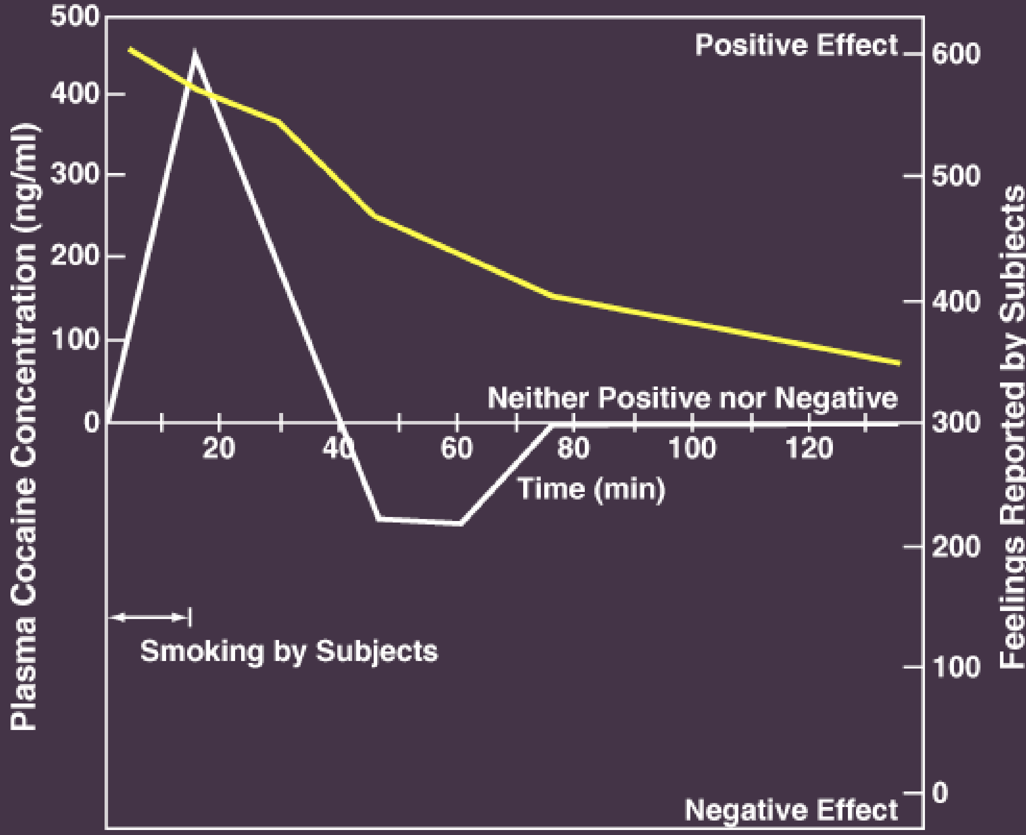
From: Martin WR, A homeostatic and redundancy theory of tolerance to and dependence on narcotic analgesics. in Wikler A (Ed.), The Addictive States (series title: *Its Research Publications*, vol. 46), Williams and Wilkins, Baltimore, 1968, pp. 206-225.

Standard Pattern of Affective Dynamics Produced by Novel and Repeated Unconditioned Stimulus



From: Solomon RL, American Psychologist, 1980, 35:691-712.

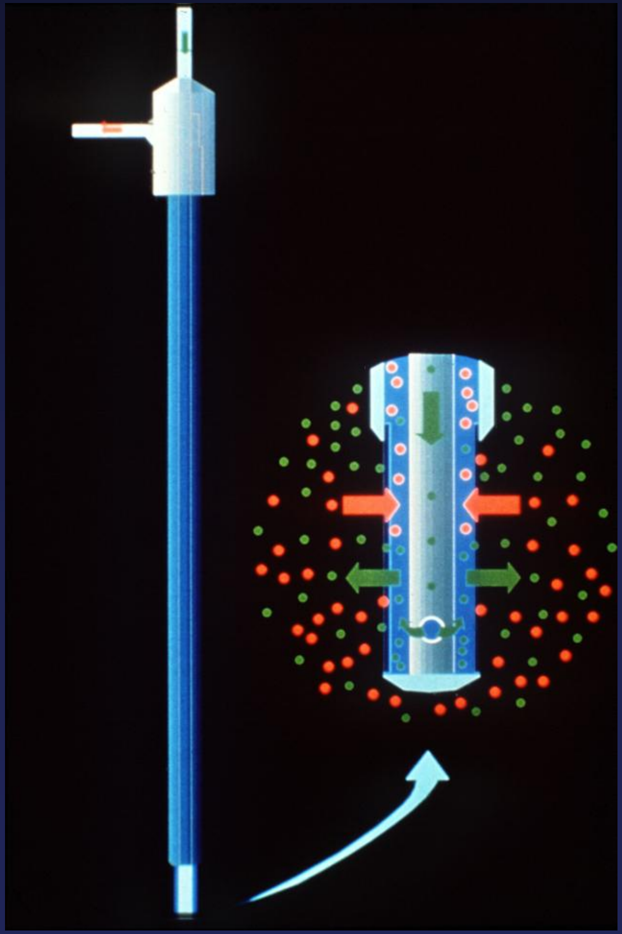
Mood Changes Associated with Plasma Levels of Cocaine During Coca Paste Smoking



Dysphoric Feelings followed the initial euphoria in experimental subjects who smoked cocaine paste, even though the concentration of cocaine in the plasma of the blood remained relatively high. The dysphoria is characterized by anxiety, depression, fatigue and a desire for more cocaine.

From: Van Dyke C and Byck R, Cocaine, Scientific American, 1982, 246:123-141.

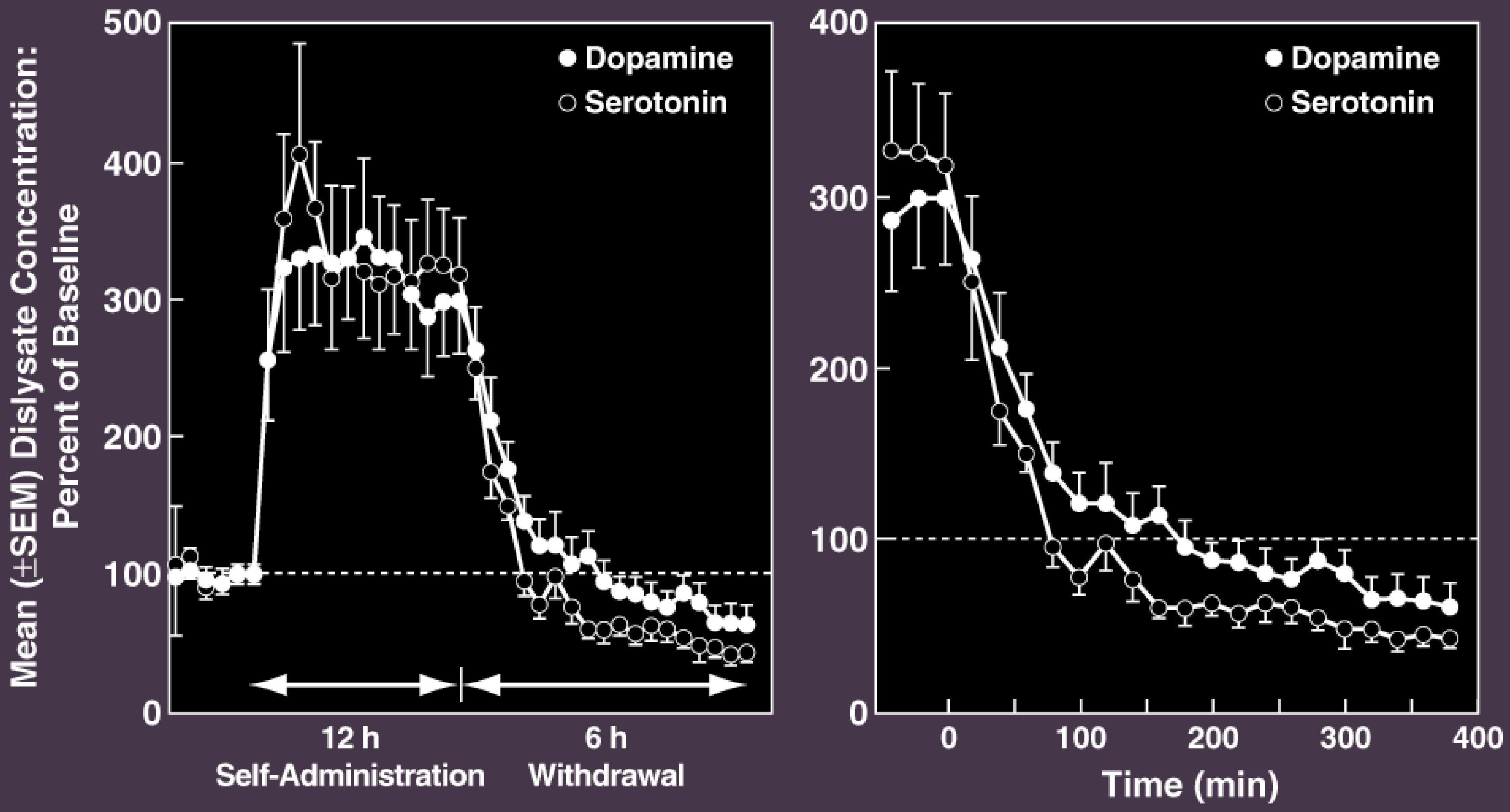
Sampling of Interstitial Neurochemicals by *in vivo* Microdialysis



- 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

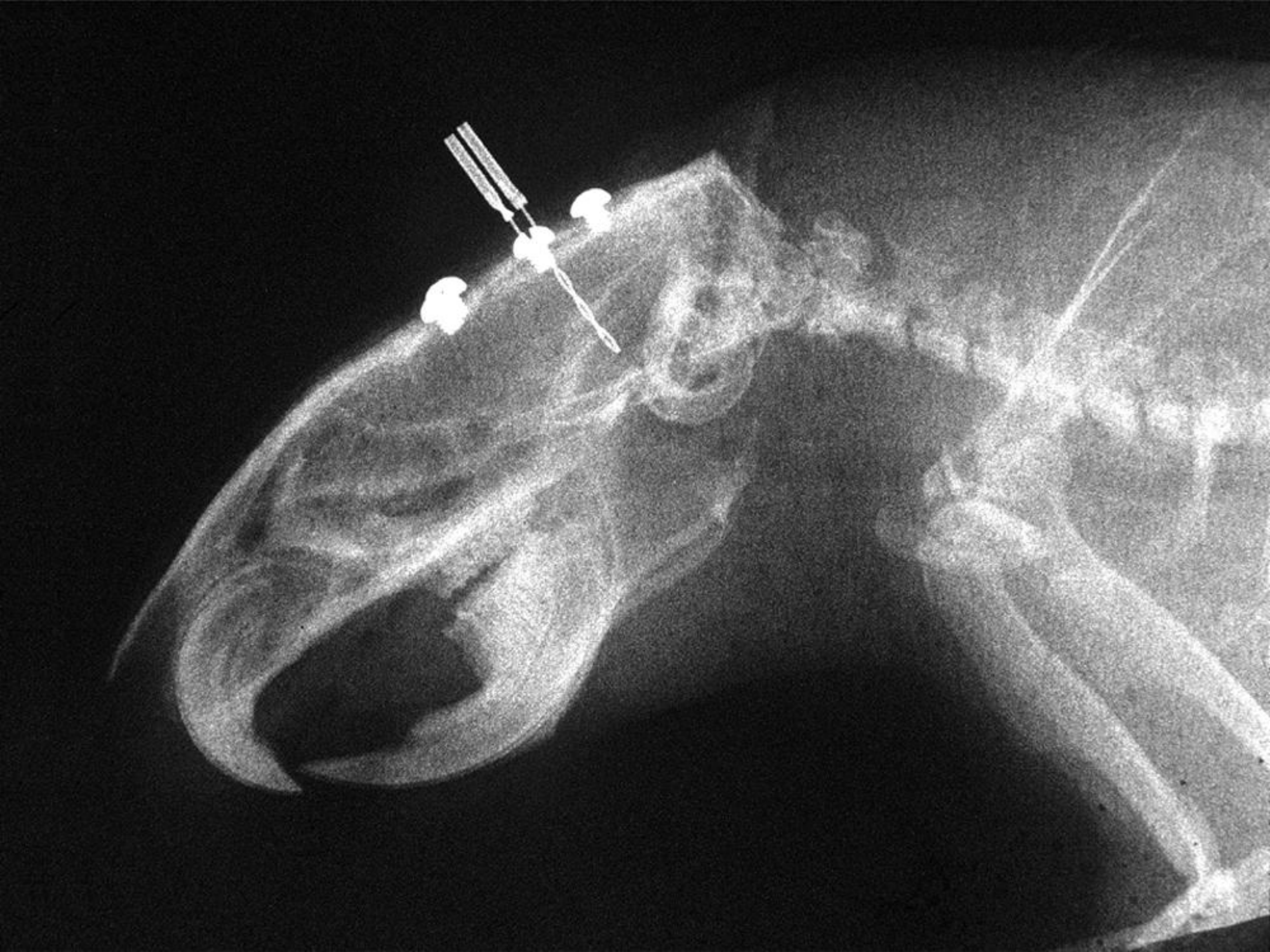
Extracellular DA and 5-HT in the Nucleus Accumbens During Cocaine Self-Administration and Withdrawal



