Neurobiology of Addiction: Springboard to New Treatments

George F. Koob, Ph.D.
Professor and Chair
Committee on the Neurobiology of Addictive Disorders
The Scripps Research Institute
La Jolla, California

Financial Disclosure

Consultant

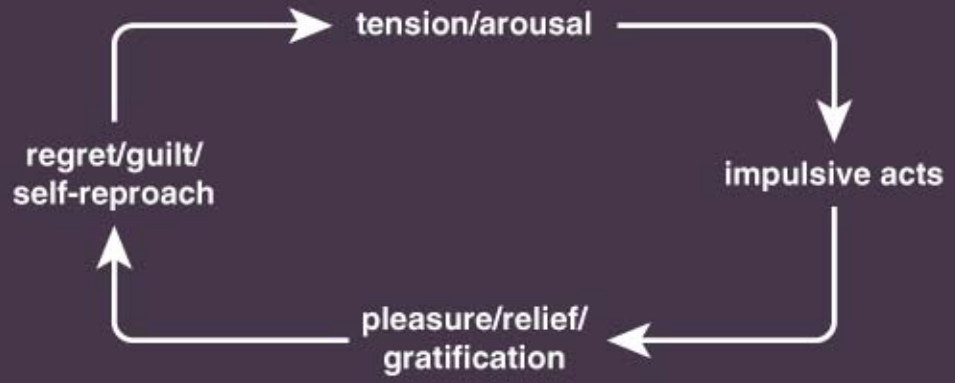
Abbott Laboratories
Boehringer-Ingelheim
Eli-Lilly & Co.
Johnson & Johnson Pharmaceutical Research & Development
Pfizer Pharmaceuticals

“When people talk about drugs, they assume people take drugs because they enjoy it,” Williams told the *Toronto Star*. “But really, it's no different from overeating or watching too much television or drinking too much. You take drugs to make yourself feel better, to fill a hole.”

- Ricky Williams

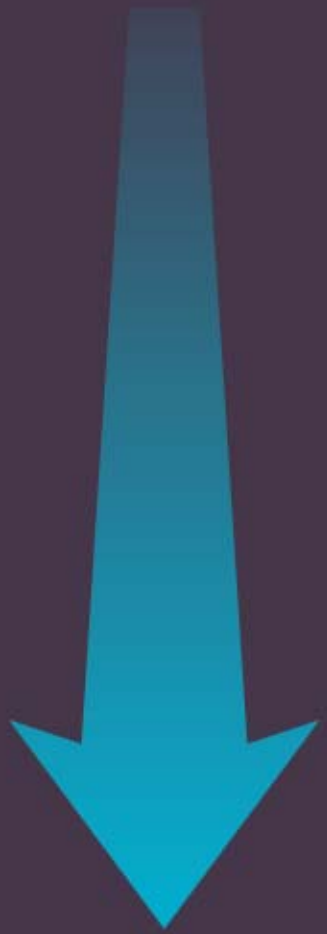
-Byline Damien Cox, Toronto Star, May 29, 2006

Impulse Control Disorders



Compulsive Disorders

Positive Reinforcement



Negative Reinforcement

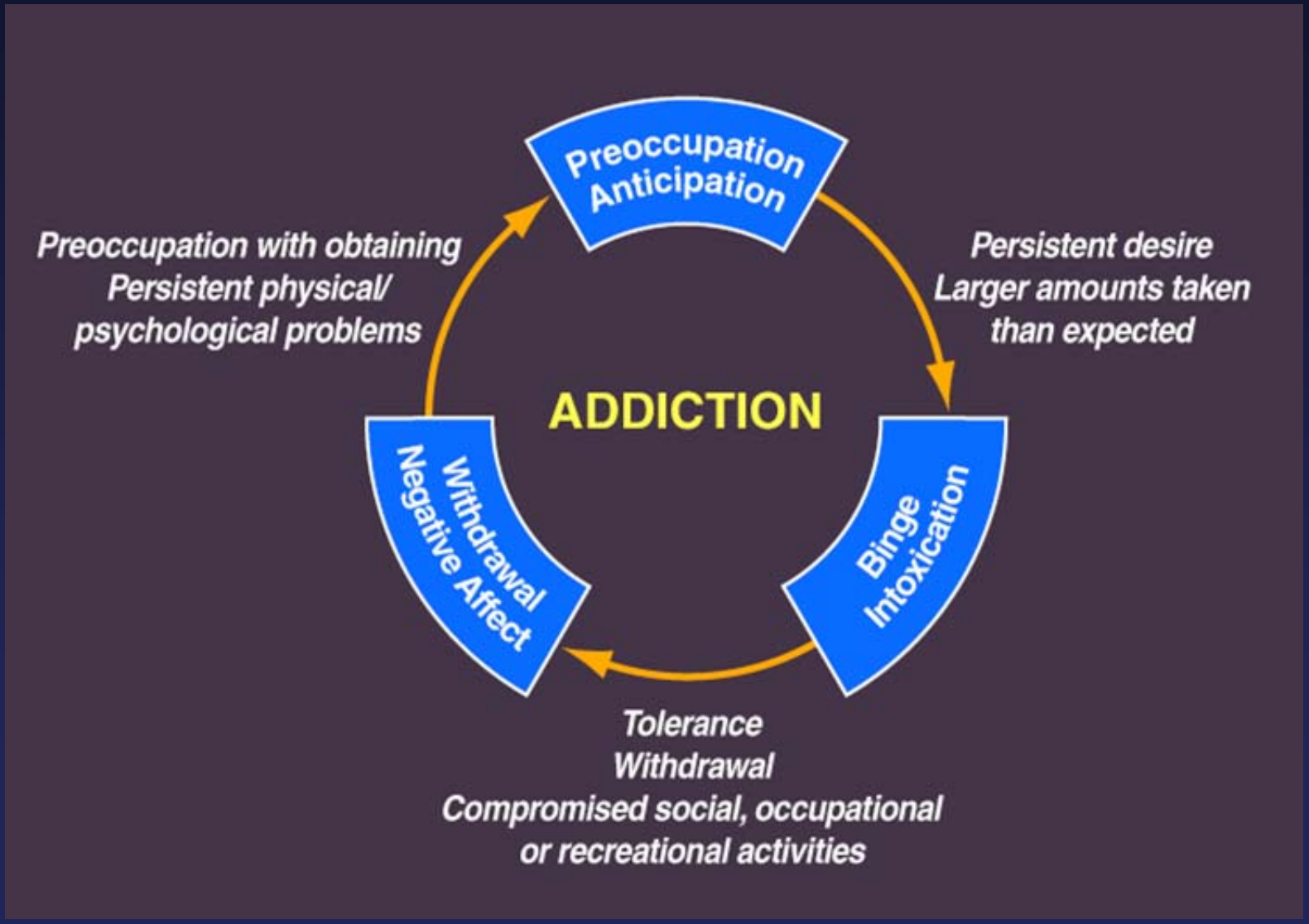
From: Koob GF, Alcohol Clin Exp Res, 2003, 27:232-243.

