Objectives

1. Definitions of Drug Addiction

2. Understand the Dopamine Hypothesis of addiction

3. Understand definitions of drug tolerance, sensitization, and dependence

4. Mechanism of action of opioids & psychostimlants

Drug Addiction

•Modern views have focused on 3 types of drug use: 1) occasional, controlled or social use; 2) drug abuse or harmful use; 3) drug addiction

•Official definition by the American Association of Psychiatry: Addiction is a **chronic relapsing disease** that is characterized by:

1) Compulsion to seek and take the drug
2) Loss of control in limiting intake
3) Emergence of a negative emotional state when access to the drug is prevented (defined as dependence).

•Dependence versus addiction—Is there a difference?

Drug Addiction

•200 million people, or 5% of the global population, consumed illicit drugs at least once in the last 12 months (2005 UN world drug report).

•22.5 million Americans aged 12 or older experienced substance dependence in 2004 (The US Department of Health). About 21.1 million people needed but did not get treatment for their addiction in the US alone.

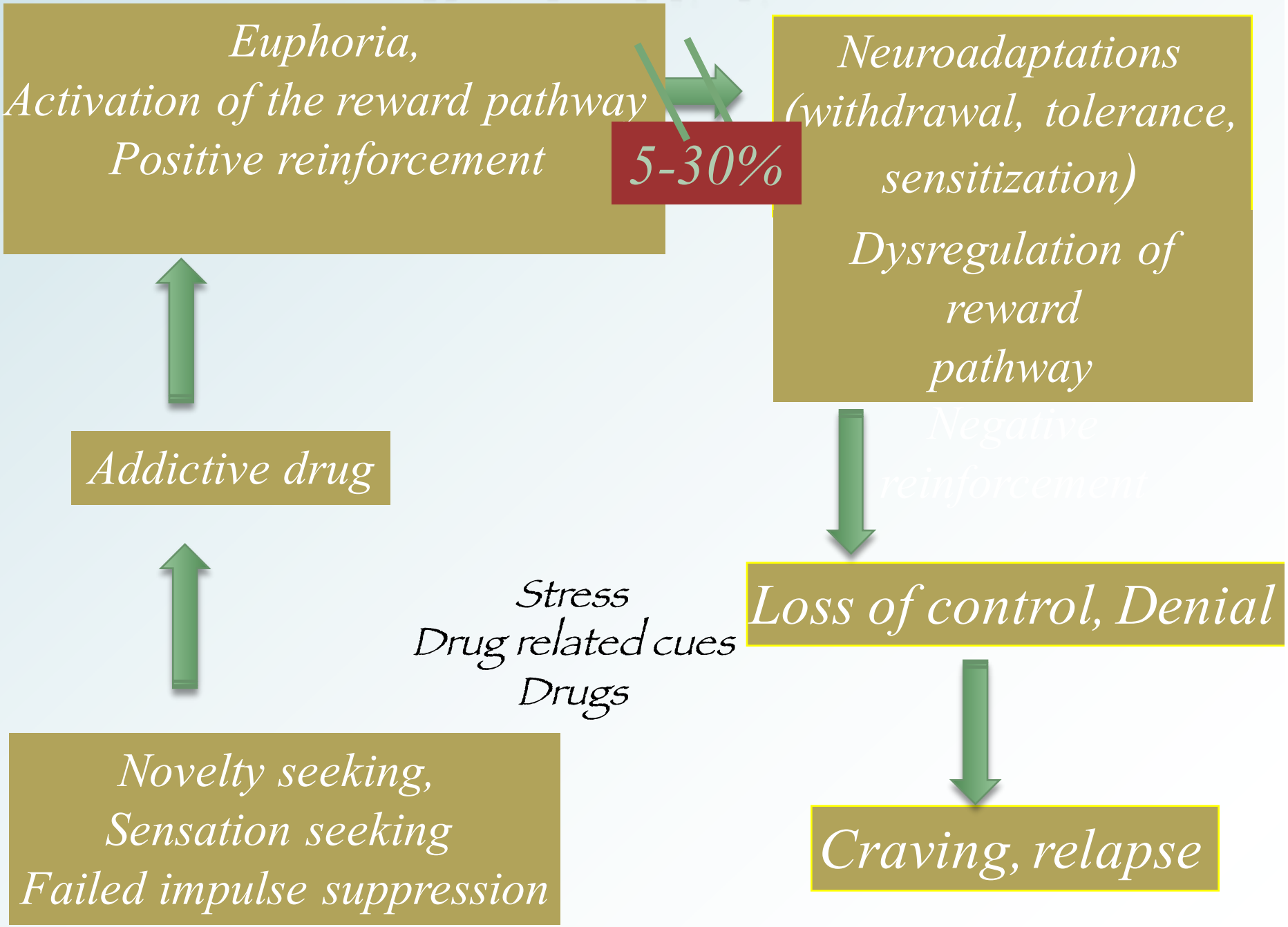
• In the US: Illicit drugs cost society $161 Billions per year (Office of National Drug Control Policy, 2001).

Drug Addiction

Estimated prevalence among 15-54 years old of drugs of abuse

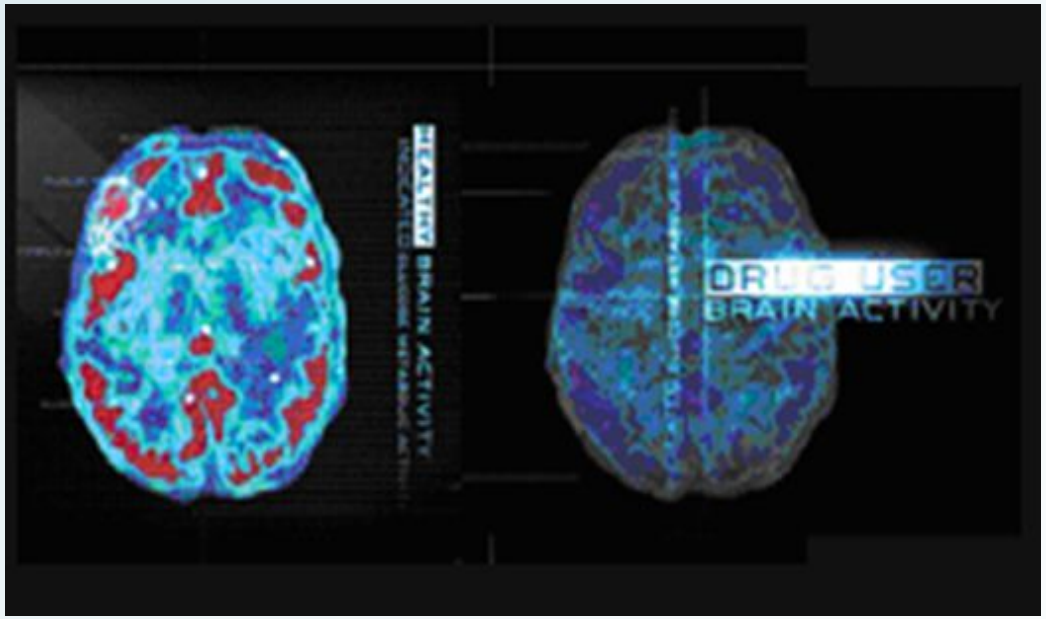
	Ever used	Dependence among
•Tobacco	75.6%	31.9%
•Alcohol	91.5%	15.4%
•Cocaine	16.2%	16.7%
•Heroin	1.5%	23.1%
•Cannabis	46.3%	14.7%

Drug addiction



What is Addiction?