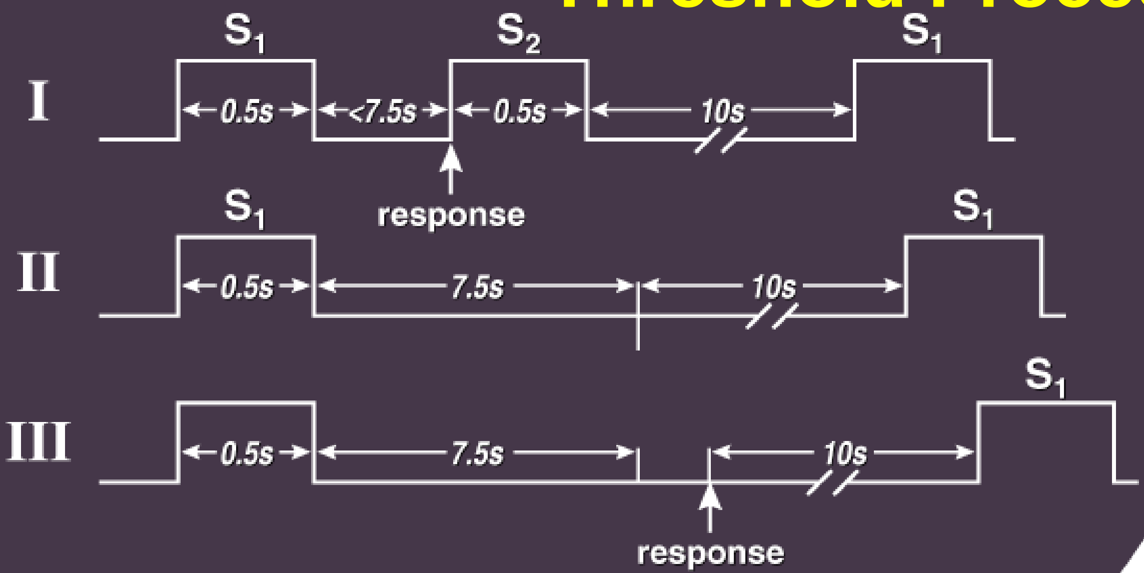
From: Parsons LH, Koob GF and Weiss F, J Pharmacol Exp Ther, 1995, 274:1182-1191.

Drug Withdrawal

Withdrawal from chronic drugs of abuse produces a reward (motivational) dysregulation as measured by thresholds for intracranial self-stimulation



Intracranial Self-Stimulation (ICSS) Threshold Procedure

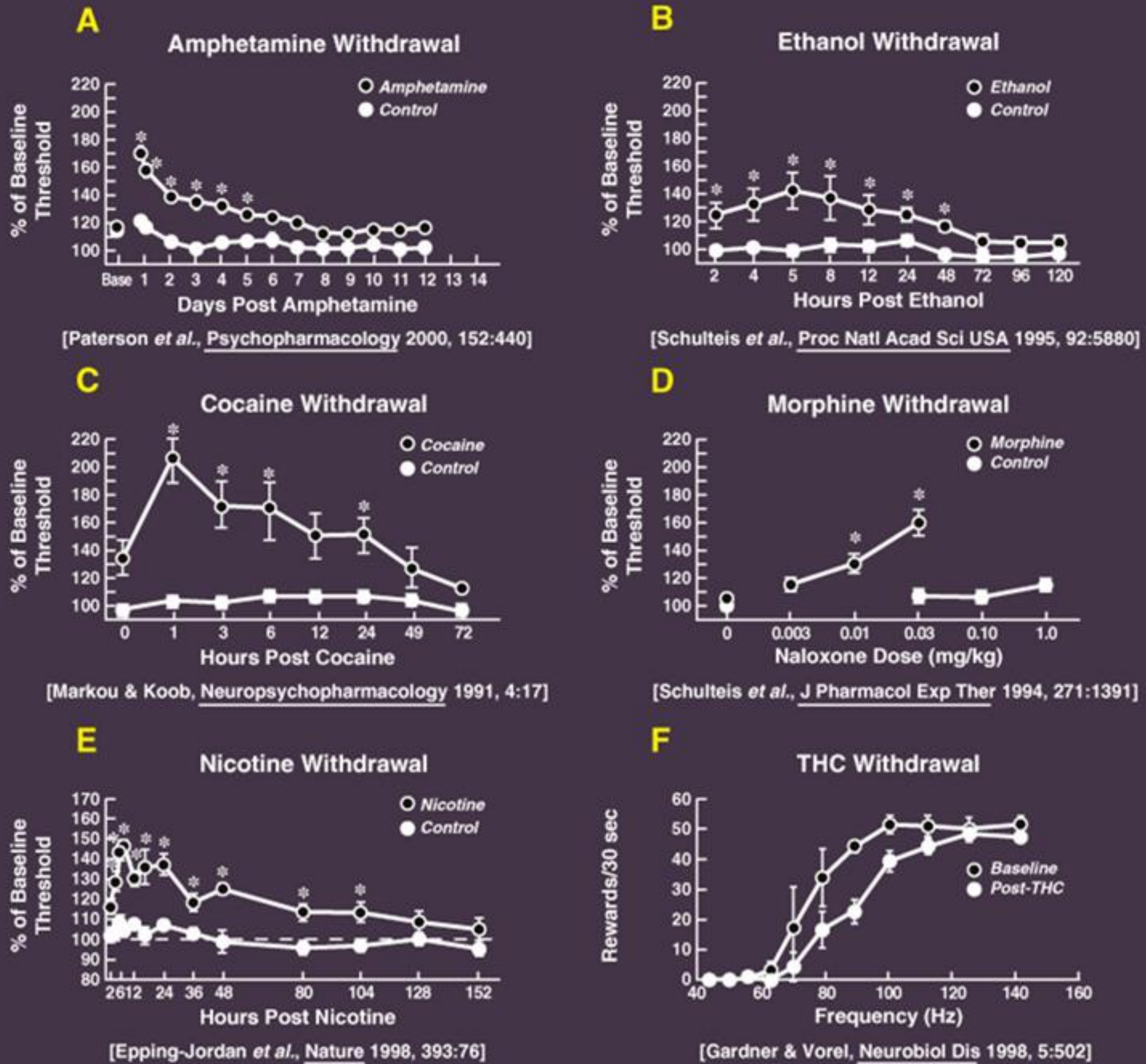


Current (µA)	Descending	Ascending	Descending	Ascending
180	+ + +		+ + +	+ + +
175	+ + +	+ + +	+ + +	+ + +
170	+ + +	+ + +	+ + +	+ + +
165	+ - +	- - -	+ - -	- - -
160	- - -	- + -	- + +	- - -
155	- - -	- - -	- - -	- - +
150		- - -	- - -	- - -
145				- - -
	162.5	167.5	157.5	167.5

Threshold = 163.75 µA

Adapted from: Markou A and Koob GF, Physiol Behav, 1992, 51:111-119.