Positive and Negative Reinforcement —Definitions—

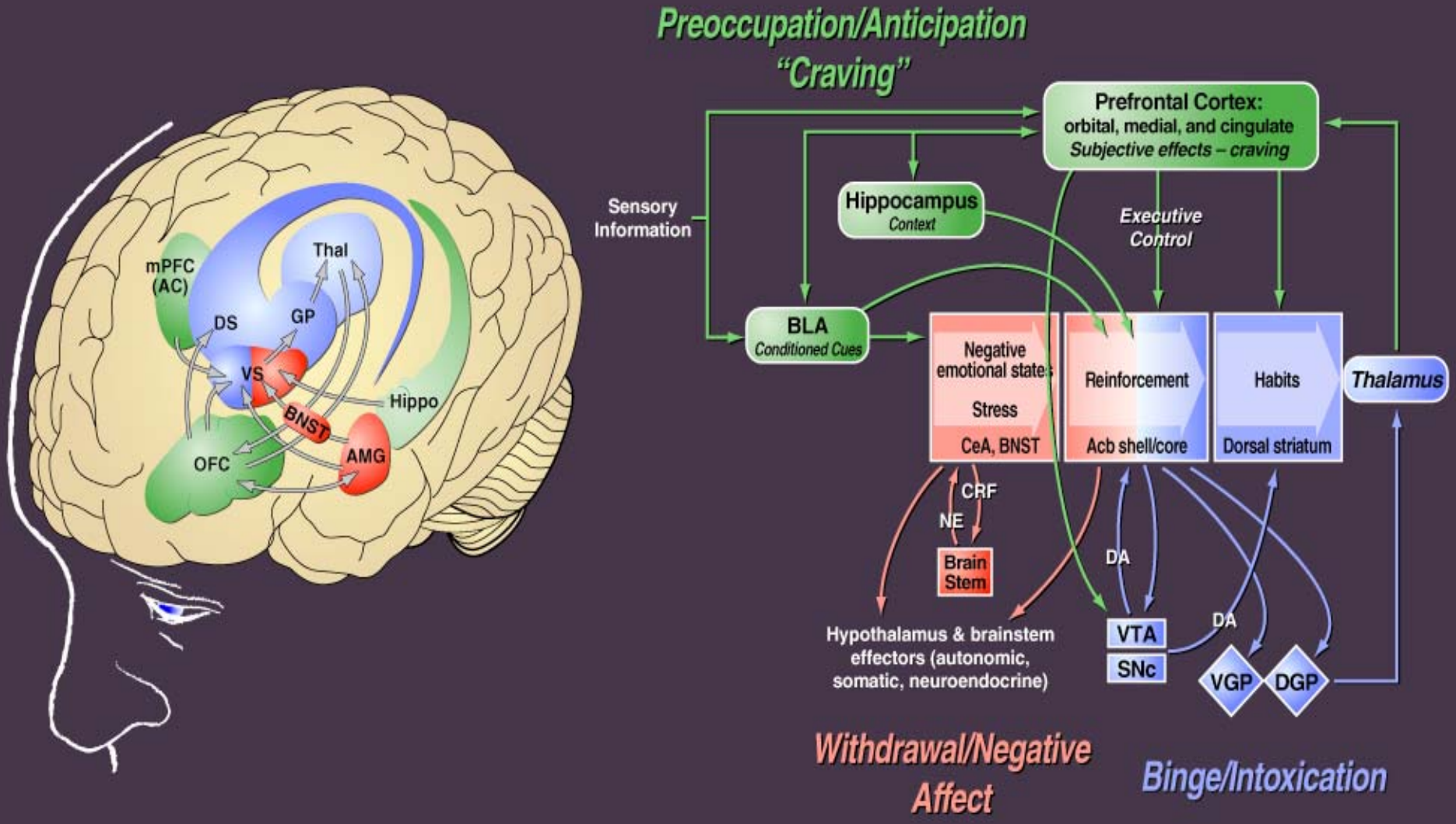
Positive Reinforcement — the process by which presentation of a stimulus (drug) increases the probability of a response (includes non dependent drug taking paradigms).

Negative Reinforcement — the process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (includes dependence-induced drug taking)

Stages of the Addiction Cycle



Neurocircuitry of Addiction



Derived from: Koob G, Everitt, B and Robbins T, Reward, motivation, and addiction. In: Squire LR, Berg D, Bloom FE, du Lac S, Ghosh A, Spitzer NC (Eds.), Fundamental Neuroscience, 3rd edition, Academic Press, Amsterdam, 2008, pp. 987-1016.

Key Common Neuroanatomical Structures in Addiction

Nucleus Accumbens Central Nucleus of the Amygdala — Forebrain structures involved in the rewarding effects of drugs of abuse and drives the binge intoxication stage of addiction. Contains key reward neurotransmitters: dopamine and opioid peptides

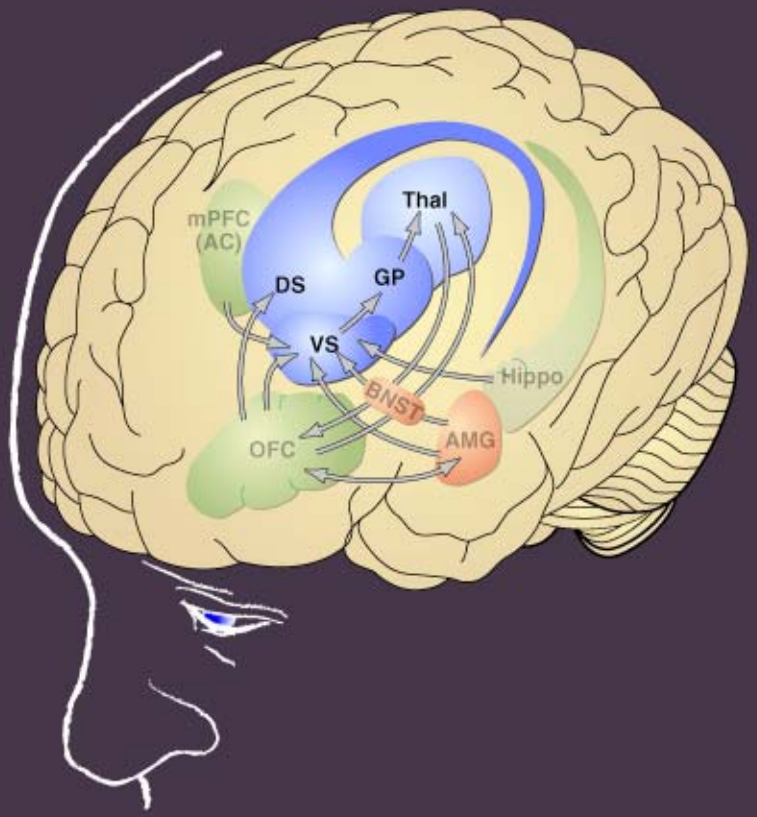
Extended Amygdala — Composed of central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition zone in the medial part of the nucleus accumbens. Contains "brain stress" neurotransmitter, corticotropin releasing factor that controls hormonal, sympathetic, and behavioral responses to stressors, and is involved in the anti-reward effects of drug dependence

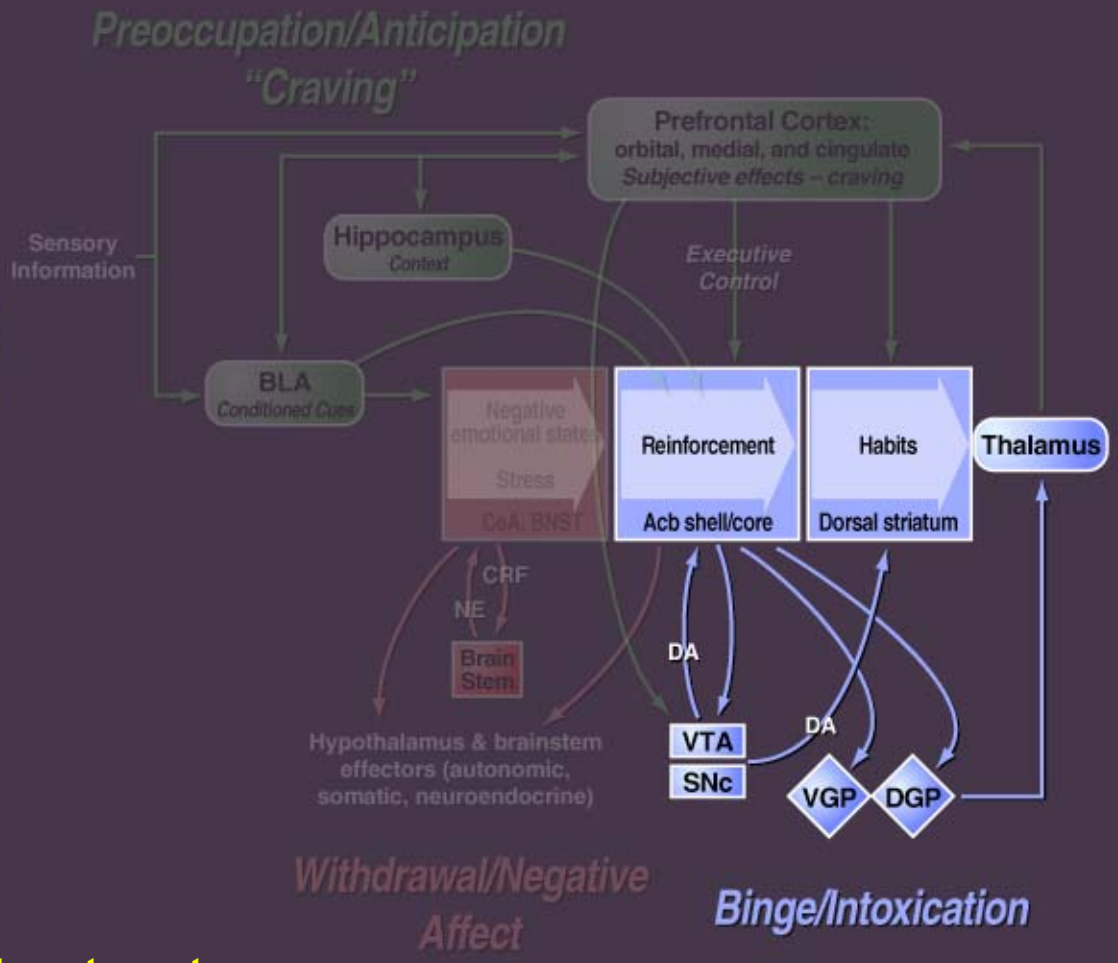
Medial Prefrontal Cortex — neurobiological substrate for "executive function" that is compromised in drug dependence and plays a key role in facilitating relapse. Contains major glutamatergic projection to nucleus accumbens and amygdala