Addiction is a Brain Disease

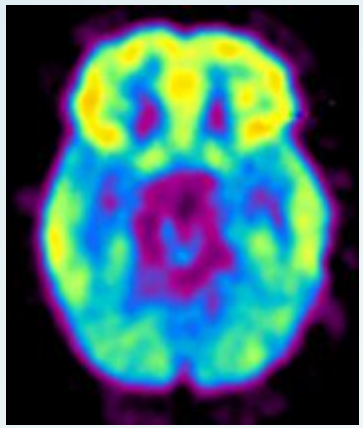


- Characterized by:
  - Compulsive Behavior
  - Continued abuse of drugs despite negative consequences
  - Persistent changes in the brain's structure and function

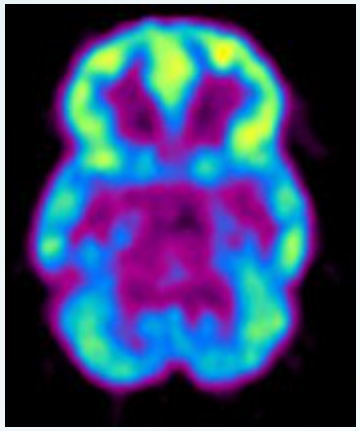
Addiction is Like Other Diseases…

- It is preventable
- It changes biology

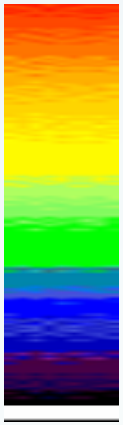
Decreased Brain Metabolism in Drug Abuser



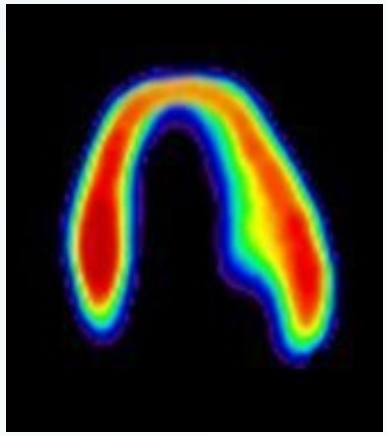
Healthy Brain



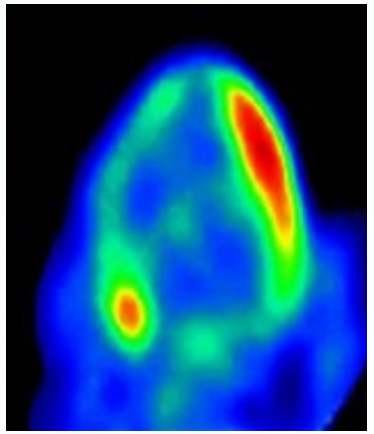
Diseased Brain/ Cocaine Abuser



Decreased Heart Metabolism in Heart Disease Patient



Healthy Heart



The Dopamine Hypothesis of Drug Addiction

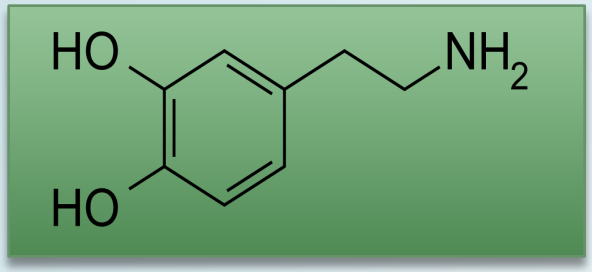
This hypothesis states that drugs of abuse act through mechanisms involving the brain neurotransmitter dopamine and the neural systems that regulate it.

Addictive drugs may act on dopamine systems either:

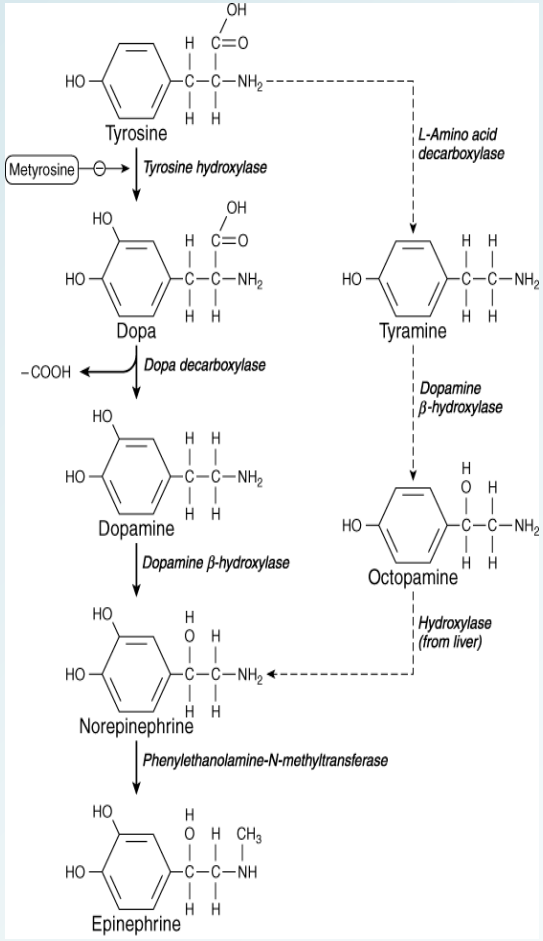
Directly -Psychostimulants (Amphetamine &Cocaine)

OR

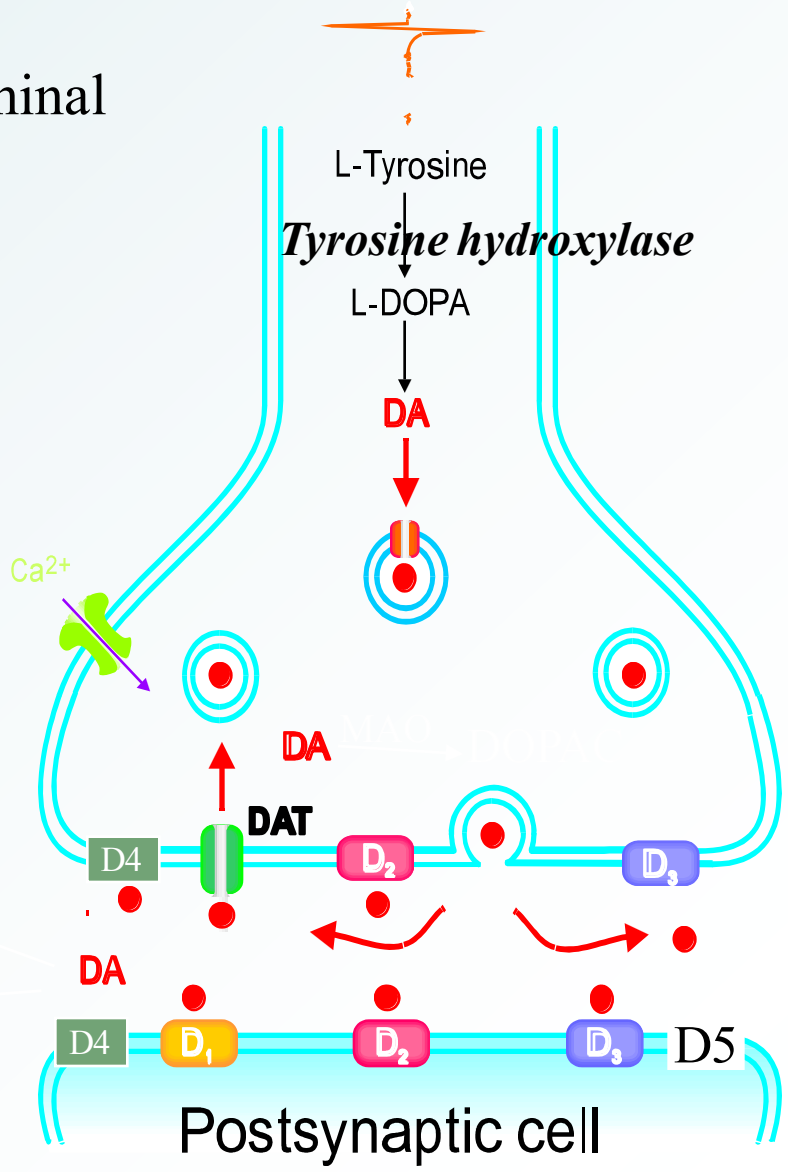
Indirectly- Nicotine, Morphine / Heroin, Alcohol, & Barbiturates