Elevations in ICSS Reward Thresholds During Withdrawal



Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

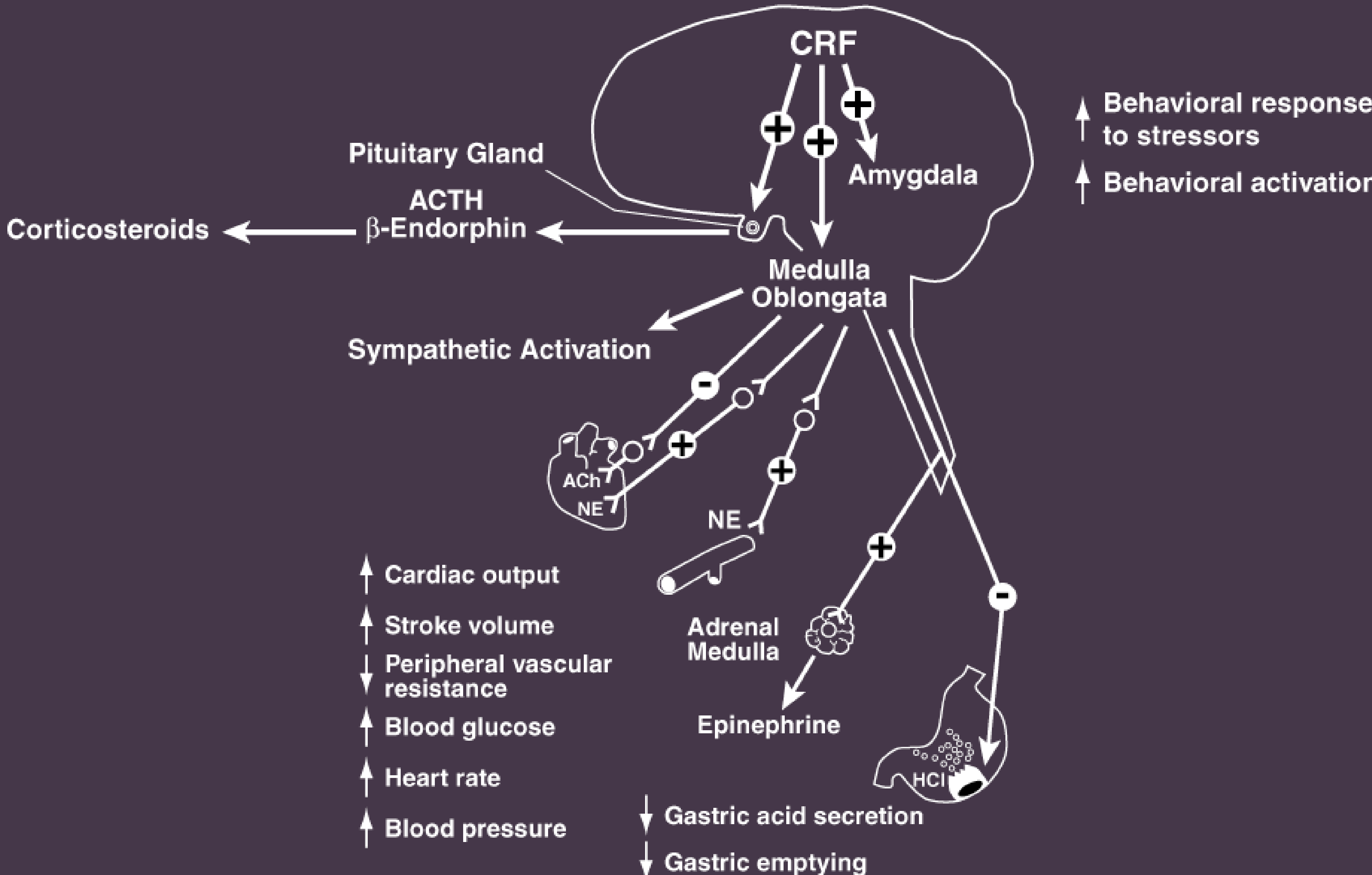
Positive Hedonic Effects

- ↑ Dopamine
- ↑ Opioid peptides
- ↑ Serotonin
- ↑ GABA

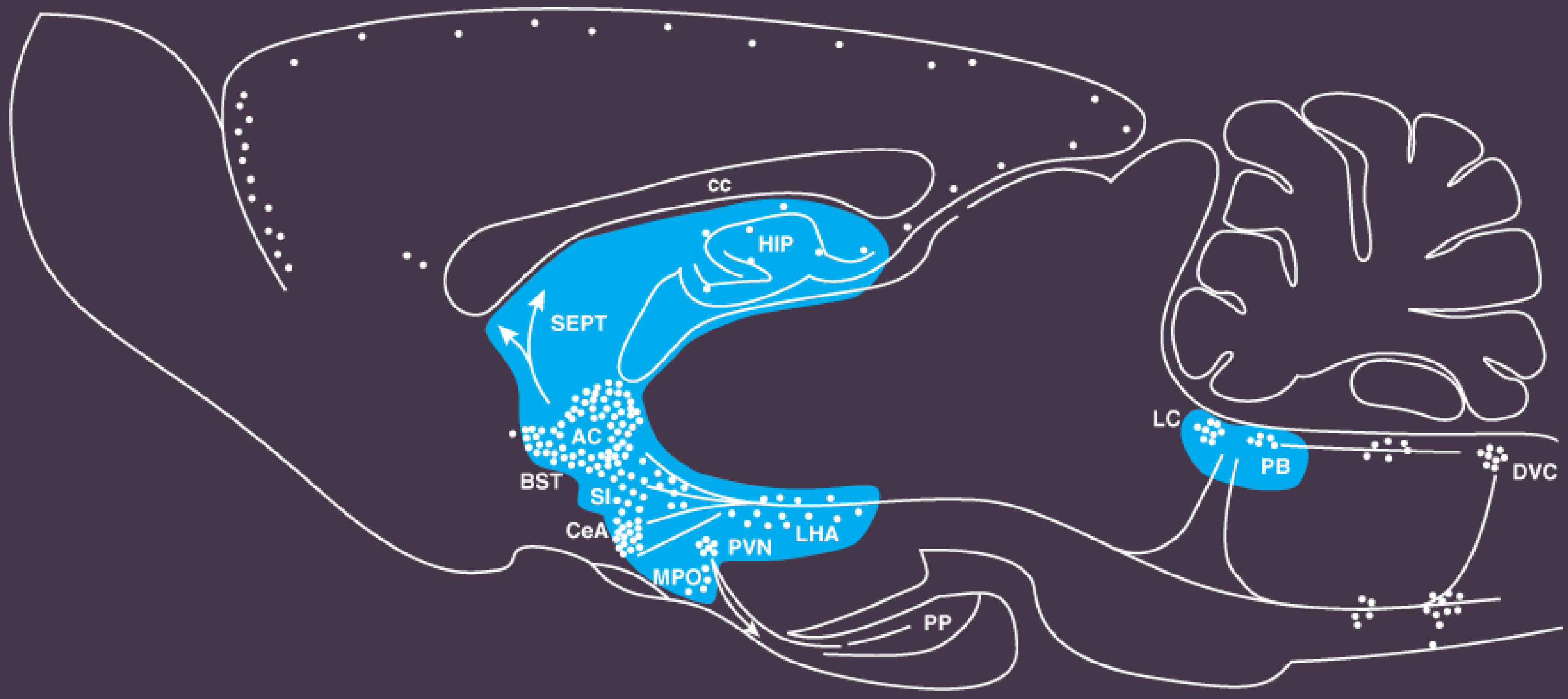
Negative Hedonic Effects of Withdrawal

- ↓ Dopamine … "dysphoria"
- ↓ Opioid peptides ... pain
- ↓ Serotonin … "dysphoria"
- ↓ GABA … anxiety, panic attacks

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

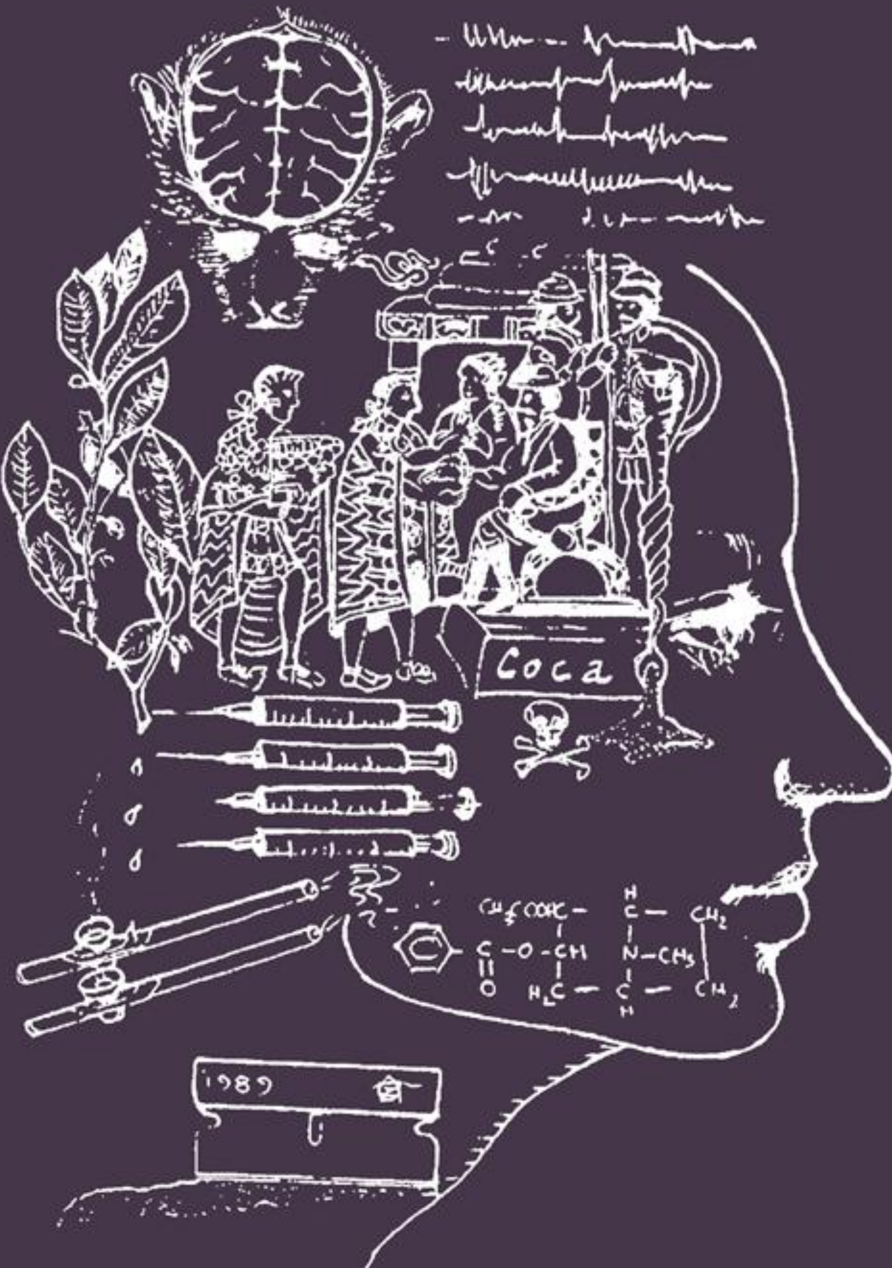


Illustration by J.R. Sanchez-Ramos, M.D.

from: *The Psychiatric Times*, February (1990) 20-22.

Cocaine

Chronic cocaine administration produces a dependence syndrome that is reversed by blockade of CRF function.

Defensive Burying: Active Anxiety-Like Behavior

Habituation

- Two 45-min sessions in test cage
- No shock probe present

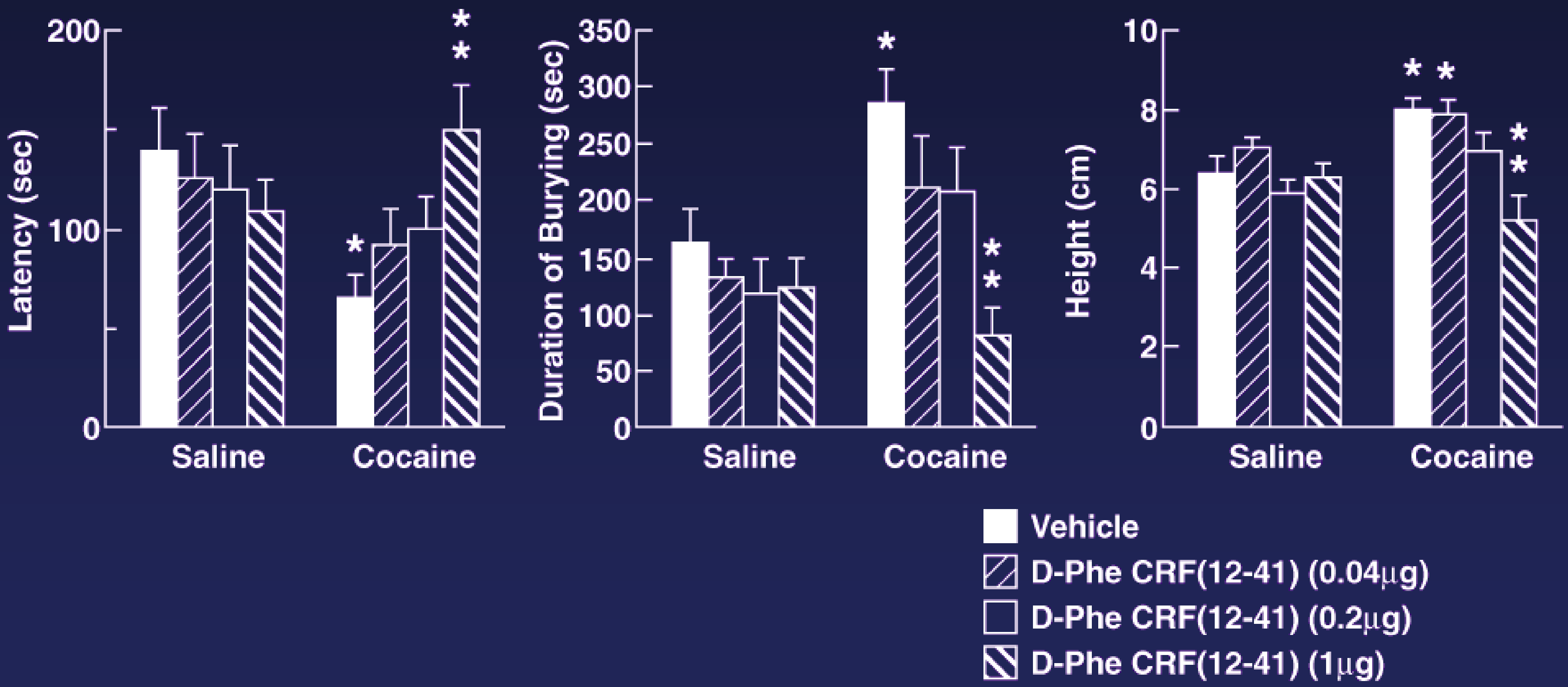
Testing

- Electrified shock probe present
- Probe delivers a single, < 1 sec, 1.5 mA shock on contact
- Probe is shut off after shock
- Defensive burying scored for 10 min

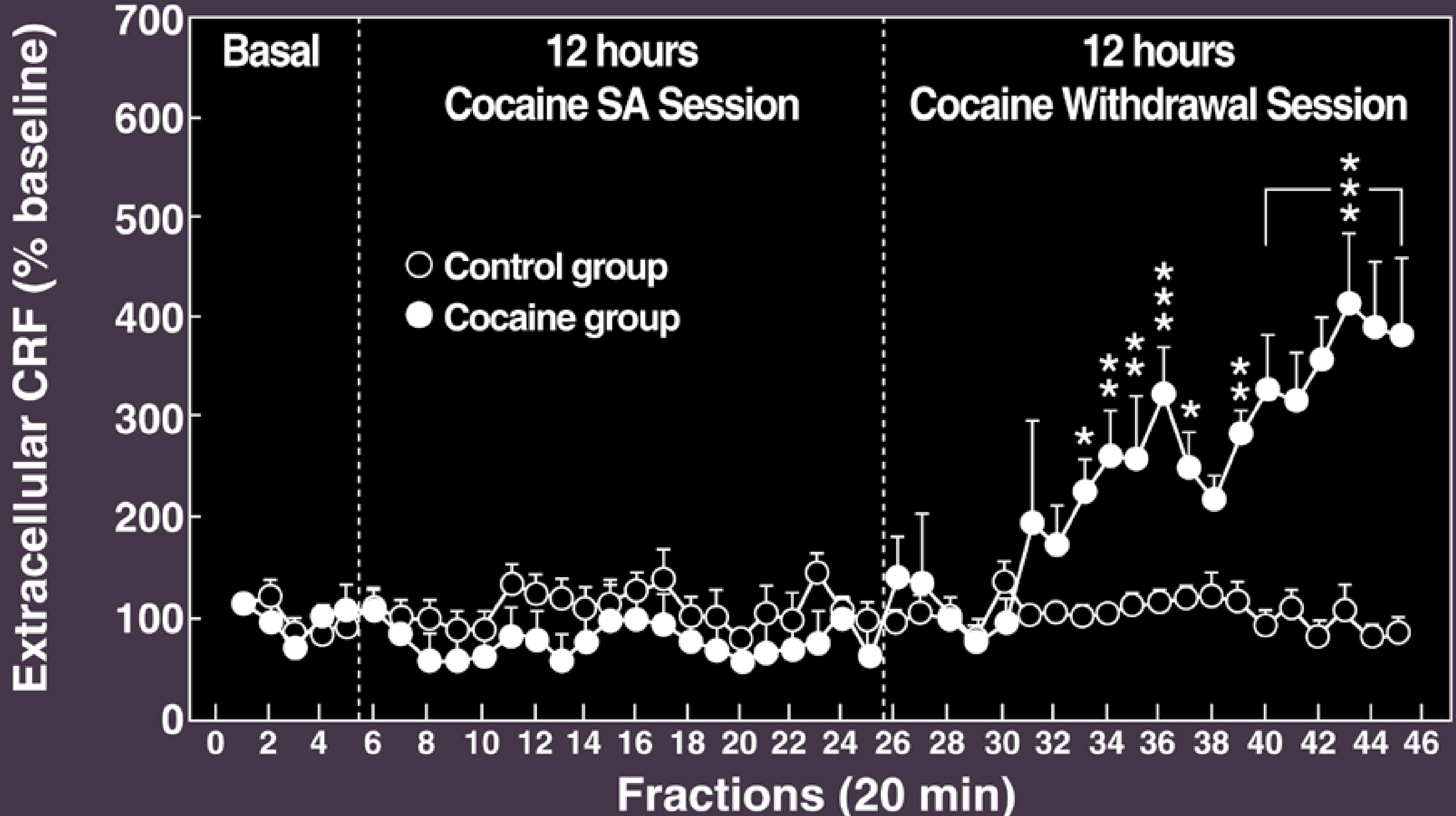
Endpoints

- Latency to bury
- Duration of burying
- Duration of other active behaviors

Effect of CRF Antagonist D-Phe-CRF_{12-41} Administered ICV on Anxiogenic-Like Effect Following Chronic Cocaine Administration



From: Basso AM, Spina M, Rivier J, Vale W and Koob GF, Psychopharmacology, 1999, 145:21-30.