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

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

Existing and Future Medications for Addiction: Binge/Intoxication Stage

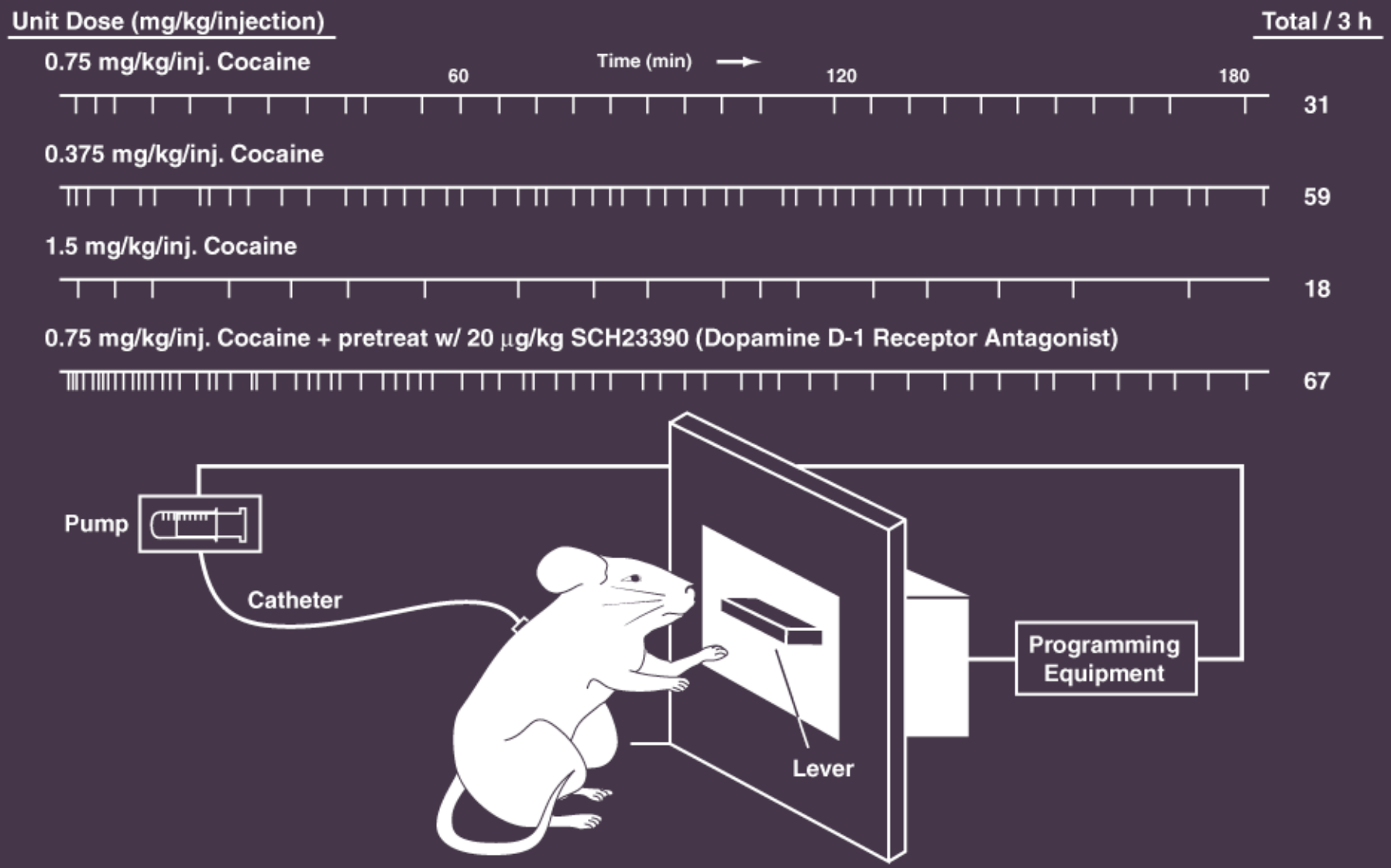




Existing medications
- disulfiram
- naltrexone
- methadone
- buprenorphine

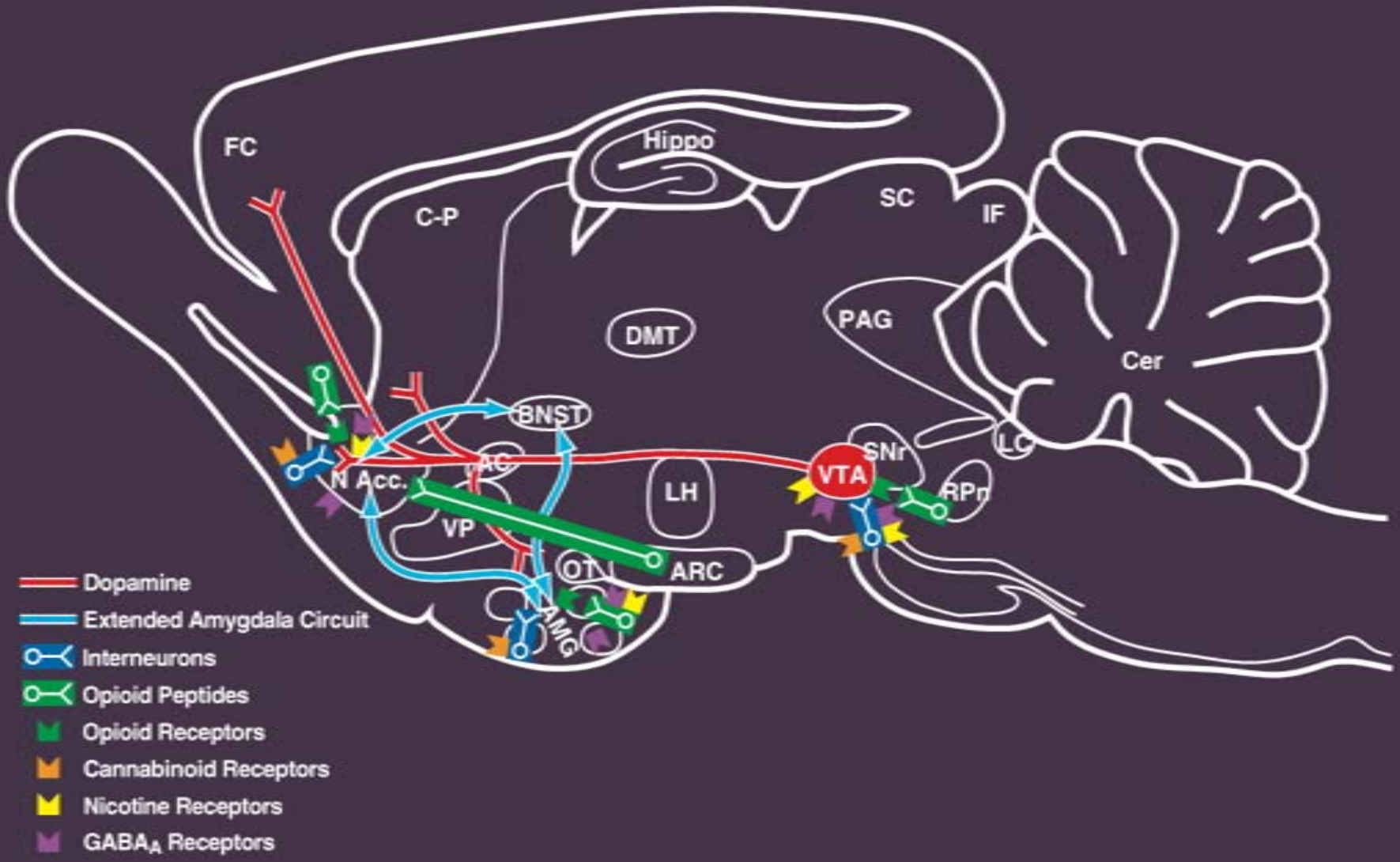
Future targets
- partial agonists
- drug vaccines

Cocaine Self-Administration



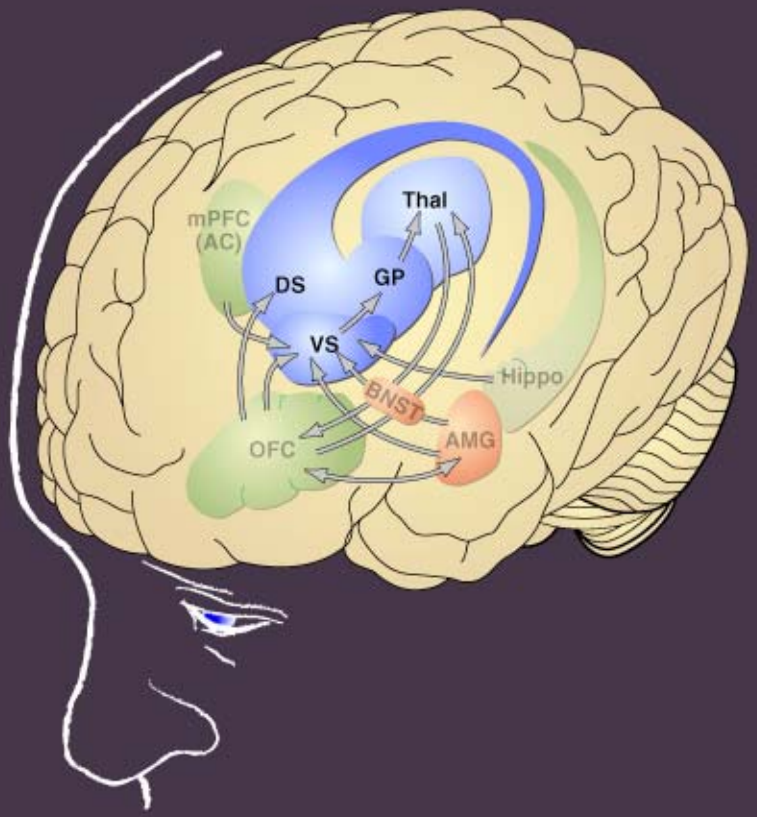
From: Caine SB, Lintz R and Koob GF. in Sahgal A (ed) Behavioural Neuroscience: A Practical Approach, vol. 2, IRL Press, Oxford, 1993, pp. 117-143.