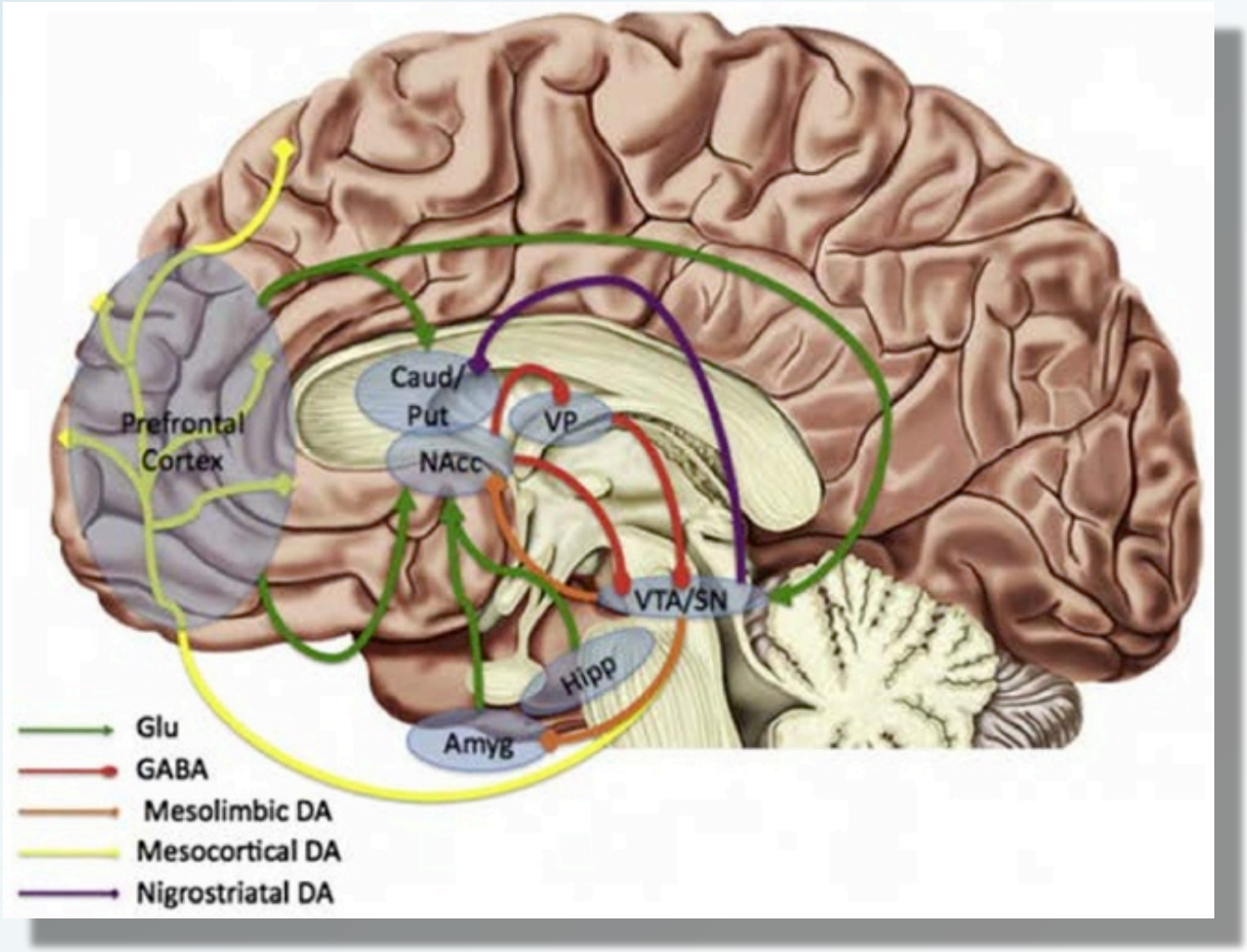
DOPAMINE



DA Nerve Terminal



MESOCORTICOLIMBIC DOPAMINERGIC CIRCUITRY



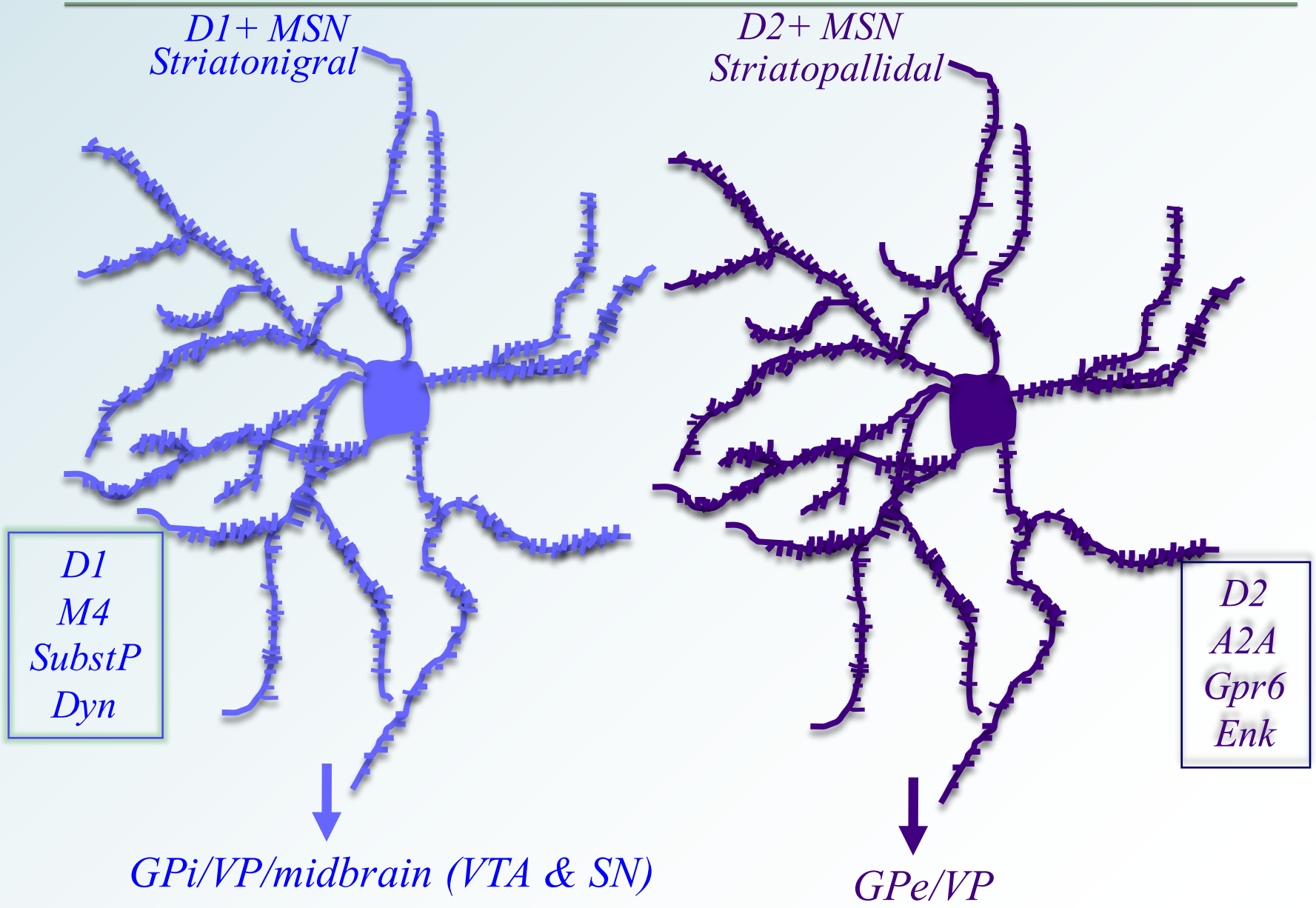
The ventral tegmental area (VTA)-accumbens dopamine system is strongly implicated in mediating drug reward

Dopamine Receptors

	D_1-like receptor family		D_2-like receptor family		
	D_1	D_5	D_{2S}/ D_{2L}	D_3	D_4
Amino Acids	446 (h)	477 (h)	415/443(h)	400 (h)	387 (h)
G-protein	*Gs*	*Gs*	*Gi/o*	*Gi/o*	*Gi/o*
Second messengers	AC	AC	AC	AC	AC
DA Affinity	µM	µM	µM	nM	µM
Agonists	SKF-38393	SKF-38393	(+)PHNO	7-OH-DPAT PD-128,907	PD-168,077
Antagonists	SCH-23390	SCH-23390	raclopride	(+)S14297 GR-103,691	L-745870

D1 and D2 Neurons

- *Projection neurons in the Nucleus Accumbens (NAc) and dorsal striatum*
- *~95% of the neurons in NAc and dStr*