Basal
12 hours
Cocaine SA Session
12 hours
Cocaine Withdrawal Session
Control group
Cocaine group
Extracellular CRF (% baseline)
Fractions (20 min)

Protocol for Drug Escalation

1) Initial Training Phase

All Rats (n=24):
2-hr SA session
Fixed Ratio 1
0.25 mg cocaine/injection

2) Escalation Phase

Short Access (n=12)
22 x 1-hr SA session

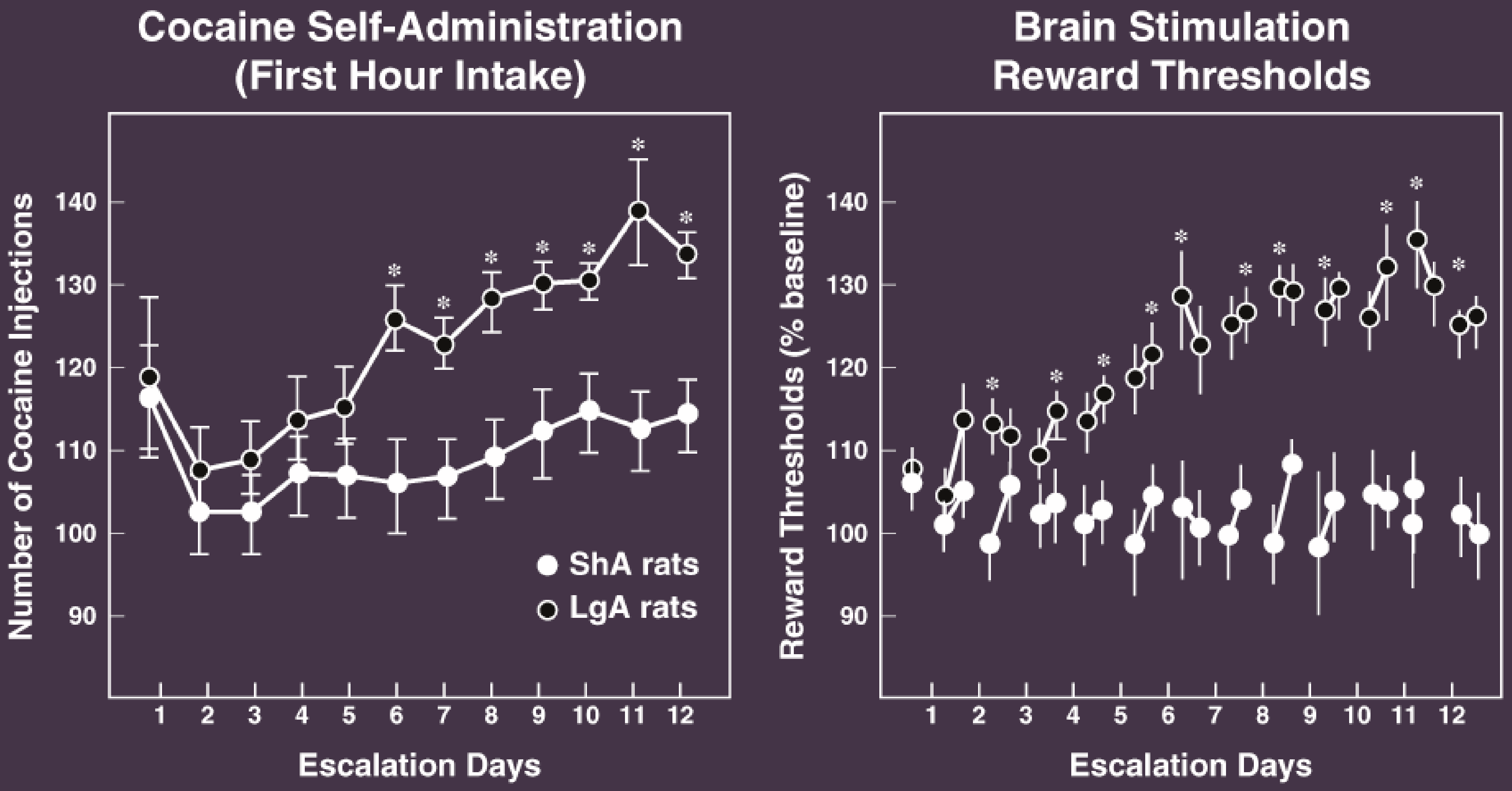
Long Access (n=12)
22 x 6-hr SA session

3) Testing Phase

Dose-response for neuropharmacological probes

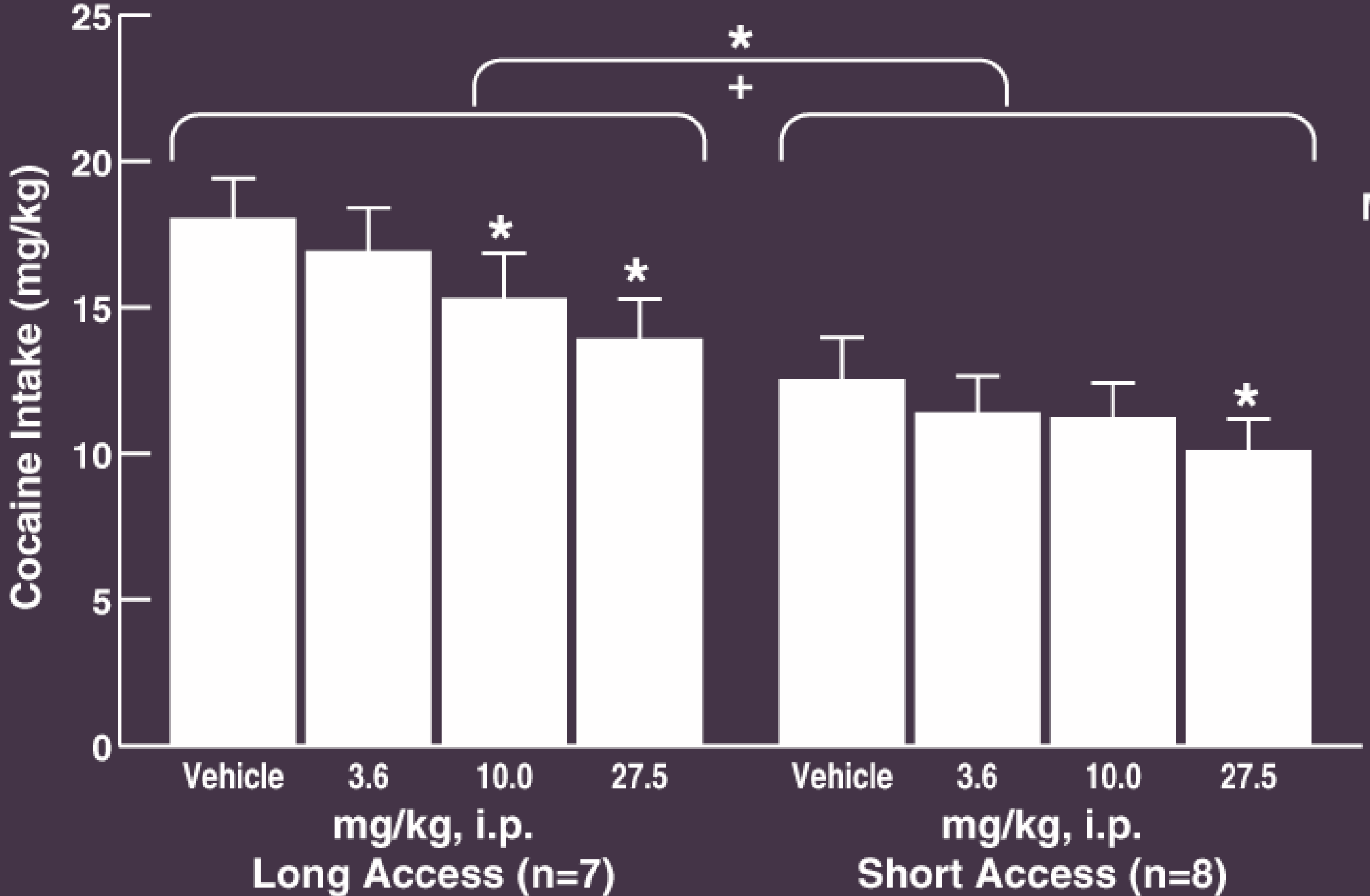
Protocol from: Ahmed SH and Koob, Science, 1998, 282:298-300.

Change in Brain Stimulation Reward Thresholds in Long-Access (Escalation) vs. Short-Access (Non-Escalation) Rats

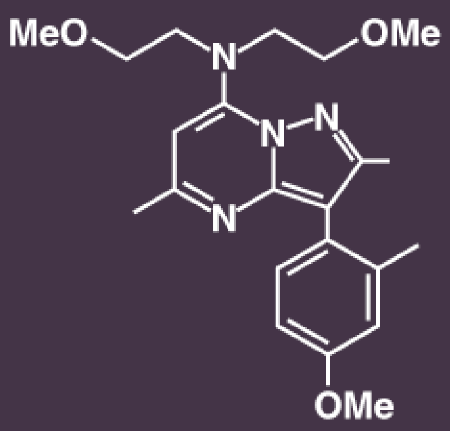


From: Ahmed SH, Kenny PJ, Koob GF and Markou A, Nature Neurosci, 2002, 5:625-627.

Dose-Dependent Decrease of Cocaine Intake with Administration of a CRF_1 Antagonist



DMP904 Analog



K_i = 10 nM
cLogP = 3.85

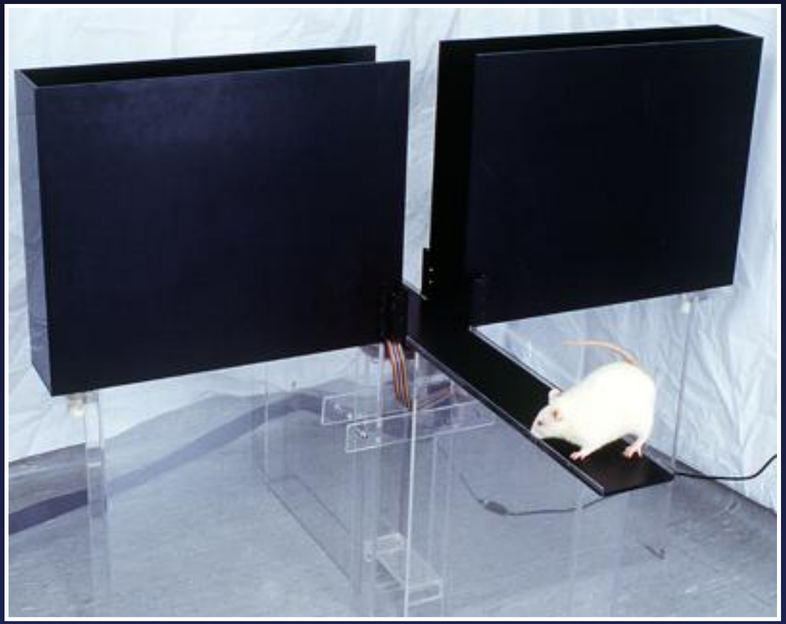
From: Specio SE, Zorrilla EP, O'Dell LE and Koob GF, unpublished results.