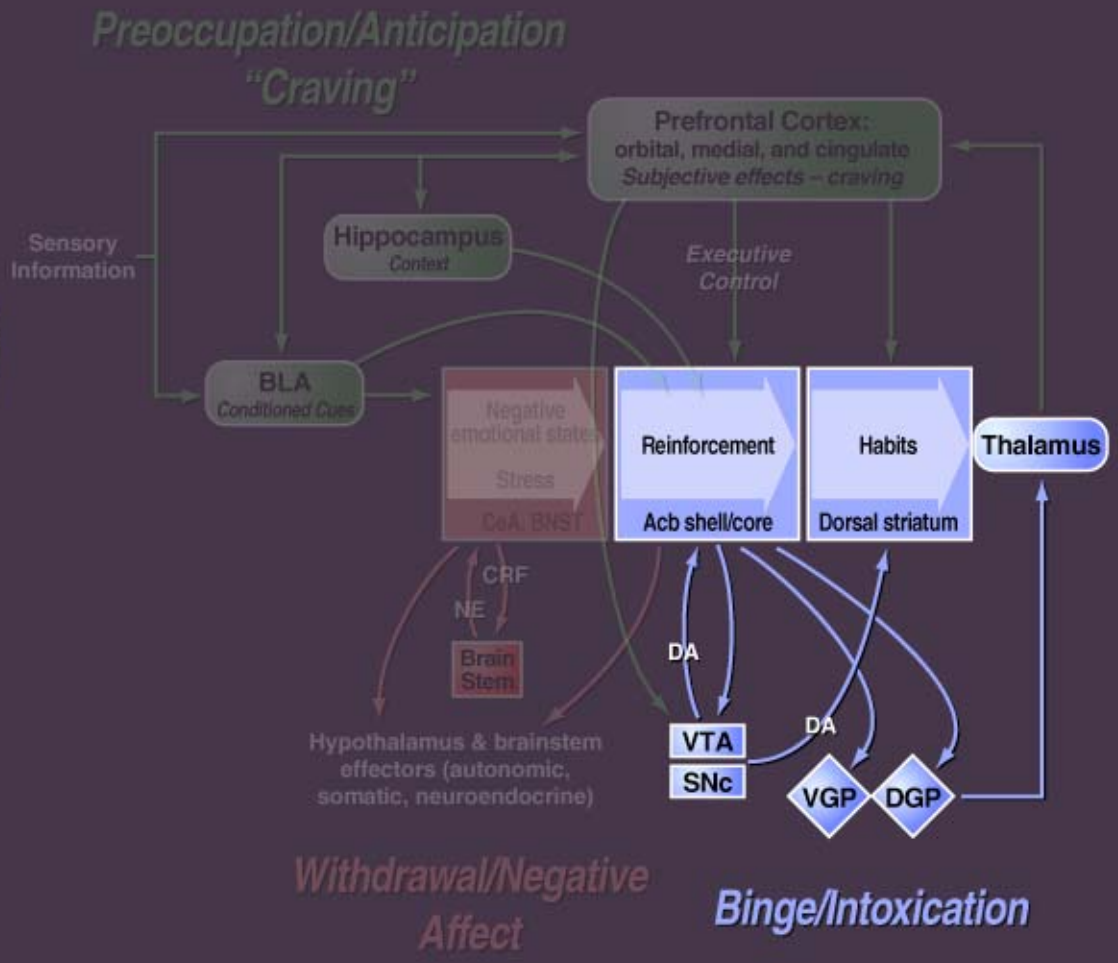
Neurochemical Circuitry in Drug Reward



From: Koob GF, Clin Neurosci Res, 2005, 5:89-101.

Existing and Future Medications for Addiction: Binge/Intoxication Stage



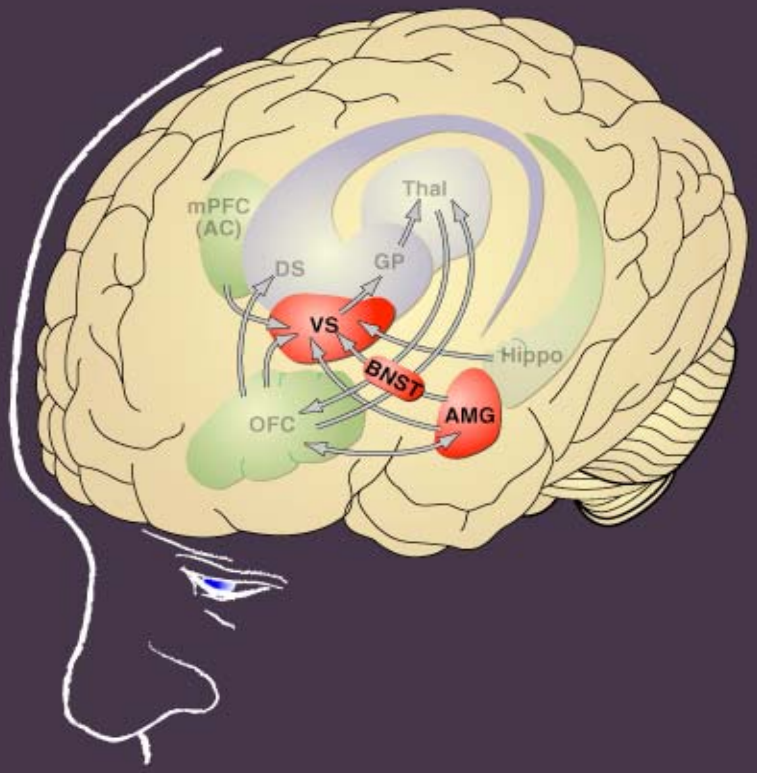


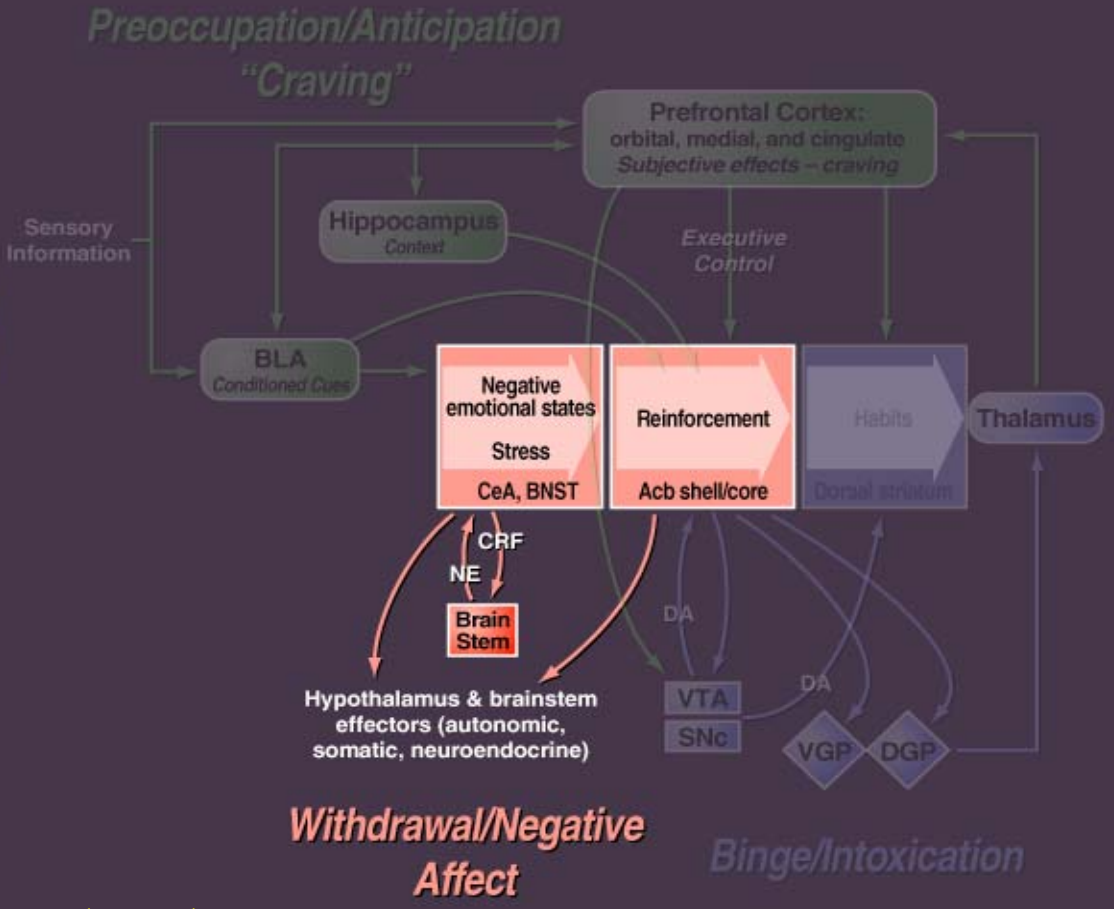
Existing medications
disulfiram
naltrexone
methadone
buprenorphine