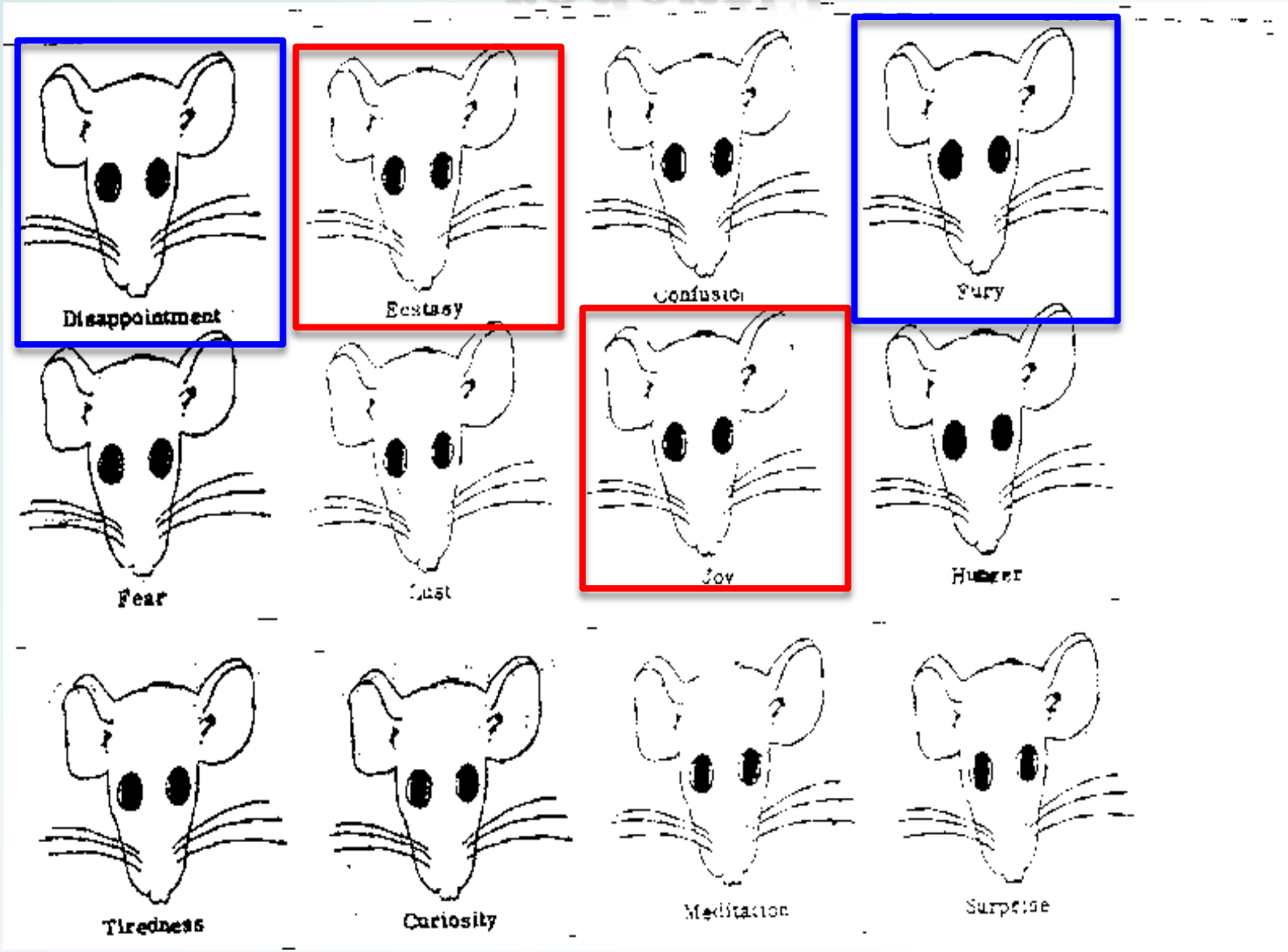


MESOCORTICOLIMBIC DOPAMINE THE NEUROTRANSMITTER OF "REWARD"?

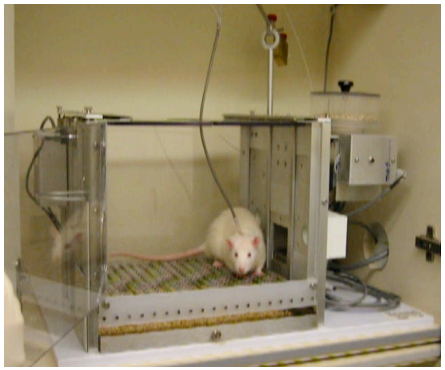
"Reward"	*Dopamine Release (NAC)*
FOOD, SEX	**50-100%**
ETHANOL	**125-200%**
CANNABIS [THC]	**125-175%**
NICOTINE	**225%**
MORPHINE/HEROIN	**150-300%**
COCAINE	**400%**
AMPHETAMINE	**1000%**

R. Wise et al., 2000

What is Addiction in a rodent!?



The Dopamine Hypothesis of Drug Addiction
Evidences for the implication of DA in drug addiction



•Rats will self-administer amphetamine or cocaine directly into the Nucleus Accumbens (NAc). More is self-administered if DA receptors are partially blocked.

• If dopamine is depleted by 6-OH-DA lesions or the NAc is destroyed then rats no longer self-administer amphetamine or cocaine.

•Withdrawal from several drugs (psychostimulants, alcohol, nicotine and opiates) is associated with a reduction in DA levels in the NAc.

Why Do People Take Drugs in The First Place?

To Feel Good

To have novel:

feelings

sensations

experiences

AND

to share them

To Feel Better

To lessen:

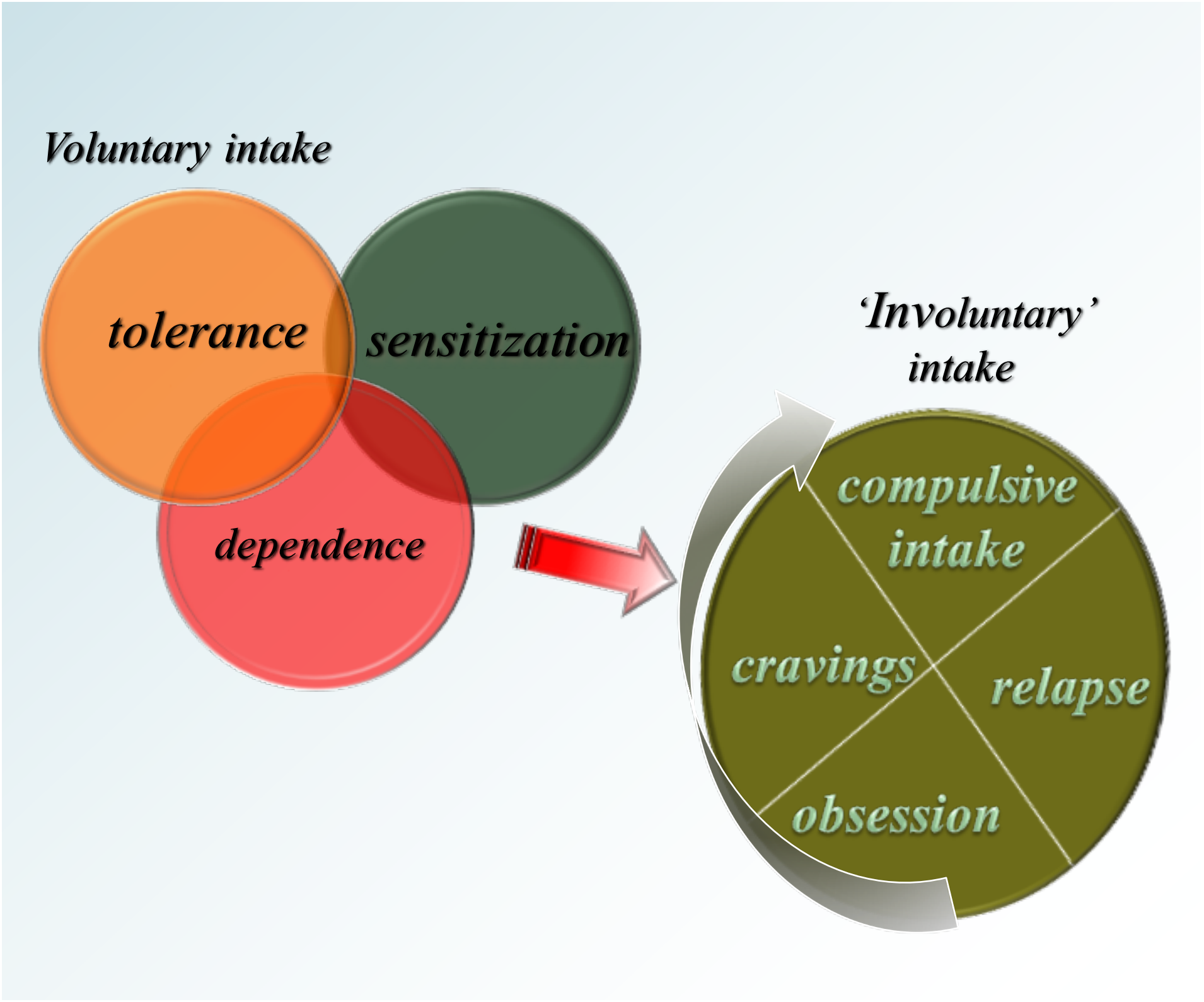
anxiety

worries

fears

depression

hopelessness


Voluntary intake
tolerance
sensitization
dependence
'Involuntary' intake
compulsive intake
relapse
obsession
cravings