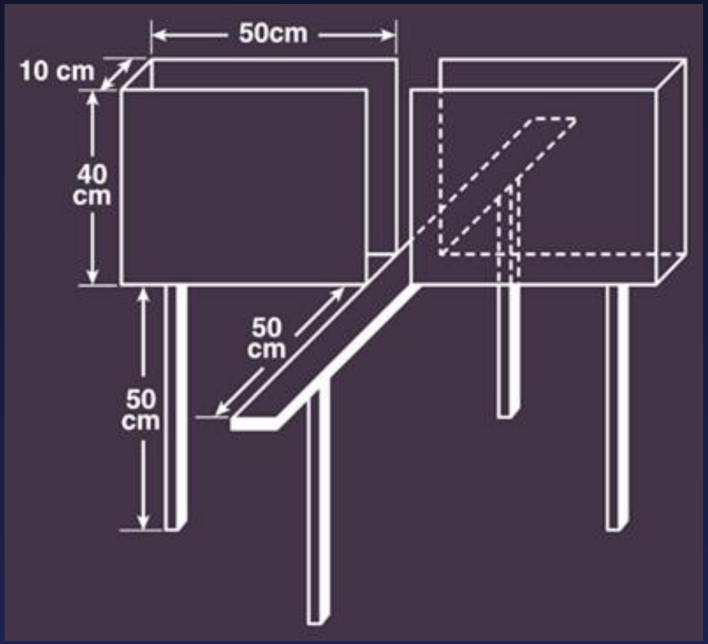
Pieter Bruegel

Alcohol

Chronic alcohol exposure produces a dependence syndrome that is reversed by blockade of CRF function.

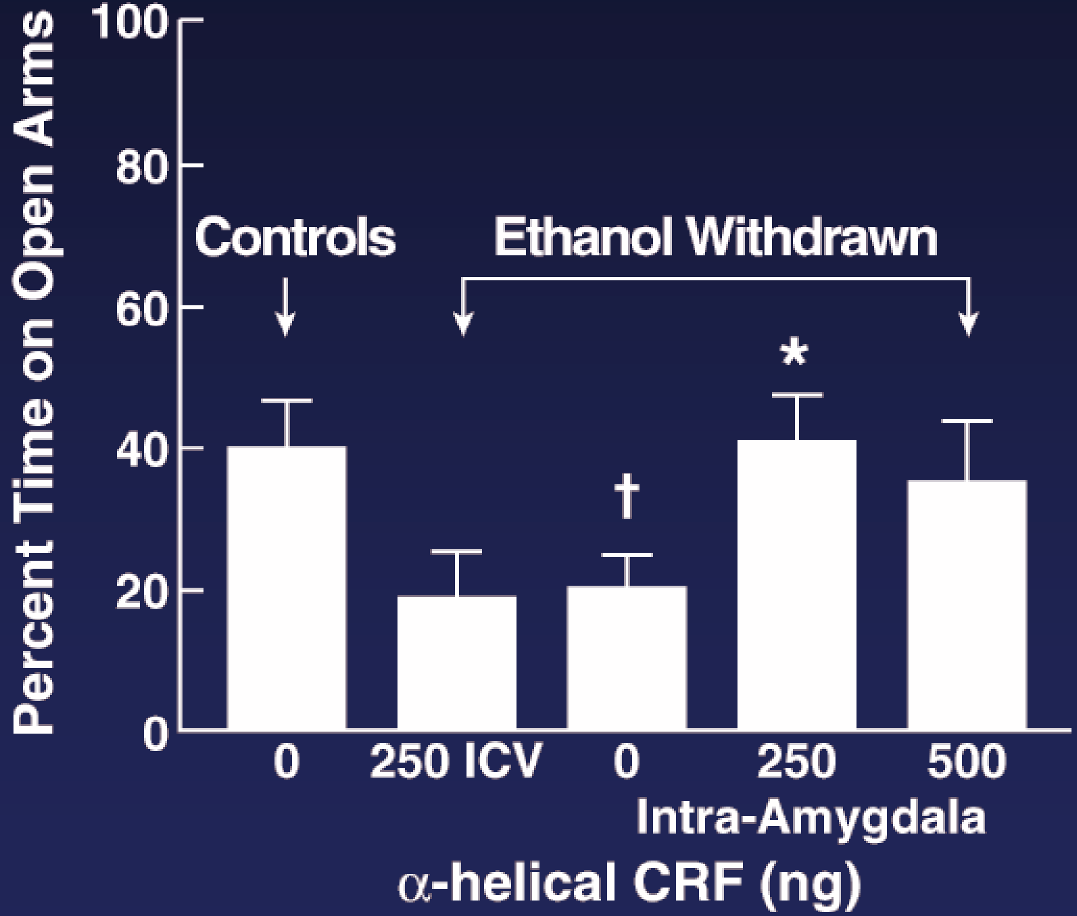
Elevated Plus Maze





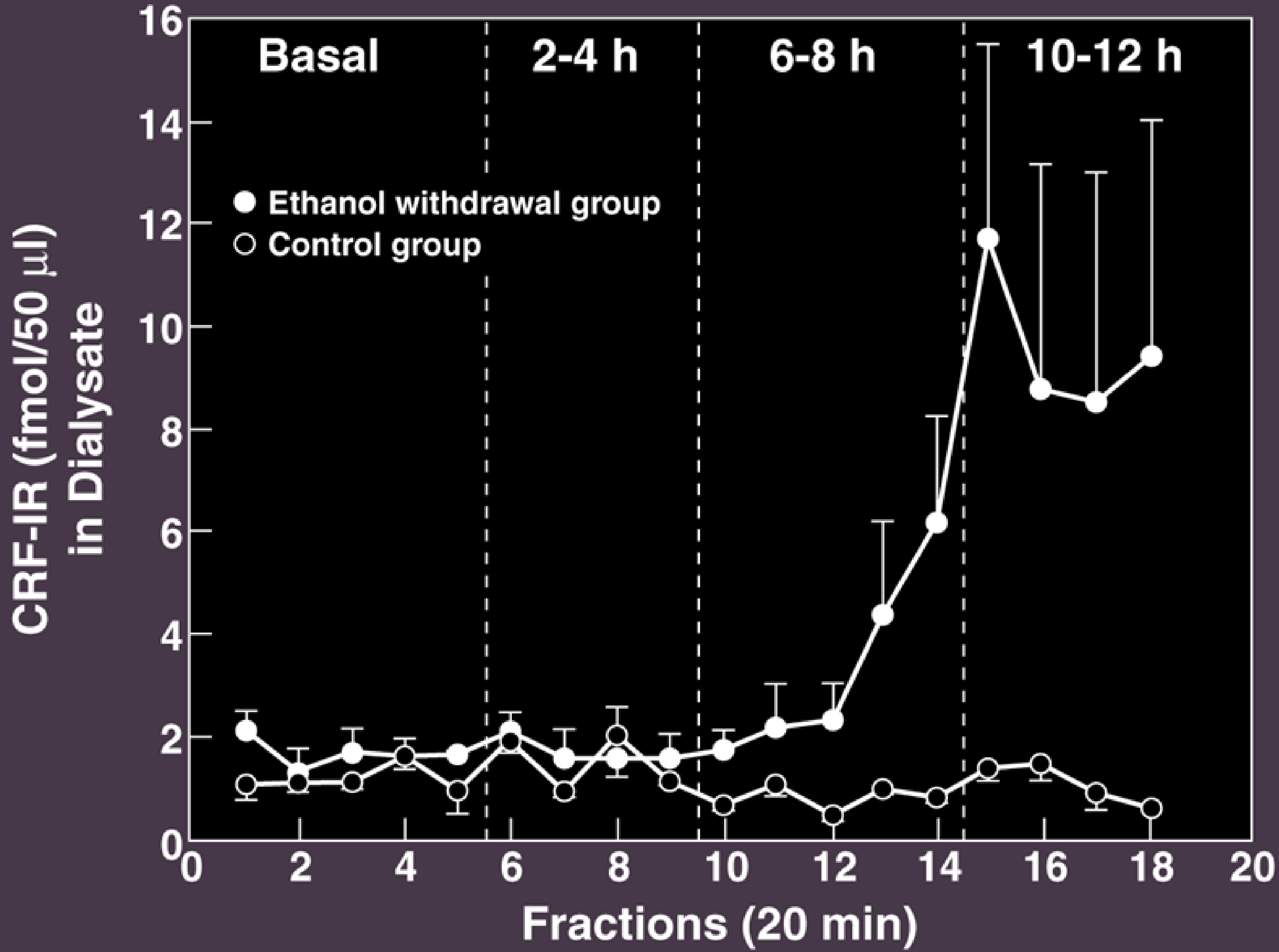
- Unconditioned approach/avoidance behavior
- 3 underlying factors: anxiety, activity, assessment of risk
- Predictive validity for anxiolytic and anxiogenic drugs

Competitive CRF Antagonist α-Helical $CRF_{9\text{-}41}$ Injected into Central Nucleus of the Amygdala Blocks the Anxiogenic Effects of Alcohol Withdrawal



From: Rassnick S, Heinrichs SC, Britton K and Koob GF, Brain Res, 1993, 605:25-32.

Extracellular CRF Levels in the Central Amygdala During Ethanol Withdrawal



From: Merlo-Pich E, Lorang M, Yeganeh M, Rodriquez de Fonseca F, Koob GF and Weiss F, J Neurosci, 1995, 15:5439-5447.

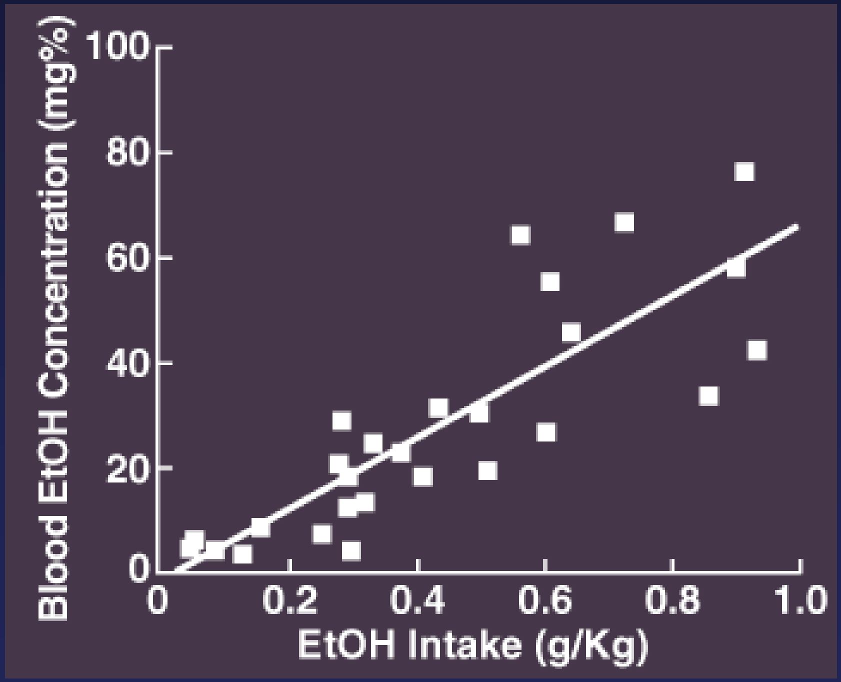
Protocol for Initiation of Lever Pressing for Oral Ethanol Self-Administration in the Rat

Training		Saccharin (w/v)	EtOH (w/v)
Days	1-3	0.2%	0% *
Days	4-9	0.2%	5% *
Day	10	-	5% *
Days	11-12	0.2%	5%
Day	13	-	5%
Day	14	0.2%	8%
Days	15-16	-	8%
Day	7	0.2%	10%
Day	18+	-	10% *

Rats trained to lever press on a FR-1 schedule

Ethanol added to the saccharin solution

Access to ethanol and water or ethanol + saccharin and water

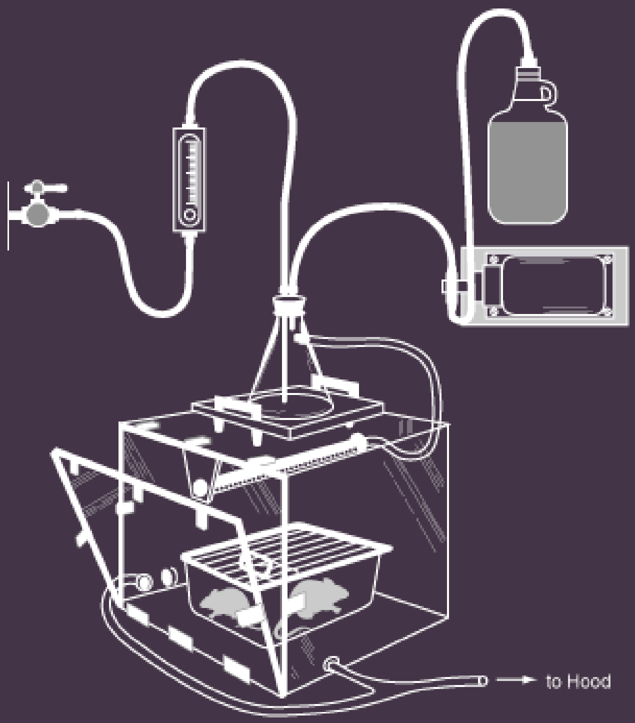


Initiation of the free-choice operant task: ethanol (10%) and water

From: Rassnick S, Pulvirenti L and Koob GF, Alcohol, 1993, 10:127-132.