Future targets
- partial agonists
- drug vaccines


SUAYASAMIN

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

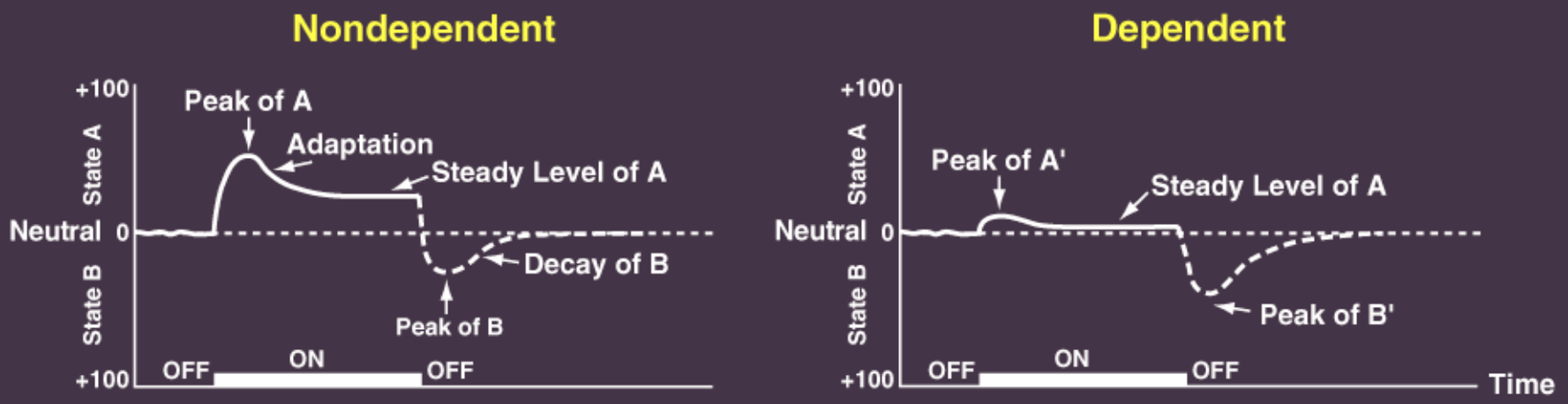




Existing medications
- methadone
- buprenorphine
- varenicline

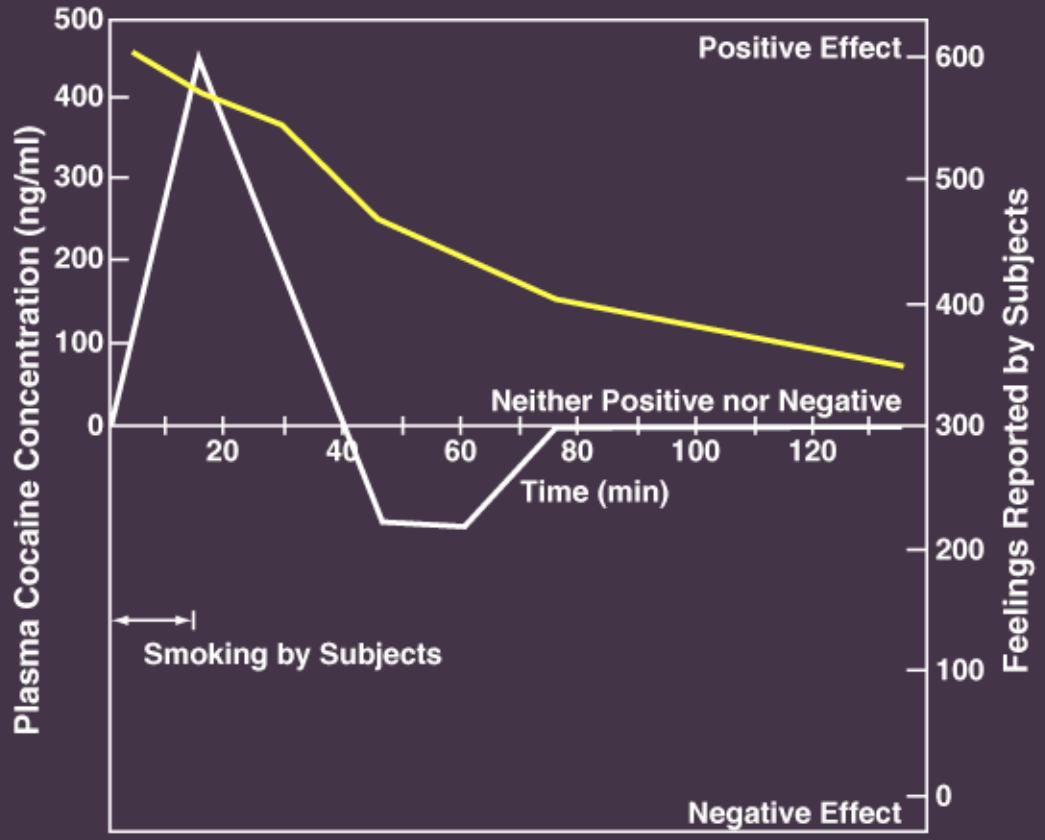
Future targets
- GABA modulators
- CRF_1 receptors
- κ opioid antagonists

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



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

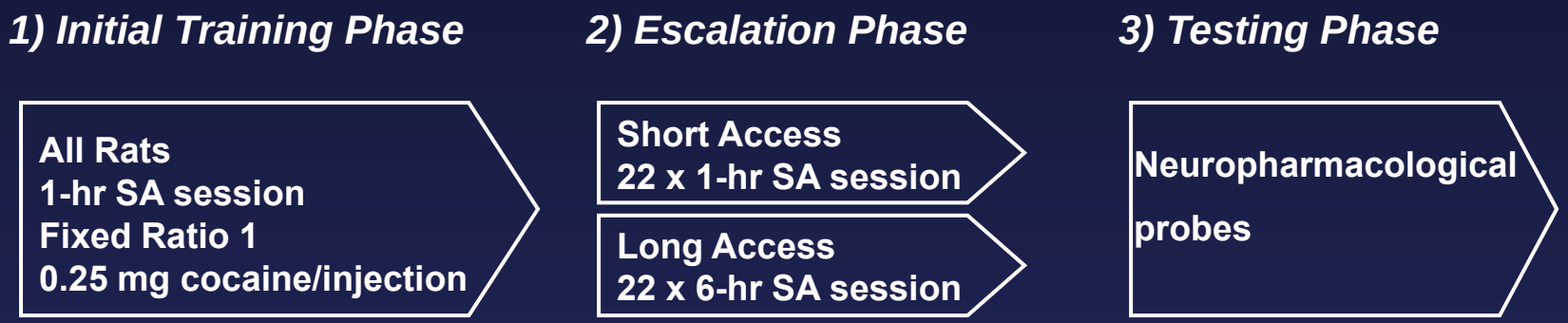
Mood Changes Associated with Plasma Levels of Cocaine During Coca Paste Smoking



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.