Pharmacological Process of Addiction

Tolerance- *The diminishing effect of a drug after repeated administration at the same dose or to the need for an increase in dose to produce the same effect*

-Tolerance may develop to some but not all effects of a drug

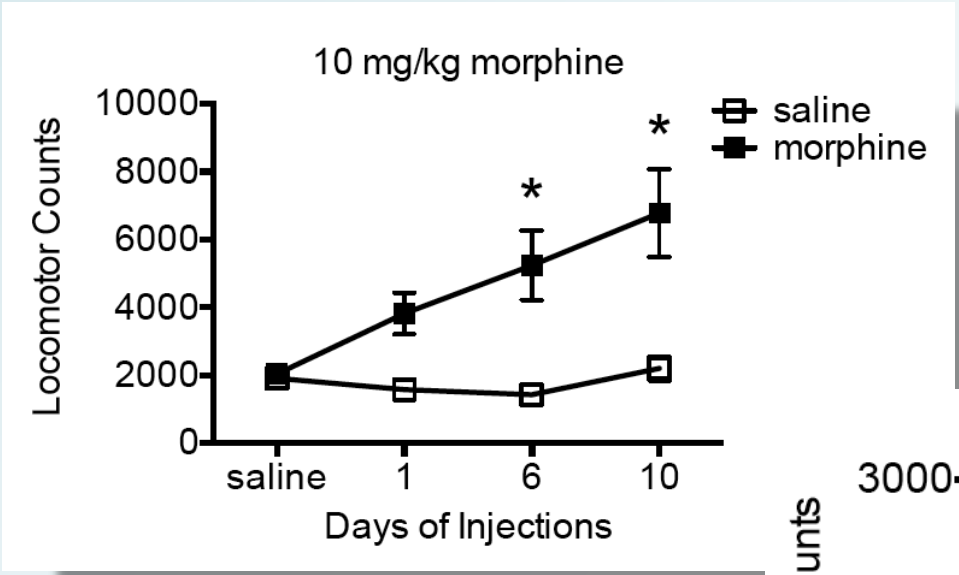
-Tolerance frequently develops to the analgesic, euphoric and respiratory depressant effects of opioids.

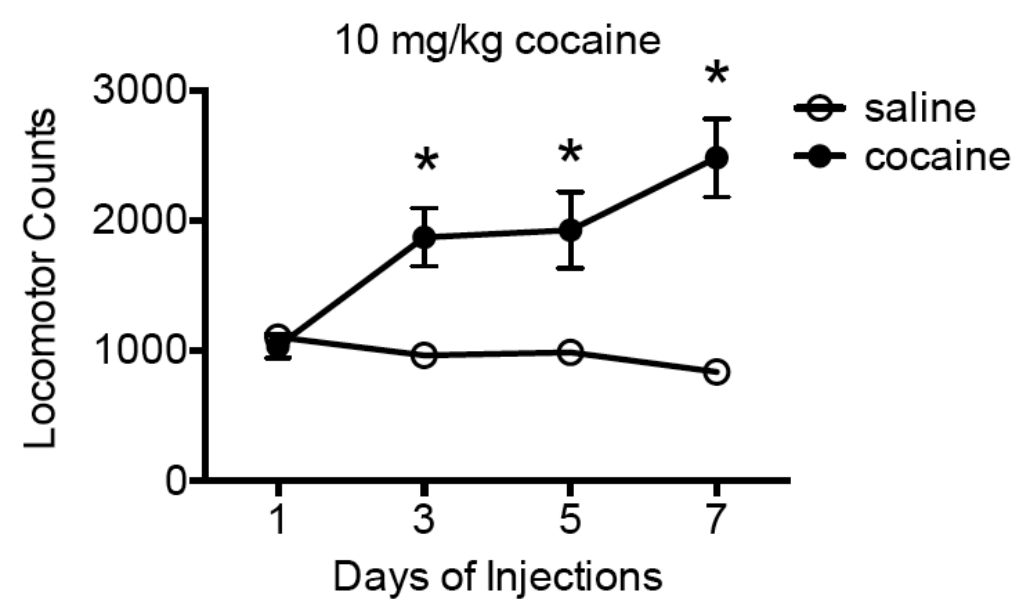
- In general there is NO tolerance to the pupillary constriction effects of opioids

Two "types" of tolerance

1) ***Pharmacokinetic****-increased drug metabolism*
2) ***Pharmacodynamic****-adaptations of the neuronal elements that respond to drugs initially (this is a key contributor to the neurobiology of addiction)*

Sensitization-also referred to as "reverse tolerance". This occurs when repeated administration of the same drug (at the same dose) elicits an escalating effect.





Dependence- is defined as the adaptive state develops in response to repeated drug administration. This state is generally unmasked during withdrawal-which occurs when drug taking is stopped.

Dependence from long-term drug (Opioids) use may have both somatic components which are manifested by:

physical symptoms

- Increased pain
- Diarrhea
- Hyperventilation

Emotional component

- Increased irritability
- Insomnia
- Dysphoria
- Anhedonia

Dependence cont…….

Physical dependence is not a useful diagnosis of addiction because they do not occur with may commonly abused drugs (i.e. cocaine and amphetamine) Moreover, physical dependence can occur with drugs not abused (i.e. propanolol, clonidine)

BAYER

PHARMACEUTICAL PRODUCTS.

We are now sending to Physicians throughout the United States literature and samples of

ASPIRIN

The substitute for the Salicylates, agreeable of taste, free from unpleasant after-effects.

HEROIN

The Sedative for Coughs,

HEROIN HYDROCHLORIDE

Its water-soluble salt.

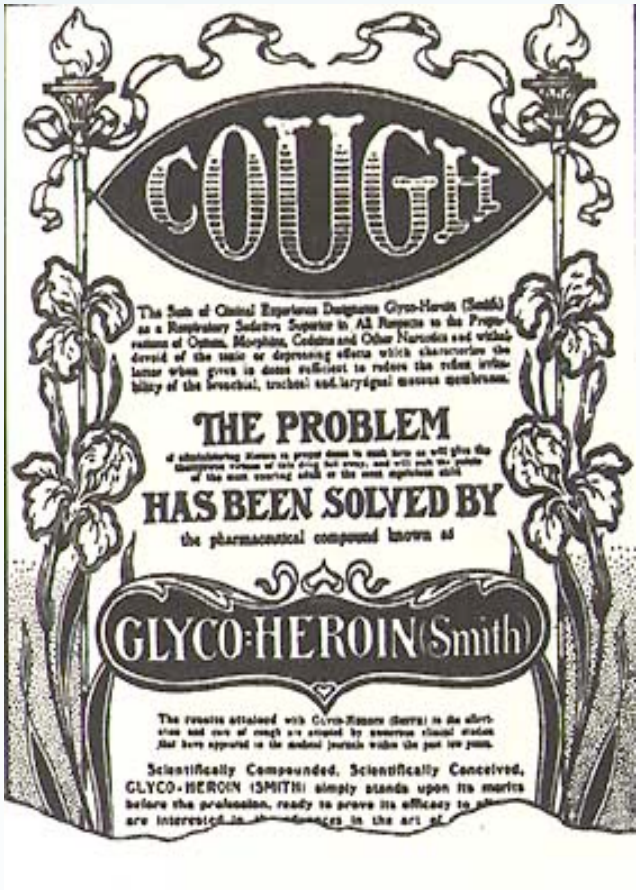
You will have call for them. Order a supply from your Jobber.