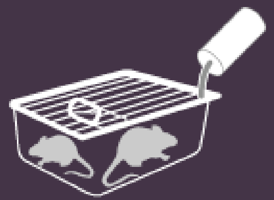
Ethanol Dependence Induction

Ethanol Vapor Chambers



- Ethanol vapor concentrations range from 22-27 mg/liter
- BAL's are determined every 3 days and ethanol flow is adjusted to maintain BAL's of 150-200 mg%
- Dependence is reliably induced following 2 weeks of exposure
- Control rats are placed in identical chambers into which only air is pumped

Ethanol Liquid Diet

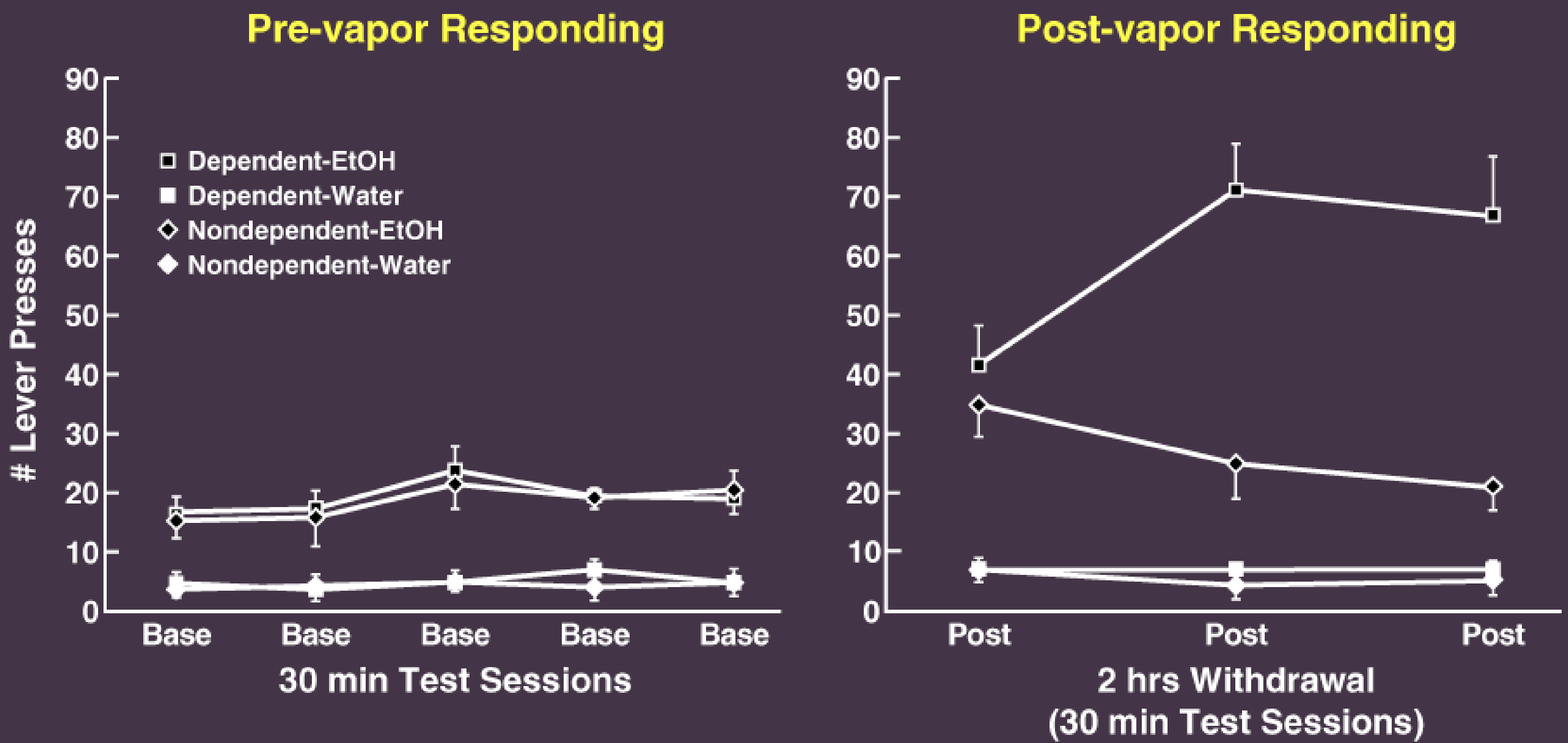


- 8.7% (w/v) ethanol with 35% ethanol-derived calories
- Consists of ethyl alcohol, chocolate flavored sustacal, vitamin and mineral diet fortification
- With unlimited access, maintains BALs over 140 mg%
- Dependence is reliably induced following 2 week exposure
- Control rats are fed liquid diet substituting sucrose for ethanol

From: Rogers J, Wiener SG and Bloom FE, Behav Neural Biol, 1979, 27:466-486.

From: Rassnick S, Heinrichs SC, Britton KT and Koob GF, Brain Res, 1993, 605:25-32.

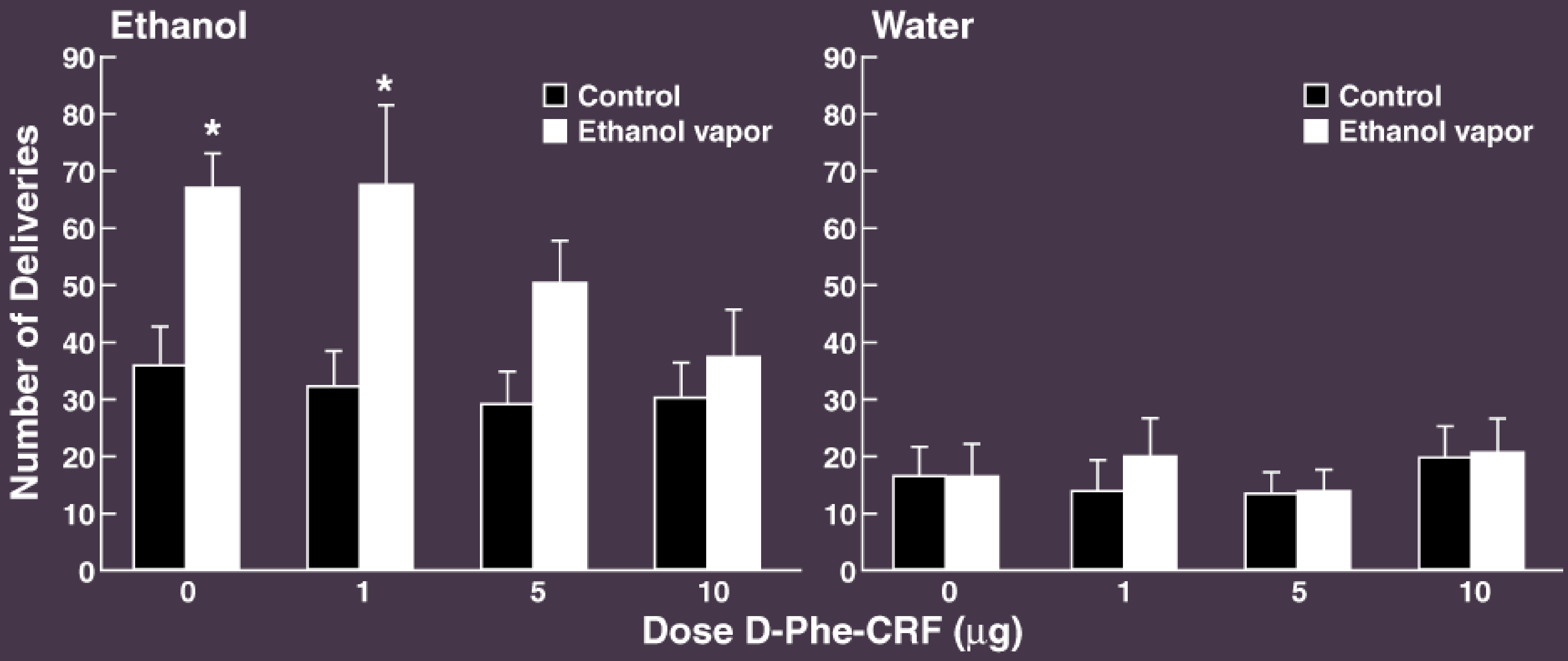
Enhanced Ethanol Self-Administration During Withdrawal in Dependent Animals



From: Funk C and Koob GF, unpublished results.

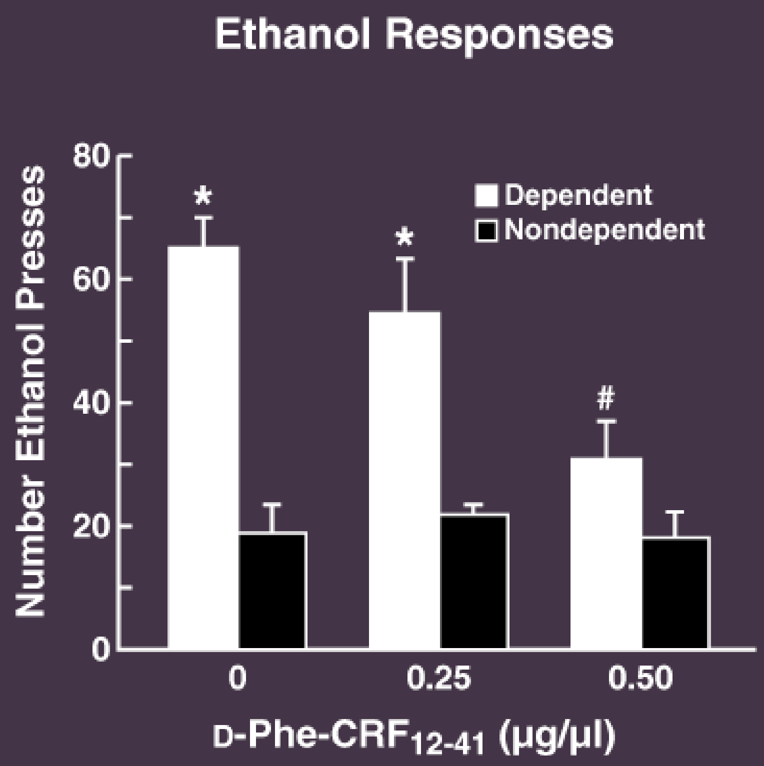
Effects of a Competitive CRF Antagonist Injected ICV on Ethanol Self-Administration During Withdrawal in Dependent Rats

(60 min session 2 h into withdrawal)

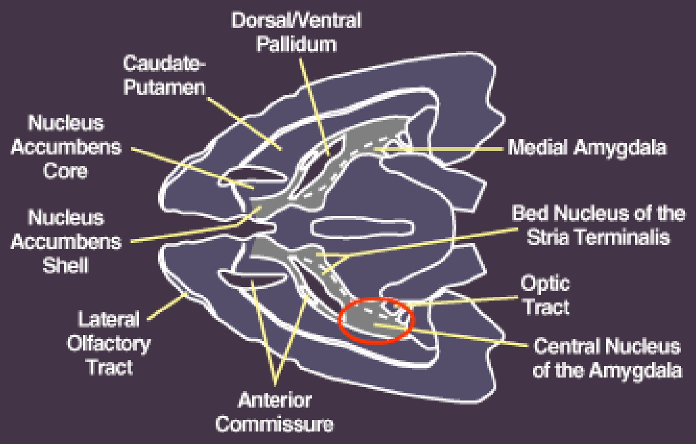


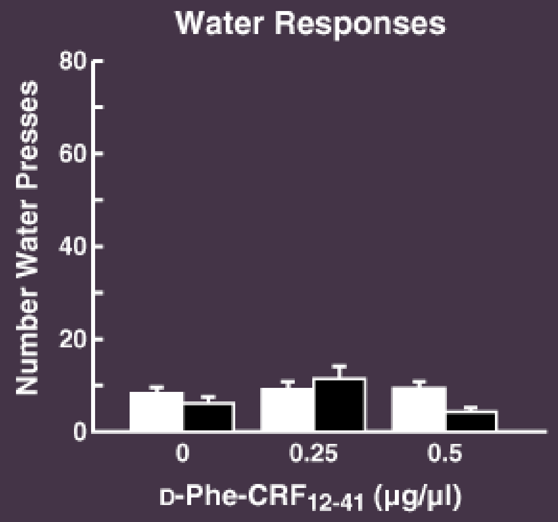
From: Valdez GR, Roberts AJ, Chan K, Davis H, Brennan M, Zorrilla EP and Koob GF, Alcohol Clin Exp Res, 2002, 26:1494-1501.