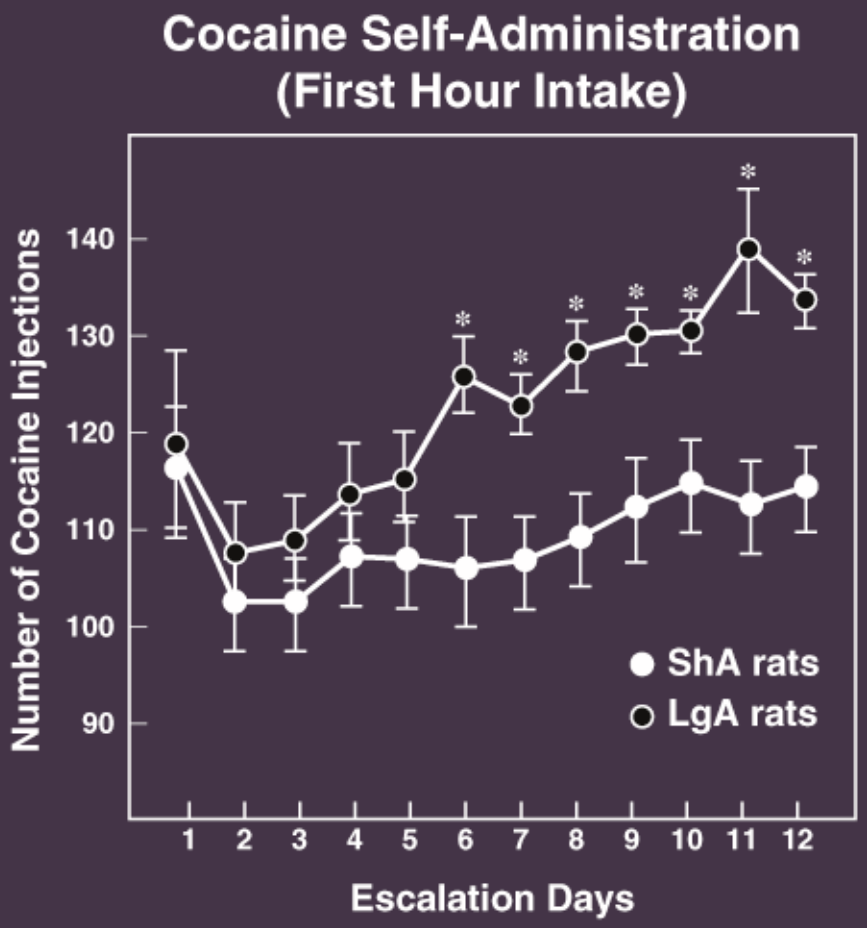
From: Van Dyke C and Byck R, Cocaine, Scientific American, 1982, 246:123-141.

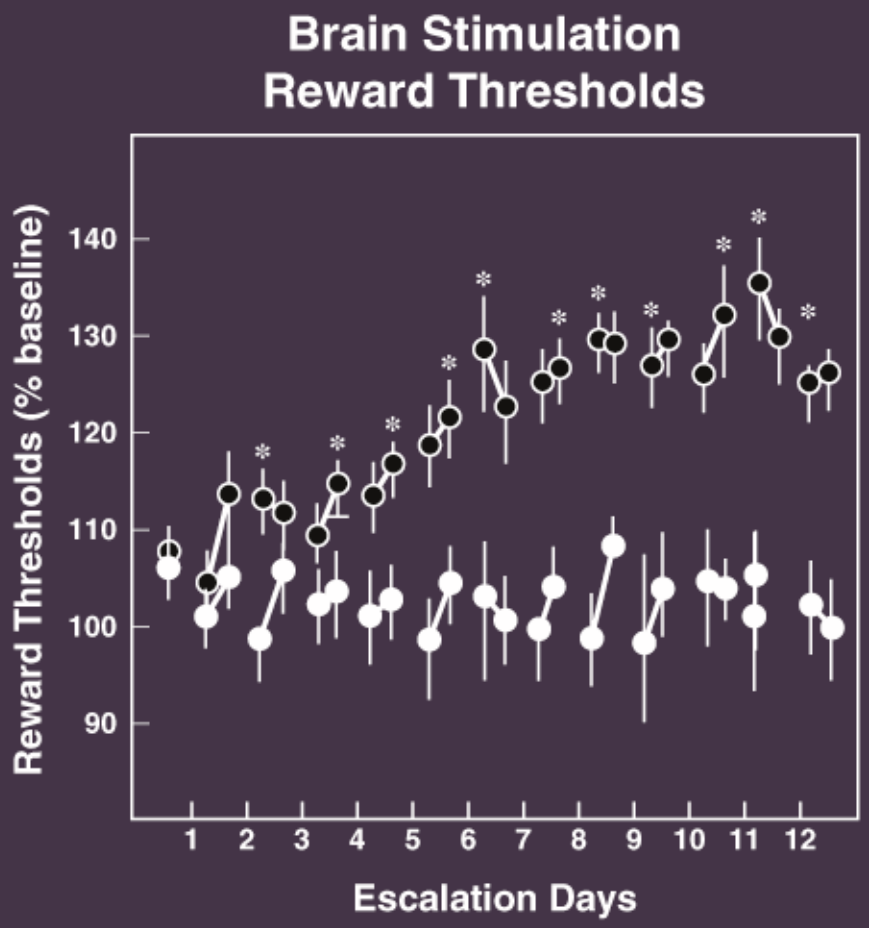
Protocol for Drug Escalation



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.

Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

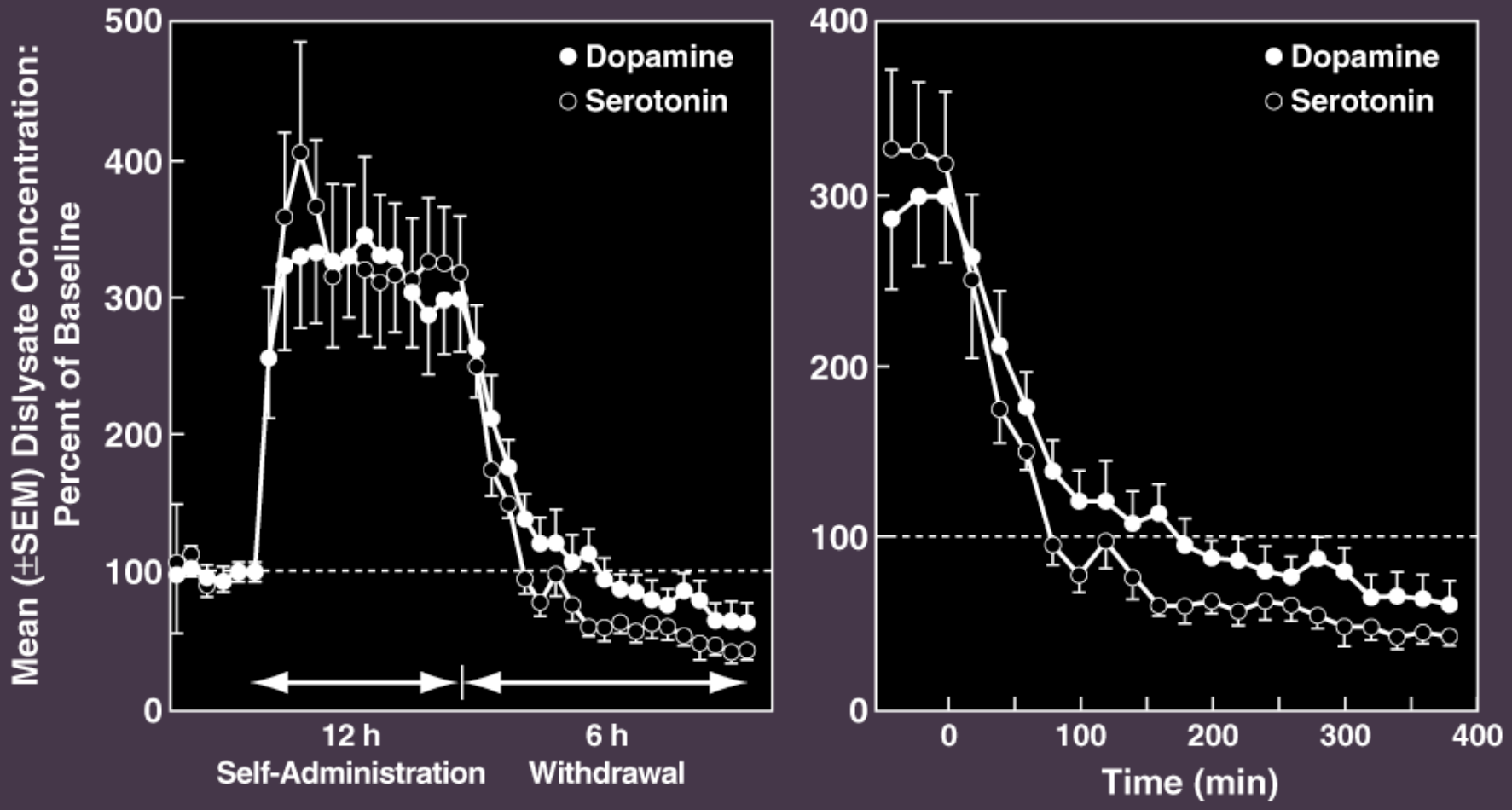
Positive Hedonic Effects

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

Negative Hedonic Effects of Withdrawal

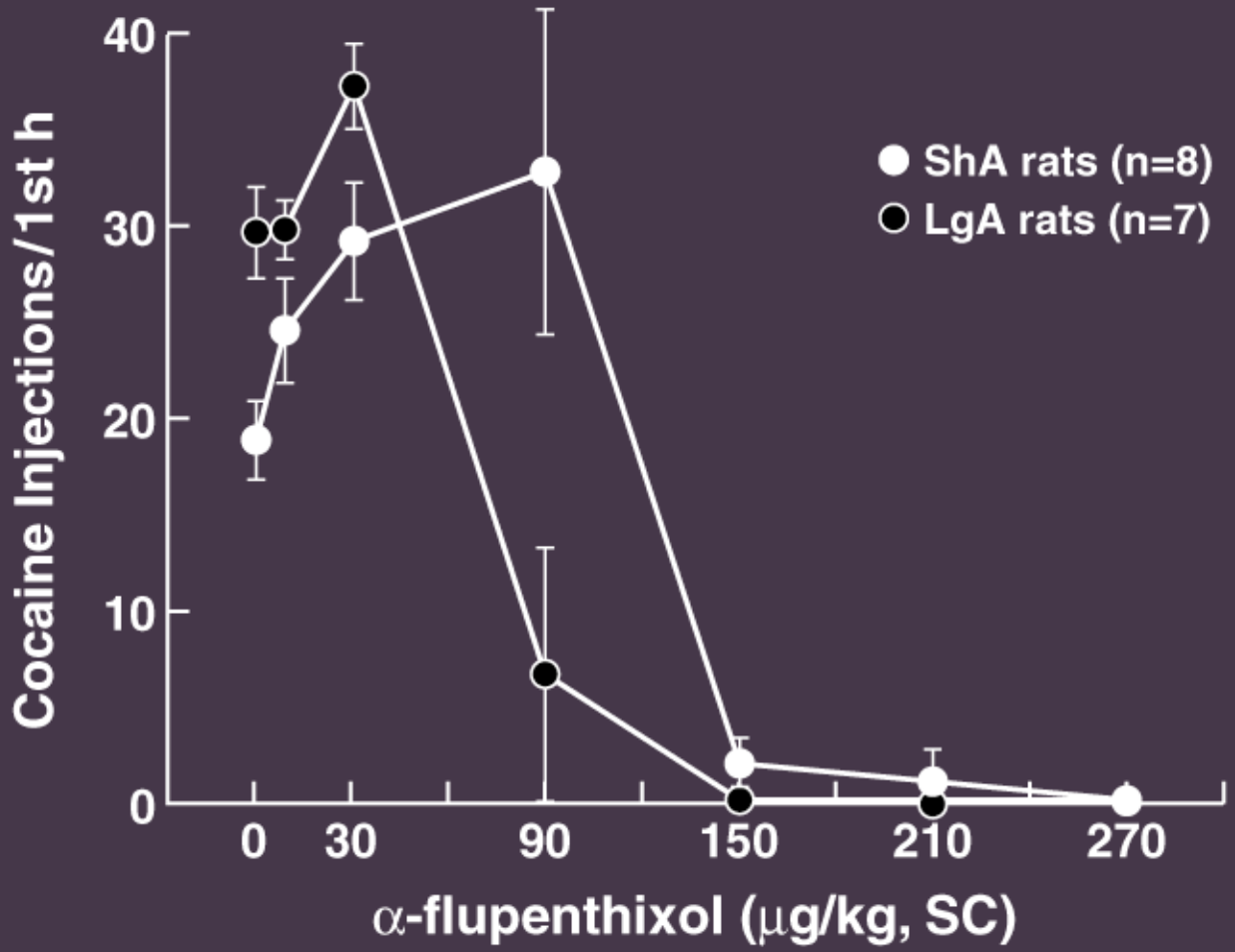
- ↓ Dopamine … “dysphoria”
- ↓ Opioid peptides ... pain
- ↓ Serotonin … “dysphoria”
- ↓ GABA … anxiety, panic attacks

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.

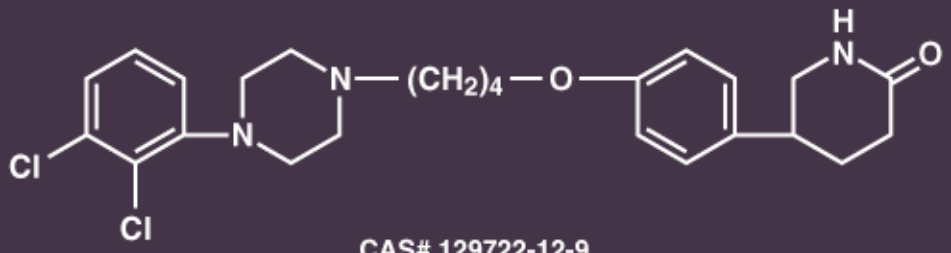
Effect of α-flupenthixol on Cocaine Self-Administration in Escalated and Non-Escalated Animals



From: Ahmed SH and Koob GF, Psychopharmacology, 2004, 172:450-454.