Write for literature to

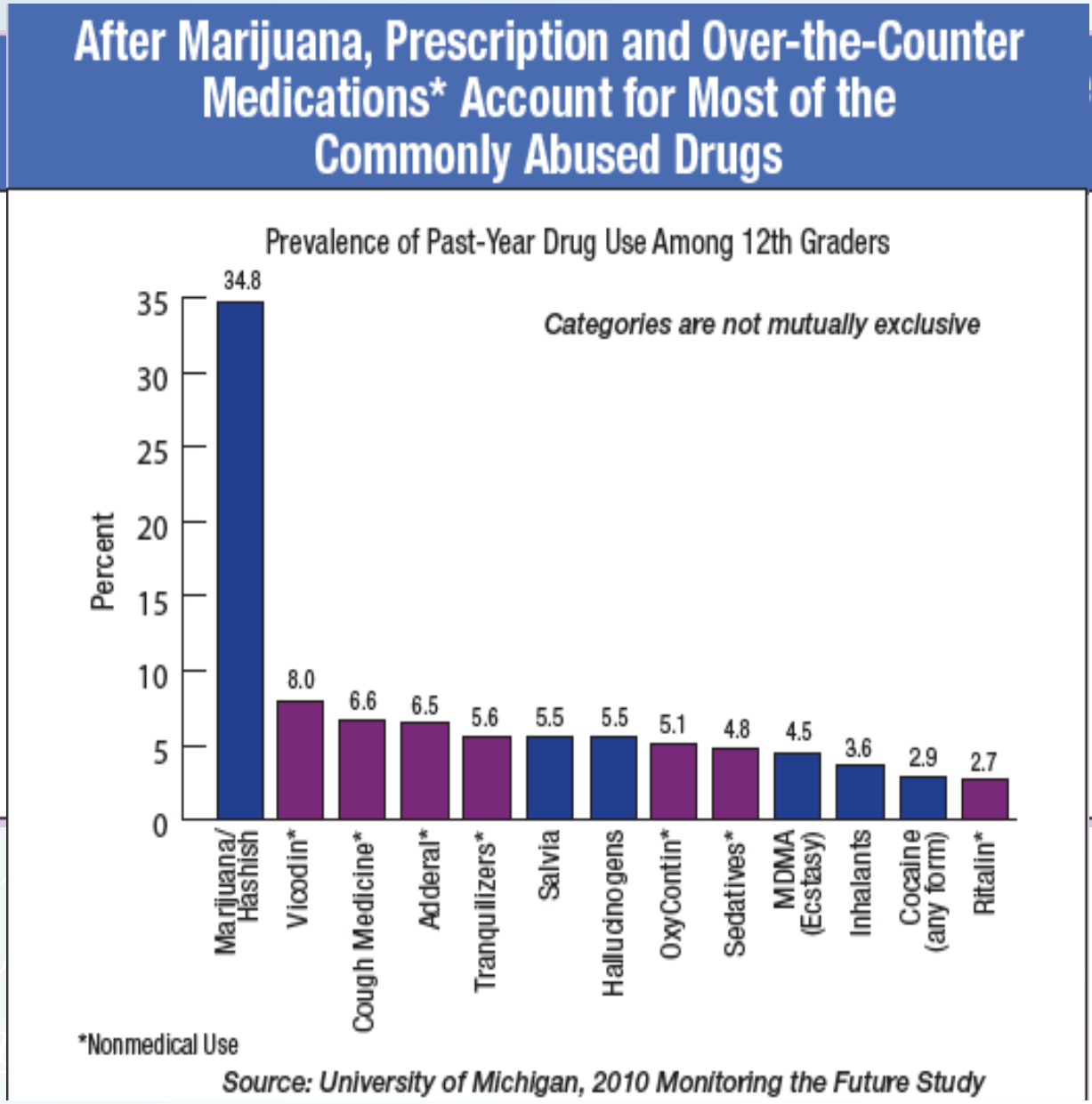
FARBENFABRIKEN OF ELBERFELD CO.

40 Stone Street, New York,

SELLING AGENTS



How Big is the problem?



U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA News Release

FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose

Naloxone in nasal spray form provides important new alternative for family members, first responders

For Immediate Release November 18, 2015

Release

Today the U.S. Food and Drug Administration approved Narcan nasal spray, the first FDA-approved nasal spray version of naloxone hydrochloride, a life-saving medication that can stop or reverse the effects of an opioid overdose. Opioids are a class of drugs that include prescription medications such as oxycodone, hydrocodone, and morphine, as well as the illegal drug heroin.

Drug overdose deaths, driven largely by prescription drug overdoses, are now the leading cause of injury death in the United States – surpassing **motor vehicle crashes (http://www-nrd.nhtsa.dot.gov/PUBS/812196.pdf)**. In 2013, the Centers for Disease

10 heroin overdoses in 24 hours point to epidemic in Buffalo

Cause is believed to be 'hot batches' of the drugs

Deadly batch of heroin has killed 23 in Erie County since Jan. 29

Buffalo records 10 heroin deaths in first 10 days of March

Medical News & Perspectives

SAMHSA: Pain Medication Abuse a Common Path to Heroin

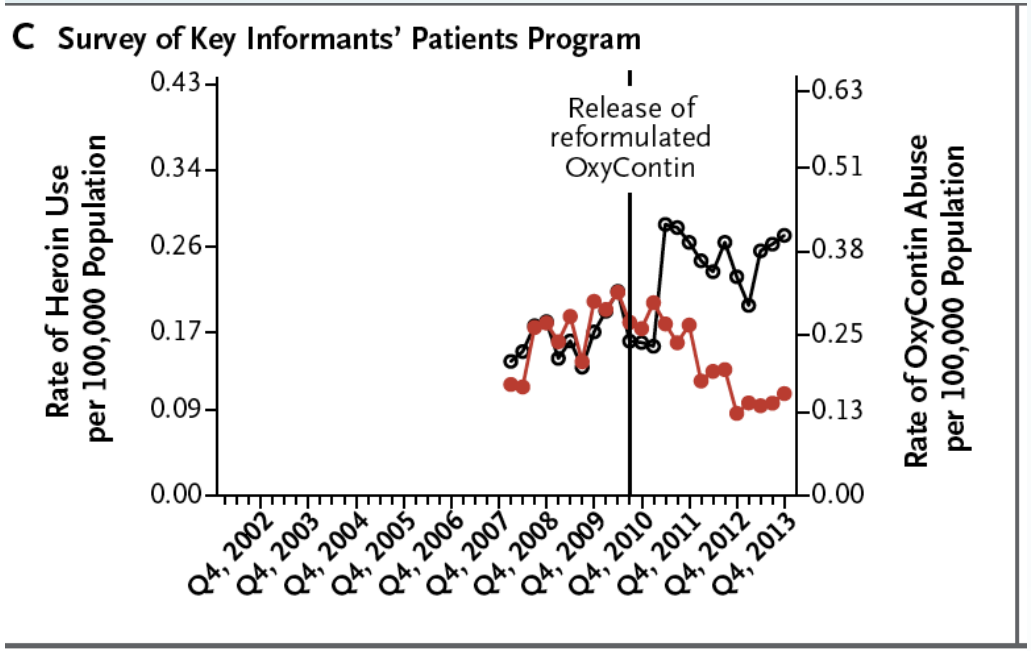
Experts Say This Pattern Likely Driving Heroin Resurgence

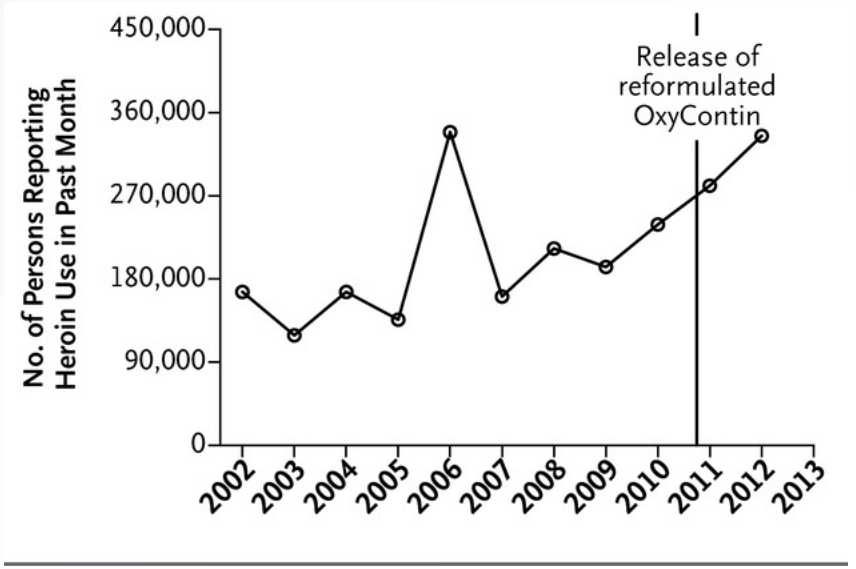
Bridget M. Kuehn, MSJ

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Trends in Opioid Analgesic Abuse and Mortality in the United States