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



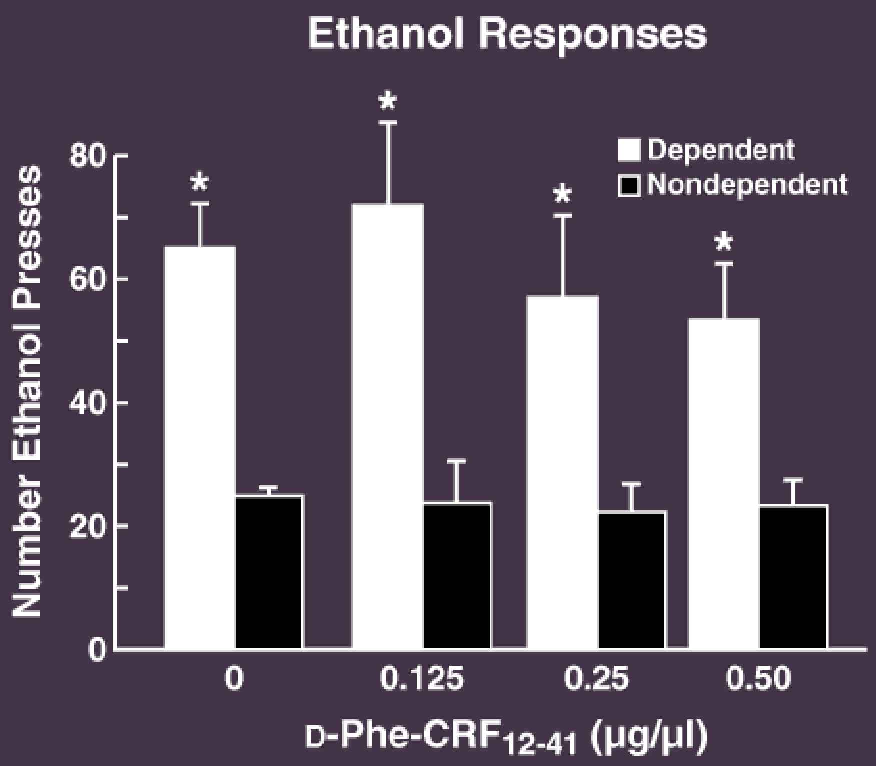
* $p < 0.001$ vs. same-dose, nondependent group
# $p < 0.001$ vs. dependent, vehicle group

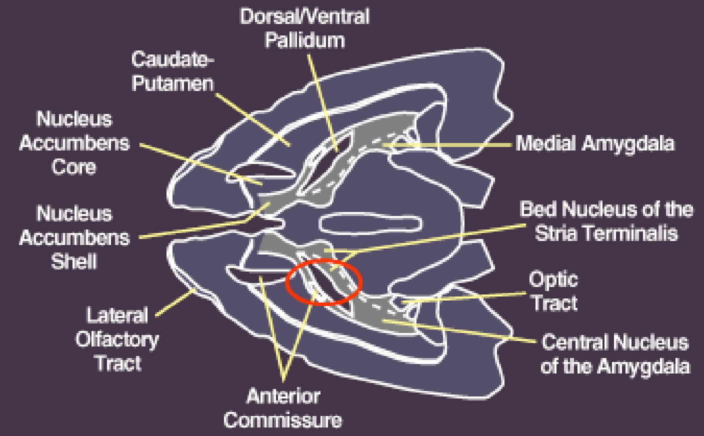


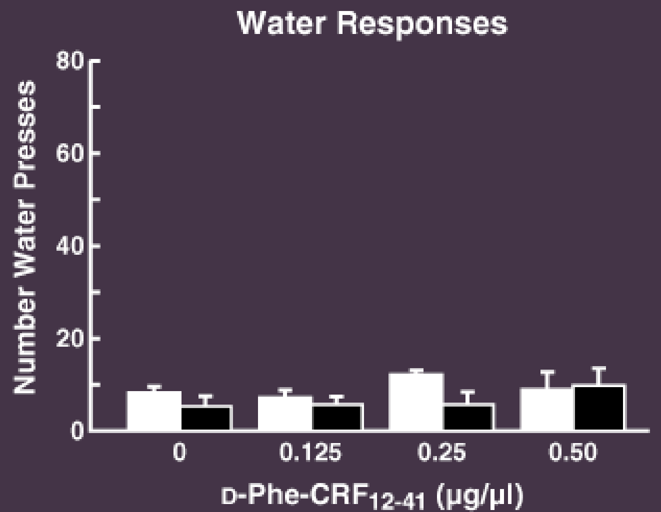


From: Funk C, O’Dell LE and Koob GF, unpublished results.

Effect of CRF Antagonist D-Phe-$CRF_{12\text{-}41}$ – Lateral Bed Nucleus of the Stria Terminalis –



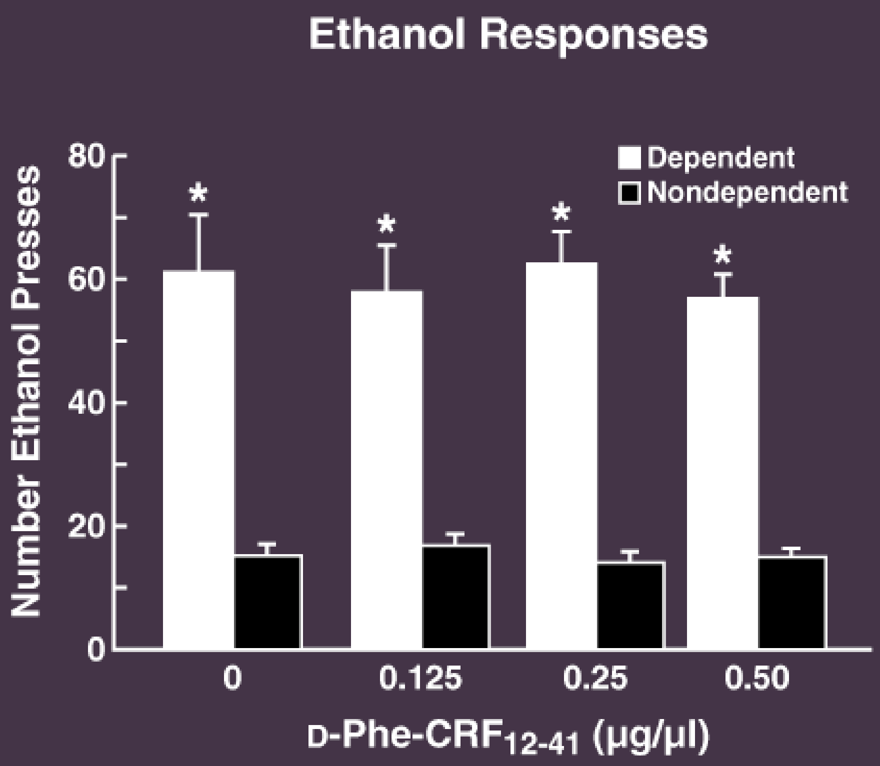




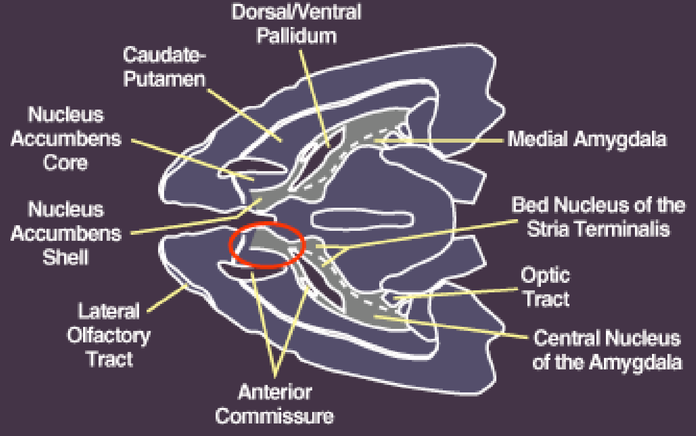
* $p < 0.001$ vs. same-dose, nondependent group

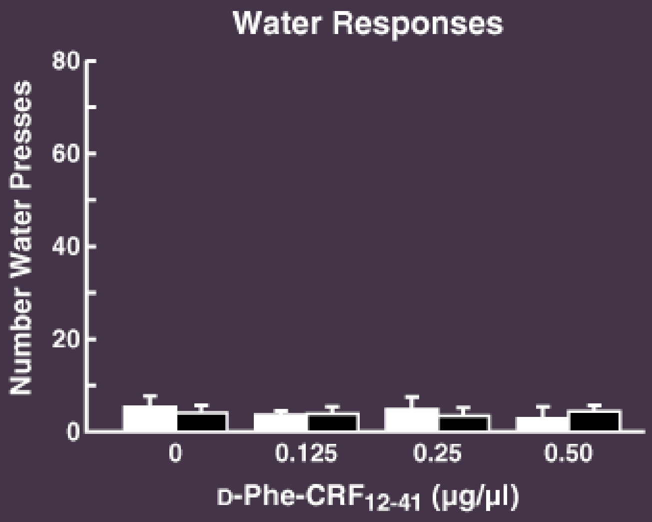
From: Funk C, O'Dell LE and Koob GF, unpublished results.

Effect of CRF Antagonist D-Phe-$CRF_{12\text{-}41}$ – Nucleus Accumbens Shell –



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





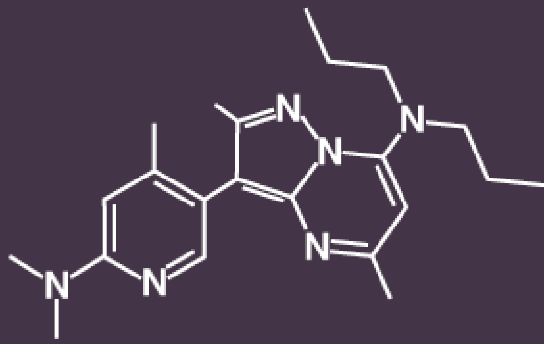
From: Funk C, O'Dell LE and Koob GF, unpublished results.

CRF_1 Specific Antagonists

Antalarmin

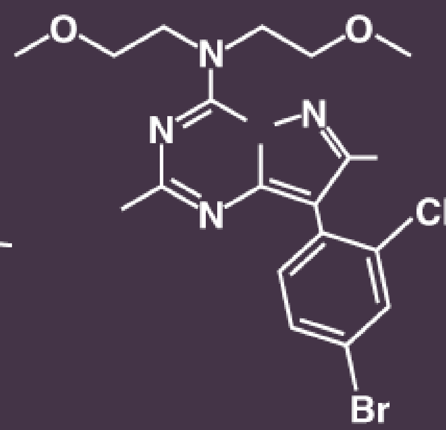
K_i = 1.0 nM
cLogP = 7

R121919
NBI-30775



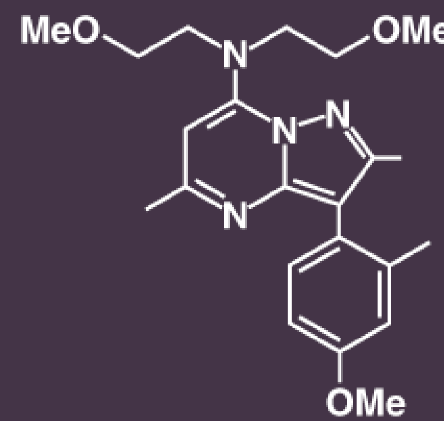
K_i = 3.5 nM
cLogP = 4.8

MJL-1-109-2



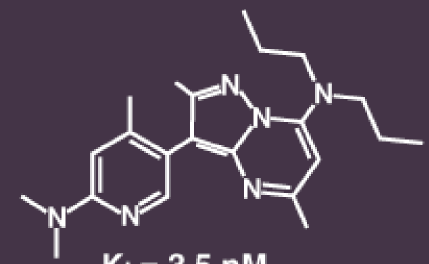
K_i = 1.9 nM
cLogP = 3

DMP904
Analog



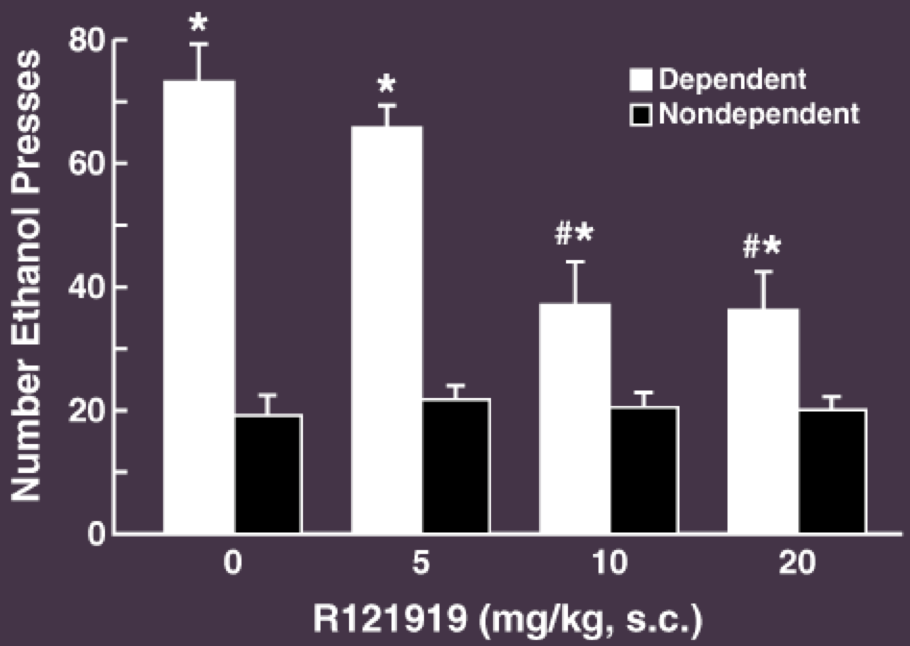
K_i = 10 nM
cLogP = 3.85

CRF$_1$ Specific Antagonists R121919



K_i = 3.5 nM
cLogP = 4.8

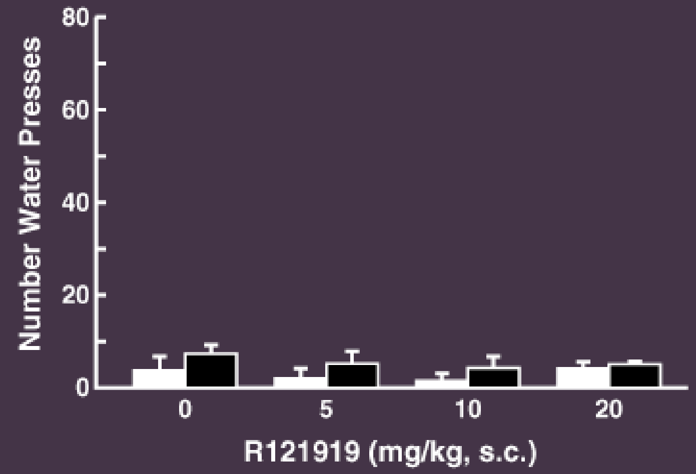
Ethanol Responses



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

- administered s.c.
- 60 min pre-incubation
- n = 9
- HBC (20% w/v)

Water Responses



From: Funk C, Zorrilla EP, Lee MJ, Rice KC and Koob GF, unpublished results.