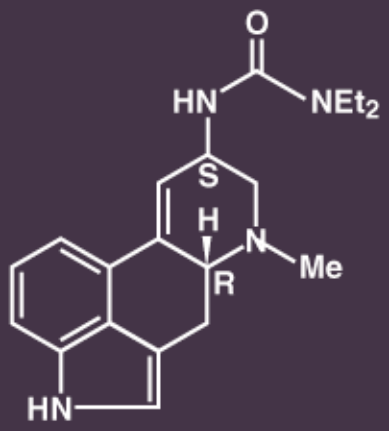
Dopamine Partial Agonists

Aripiprazole



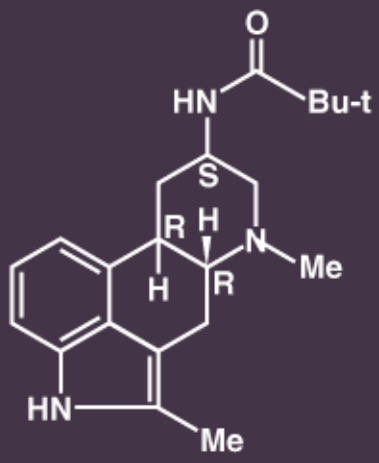
CAS# 129722-12-9

Lisuride



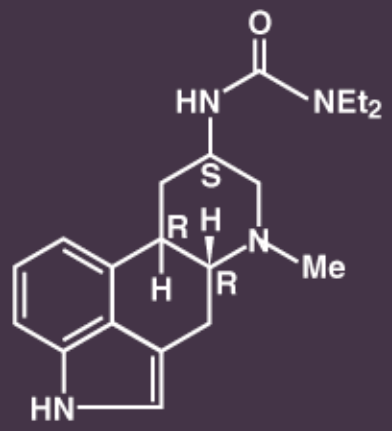
CAS# 18016-80-3

SDZ 208-911



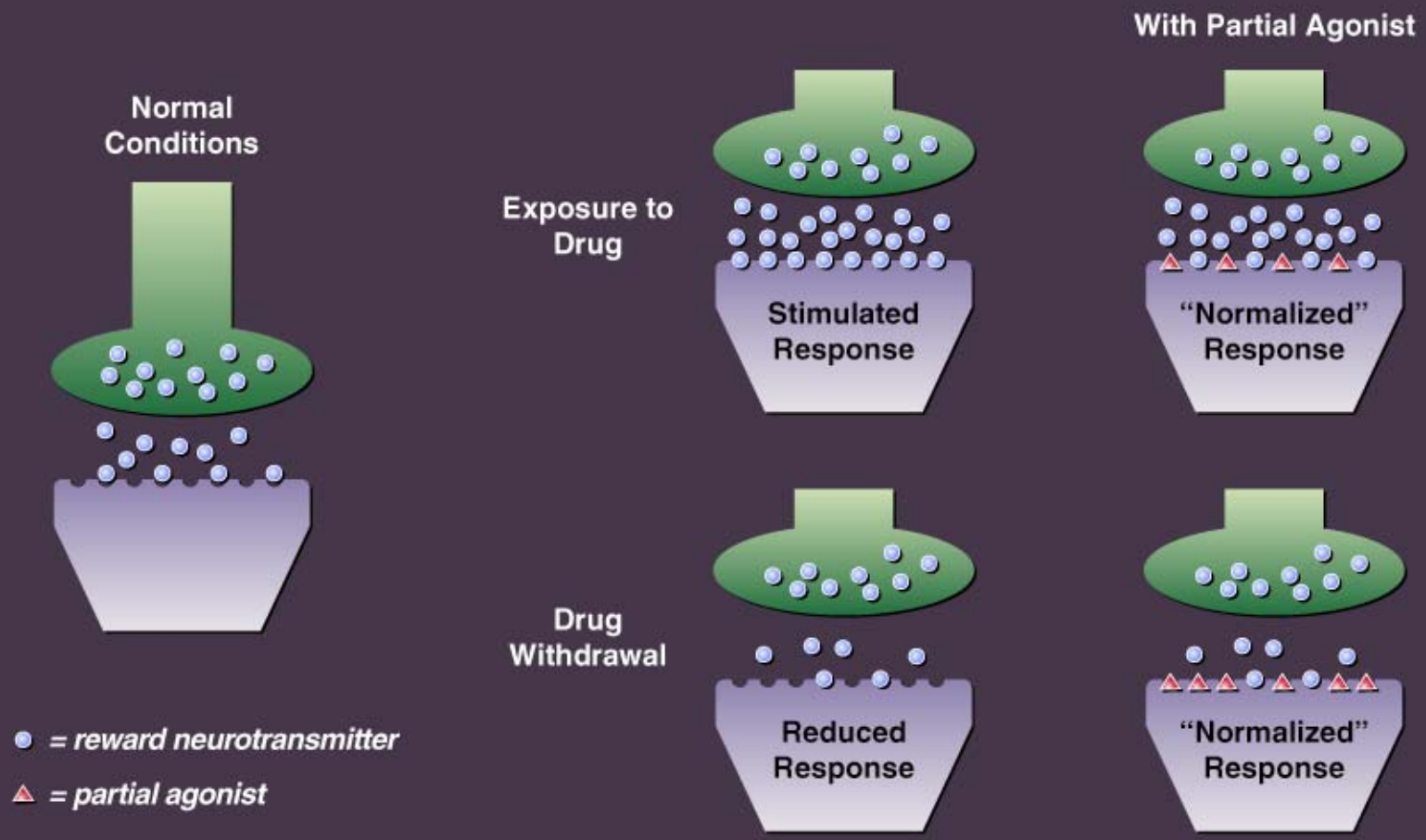
CAS# 120478-64-0

Terguride

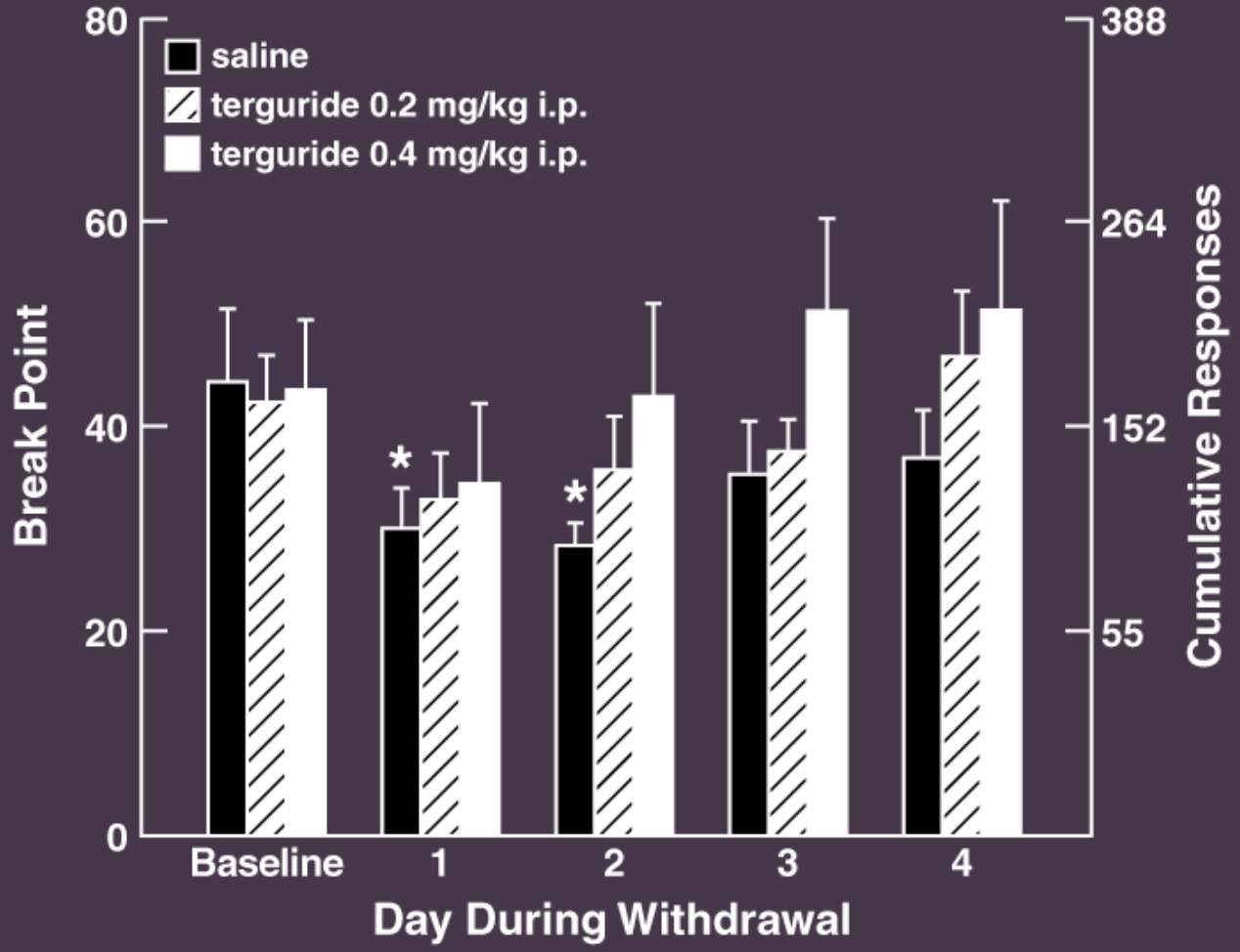


CAS# 37686-84-3

Partial Agonists: Hypothesized Mechanism of Action

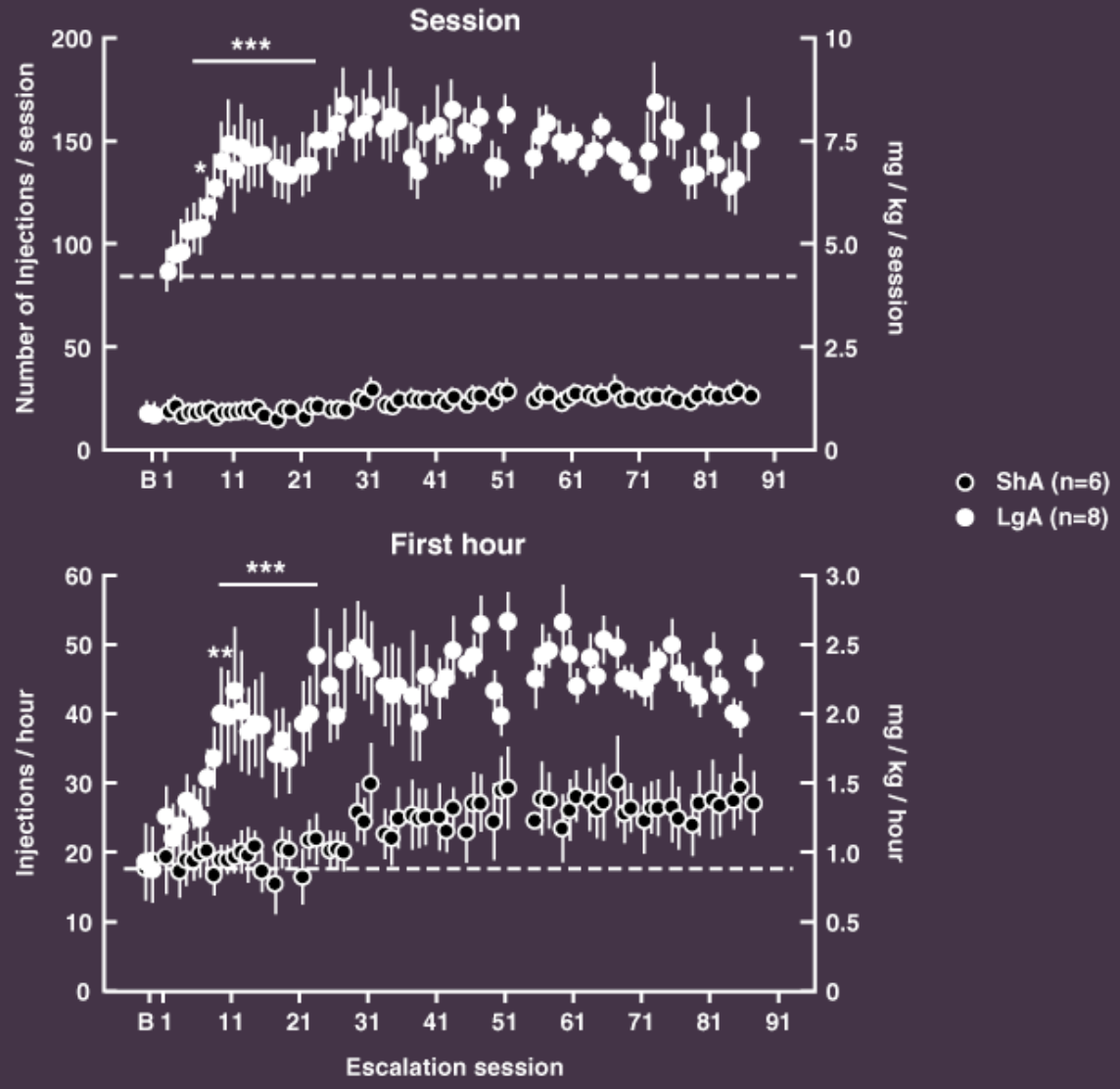


Dopamine Partial Agonist Terguride in Reverses Motivational Withdrawal following Chronic Amphetamine



From: Orsini C, Koob GF and Pulvirenti L, Neuropsychopharmacology, 2001, 25:789-792.

Escalation of Methamphetamine Self-administration in Rats



From: Wee S, Wang Z, Woolverton WL, Pulvirenti L and Koob GF, Neuropsychopharmacology, in press.