Mechanisms of Action

Table 1 | **Acute actions of some drugs of abuse**

Drug	Action	Receptor signalling mechanism
Opiates	Agonist at μ-, δ- and κ-opioid receptors*	G_i
Cocaine	Indirect agonist at dopamine receptors by inhibiting dopamine transporters‡	G_i and G_s§
Amphetamine	Indirect agonist at dopamine receptors by stimulating dopamine release‡	G_i and G_s§
Ethanol	Facilitates $GABA_A$ receptor function and inhibits NMDA receptor function‖	Ligand-gated channels
Nicotine	Agonist at nicotinic acetylcholine receptors	Ligand-gated channels
Cannabinoids	Agonist at CB_1 and CB_2 cannabinoid receptors¶	G_i
Phencyclidine (PCP)	Antagonist at NMDA glutamate receptors	Ligand-gated channels
Hallucinogens	Partial agonist at 5-HT_{2A} serotonin receptors	G_q
Inhalants	Unknown	

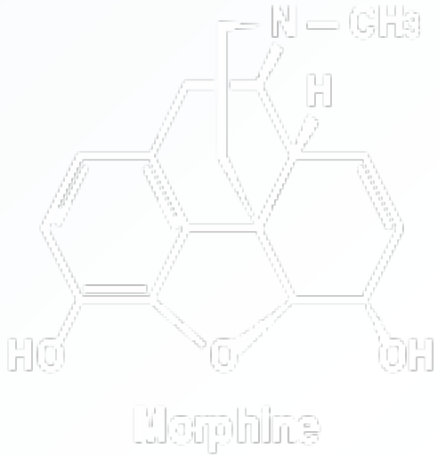
Opioids

Opiates

- alkaloids found in the opium poppy for example Opium Morphine and Codine

Heroin = diacetylmorphine

- addition of two acetyl groups to morphine
  - ~ 10x more potent than morphine
  - pharmacological effect usually thought to be identical to morphine



Types of Opioids

Endogenous Opioid that bind to specific opiate receptor

- Endorphins-*mu receptors*
- Enkephalins- *delta receptors*
- Dynorphins- *kappa*

Endorphins

***discrete**

***hypothalamic - endocrine related**

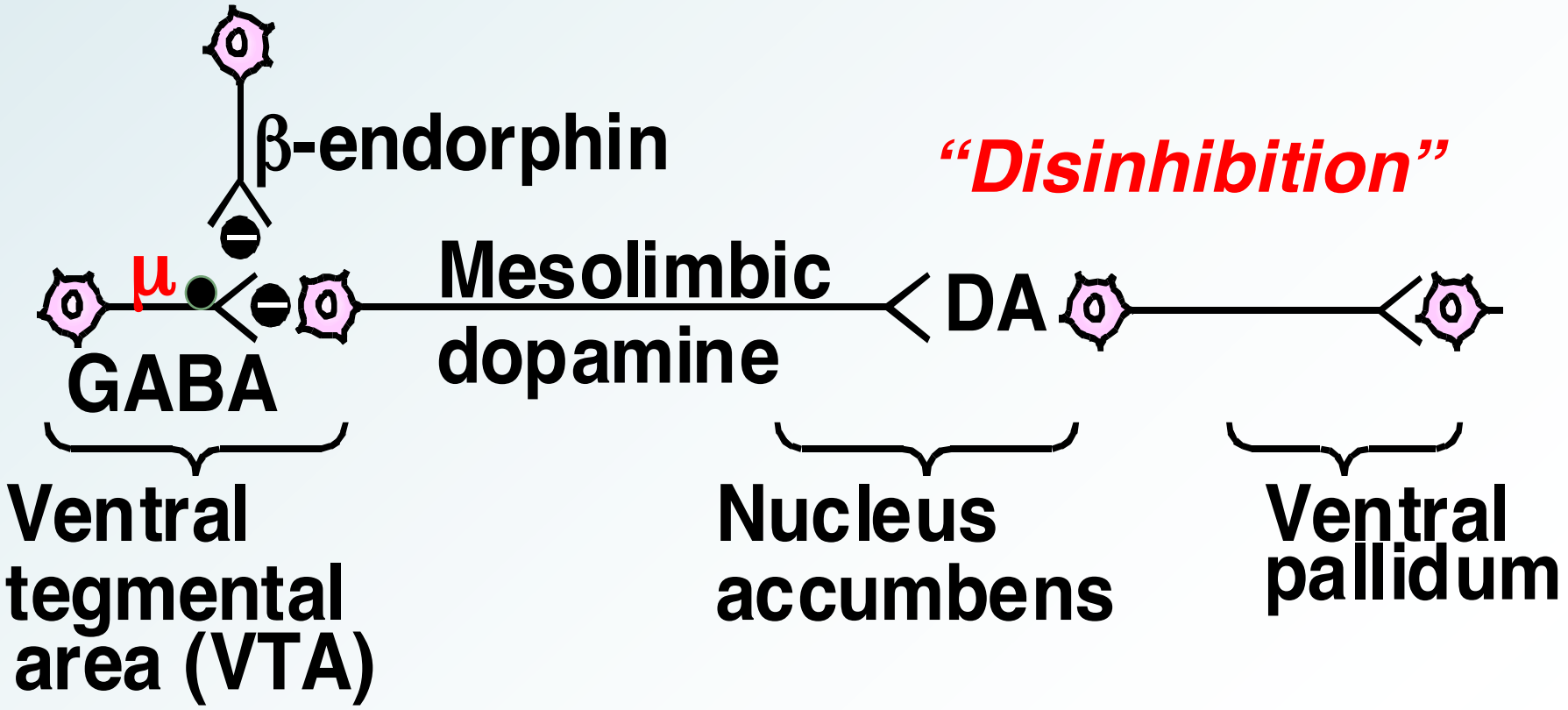
Enkephalins and Dynorphins

***wide distribution, local circuit and short axon projections**

OPIATES AND DOPAMINE

• The reinforcing actions of heroin and morphine appear to be mediated by the mu opiate receptor subtype located at the in the VTA.

VTA ➡ accumbens DA system



Opioids: mechanisms of action

Opioids: G protein linked-- affecting

*Activate **mu** (μ); **delta** (σ), or **kappa** (κ) receptors

* Opioid receptors are members of the 7 Trans-membrane, G protein- coupled receptor superfamily

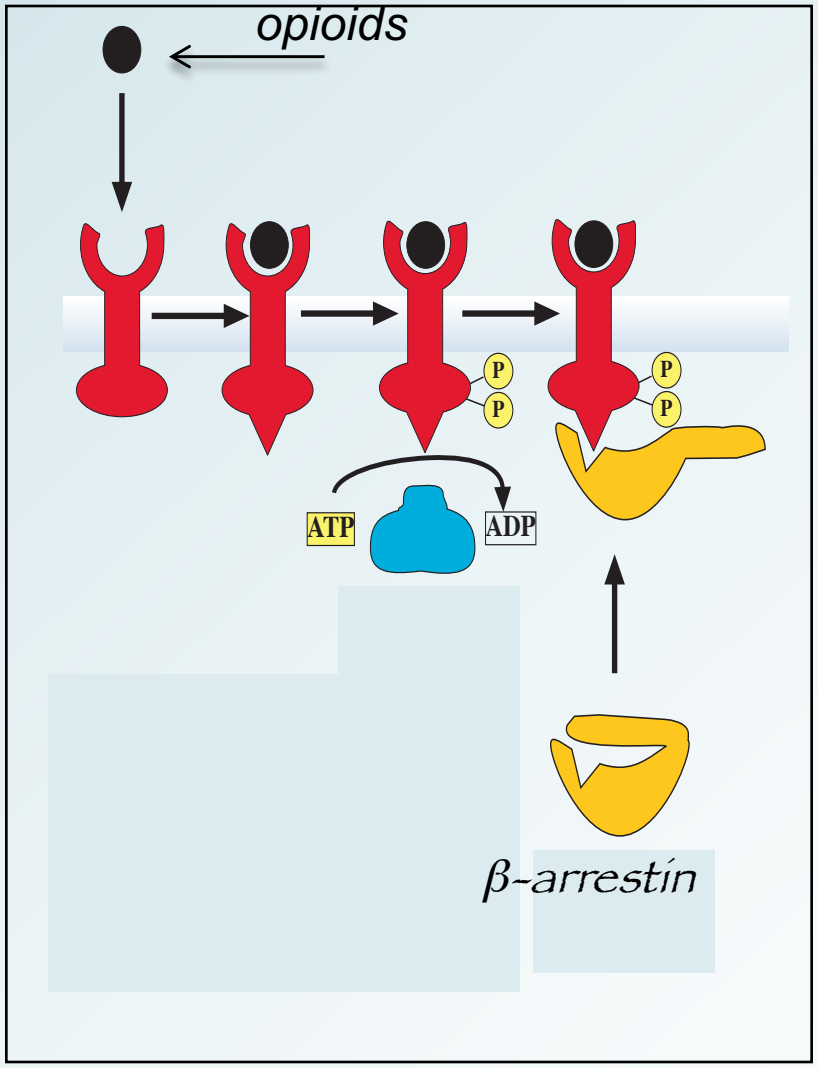
* Ion channel state
* Intracellular Ca2+ levels
* Protein phosphorylations states