Interaction of CRF Antagonists in Animal Models of Protracted Abstinence

1. **CRF antagonists injected into the extended amygdala block stress-induced reinstatement of drug seeking**

   Erb S, Salmaso N, Rodaros D and Stewart J, Psychopharmacology, 2001, 158:360-365
   Liu X and Weiss F, J Neurosci, 2002, 22:7856-7861
   Funk D, Li Z, Shaham Y and Le AD, Neuroscience, 2003, 122:1-4

2. **CRF antagonists injected i.c.v. block stress-induced anxiogenic-like responses and excessive drinking during protracted abstinence**

   Valdez GR, Zorrilla EP, Roberts AJ and Koob GF, Alcohol, 2003, 29:55-60.

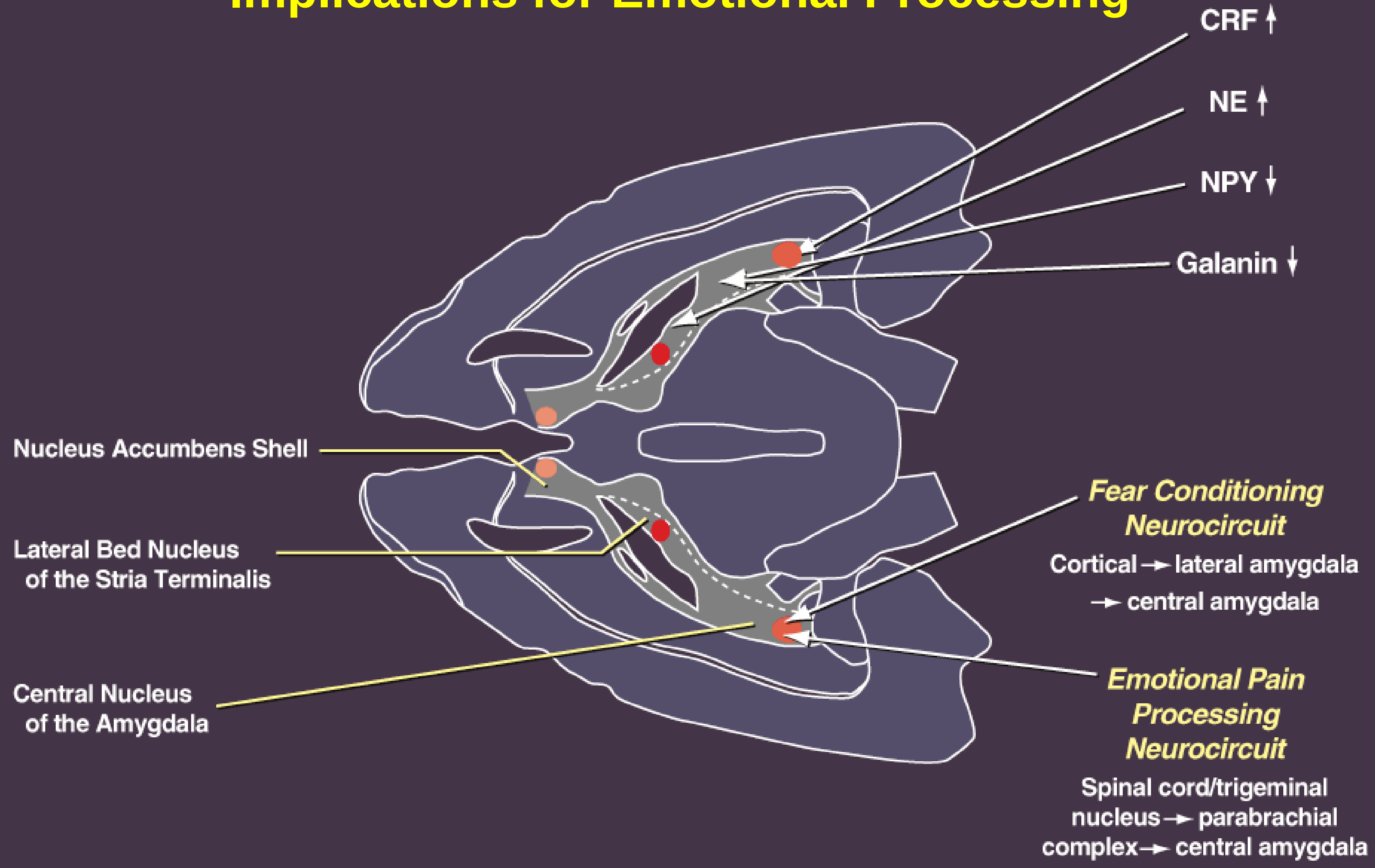
3. **CRF_1 knockout mice show a blunted anxiogenic-like response to alcohol withdrawal and a blockade of excessive drinking during protracted abstinence**

   Chu K, Koob GF, Cole M and Roberts AJ, submitted

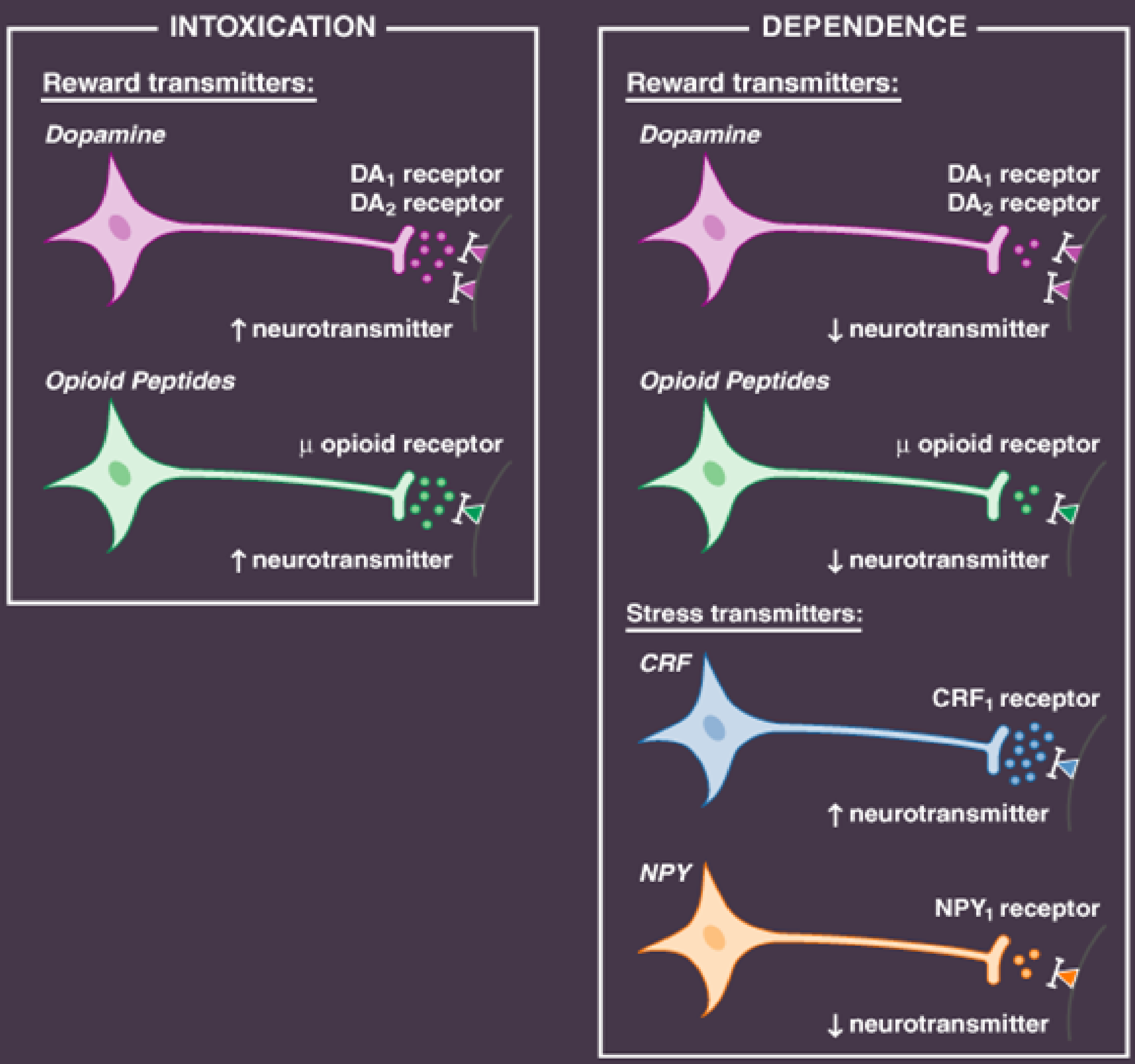
Extended Amygdala

The extended amygdala is a rich substrate for neurochemical and neurocircuitry interactions that produce the "dark side" of motivation.

Neurochemical Changes in the Extended Amygdala during the Development of Dependence: Implications for Emotional Processing



Neurochemical Changes Associated with the Transition from Drug Use to Dependence



From: Roberts AJ and Koob GF, Alcohol: ethanol antagonists/amethystic agents. in Adelman G and Smith BH (Eds.), Encyclopedia of Neuroscience, 3rd edn, Elsevier, New York, 2003 [http://203.200.24.140:8080/Neuroscience].

Conclusions

CRF in the extended amygdala is recruited during the development of dependence and has motivational significance for drug seeking.

Compulsive drug taking associated with addiction derives both from decreases in reward neurotransmission and from recruitment of anti-reward systems ("dark side" of addiction).

Other neurochemical elements in the extended amygdala—such as norepinephrine, NPY and galanin—may have a role in motivational neuroadaptation associated with drug dependence.

The common interface in the extended amygdala of the neurochemistry of addiction and pain and fear conditioning pathways provides a heuristic framework for exploring the neural basis of negative emotional states.

Neurobiology of Drug Addiction
Koob Laboratory

Post-Doctoral Fellows

Cindy Funk
Brendan Walker
Tom Greenwell
Sandy Ghozland
Nick Gilpin
Chitra Mandyam
Sunmee Wee

Research Assistants

Bob Lintz
Richard Schroeder
Elena Crawford
Molly Brennan
Maury Cole
Tess Kimber
Yanabel Grant
Ron Smith

Administrative Assistants

Lisa Maturin
Mellany Santos
Marisa Gallego

Special thanks to:

Mike Arends
(Senior Research Assistant)

Janet Hightower
(Biomedical Graphics Dept)

Neurobiology of Drug Addiction
Current Collaborators

Floyd Bloom
Barbara Mason
Michel Le Moal
Luis Stinus
Friedbert Weiss
Athina Markou
Amanda Roberts
Larry Parsons
Pietro Sanna
Luigi Pulvirenti
Eric Zorrilla
Wylie Vale

Jean Rivier
Catherine Rivier
Tamas Bartfai
George Siggins
Marisa Roberto
Kenner Rice
Kim Janda
Laura O'Dell
Robert Purdy
Walter Francesconi
Sheila Specio
Marc Azar

Support from:

National Institute on Alcohol Abuse and Alcoholism

National Institute on Drug Abuse

National Institute of Diabetes and Digestive and Kidney Diseases

Pearson Center for Alcoholism and Addiction Research