Two well-defined opioid actions:

*Reduce neurotransmitter release; by closing a voltage-gated Ca2+ channel on presynaptic neuronal terminals

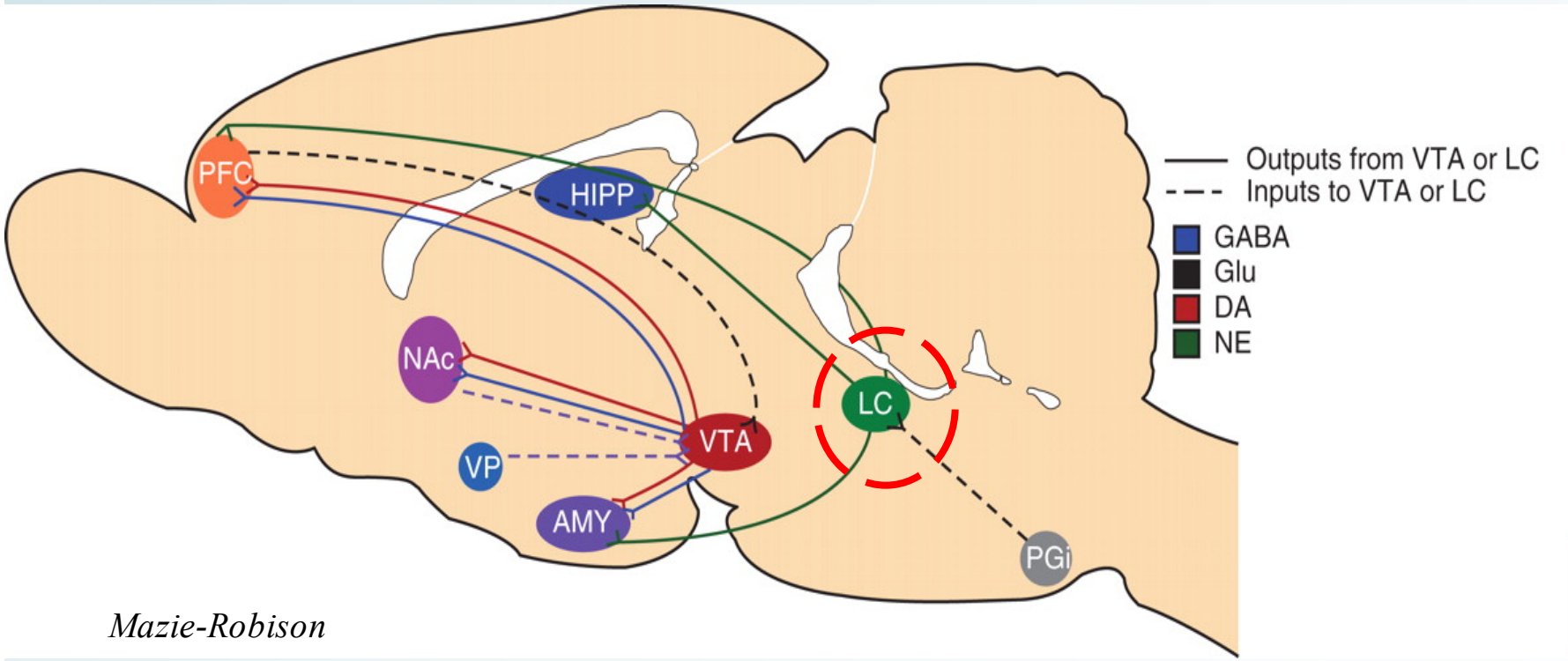
* Inhibit postsynaptic neurons by increasing K+ channel conductance

β-arrestin produces GPCR tolerance in a series of resolvable steps



- *GPCR-PO4 activates β-arrestin*
- *Newly exposed β-arr domain binds GPCR*
- *GPCR- β-arr prevents G-protein association*
- *GPCR- β-arr complex is internalized by a dynamin and clathrin dependent mechanism*

LOCUS COERULEUS (LC)



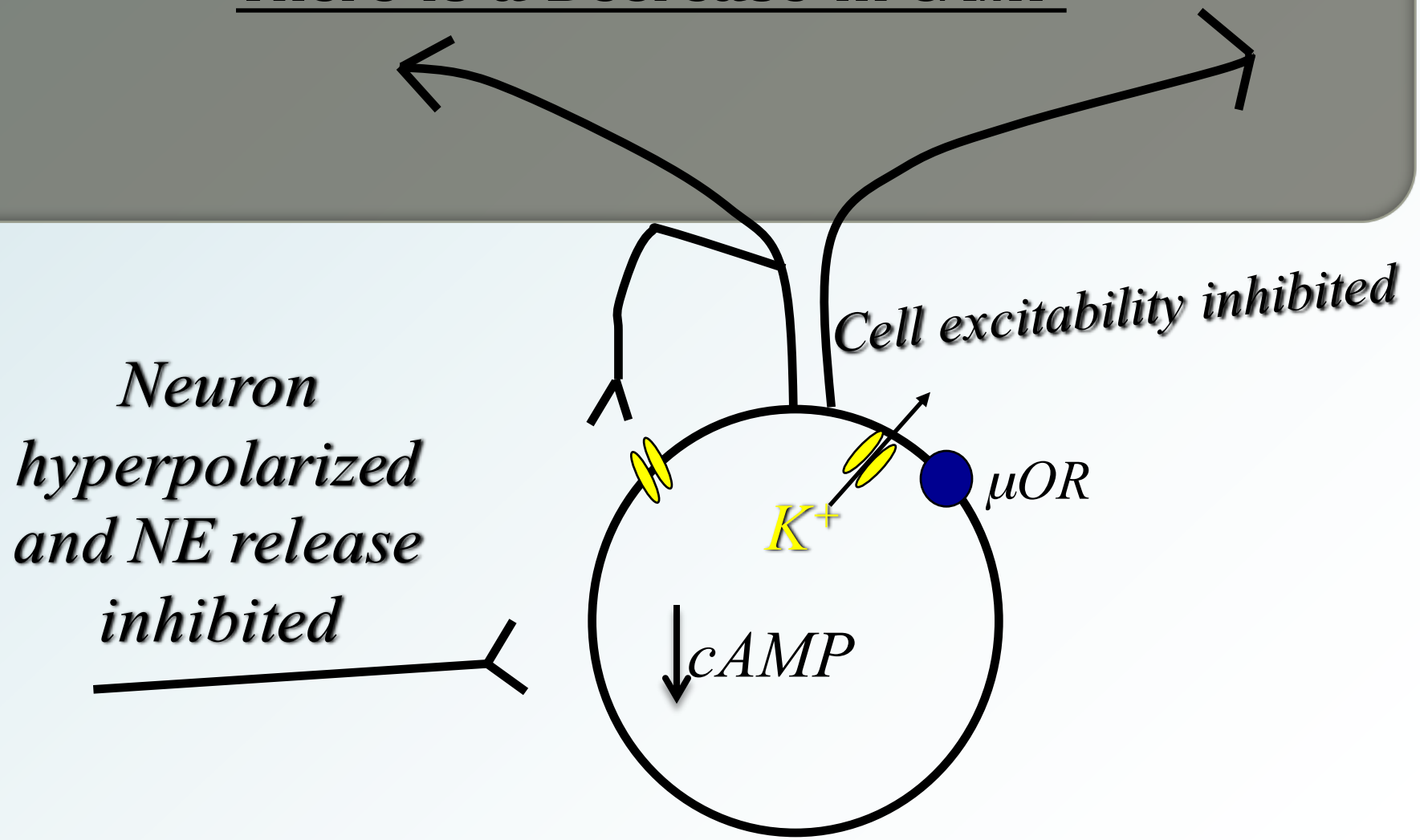
Mazie-Robison

LC is a discrete, compact, homogeneous nucleus, consisting of almost exclusively Nor Epinephrine (NE) neurons.
LC neurons express the three main classes of opioid receptors: MOR, DOR, and KOR with distinct distribution, although, as with the VTA, MOR is most directly implicated in opiate dependence and addiction.

Acutely:

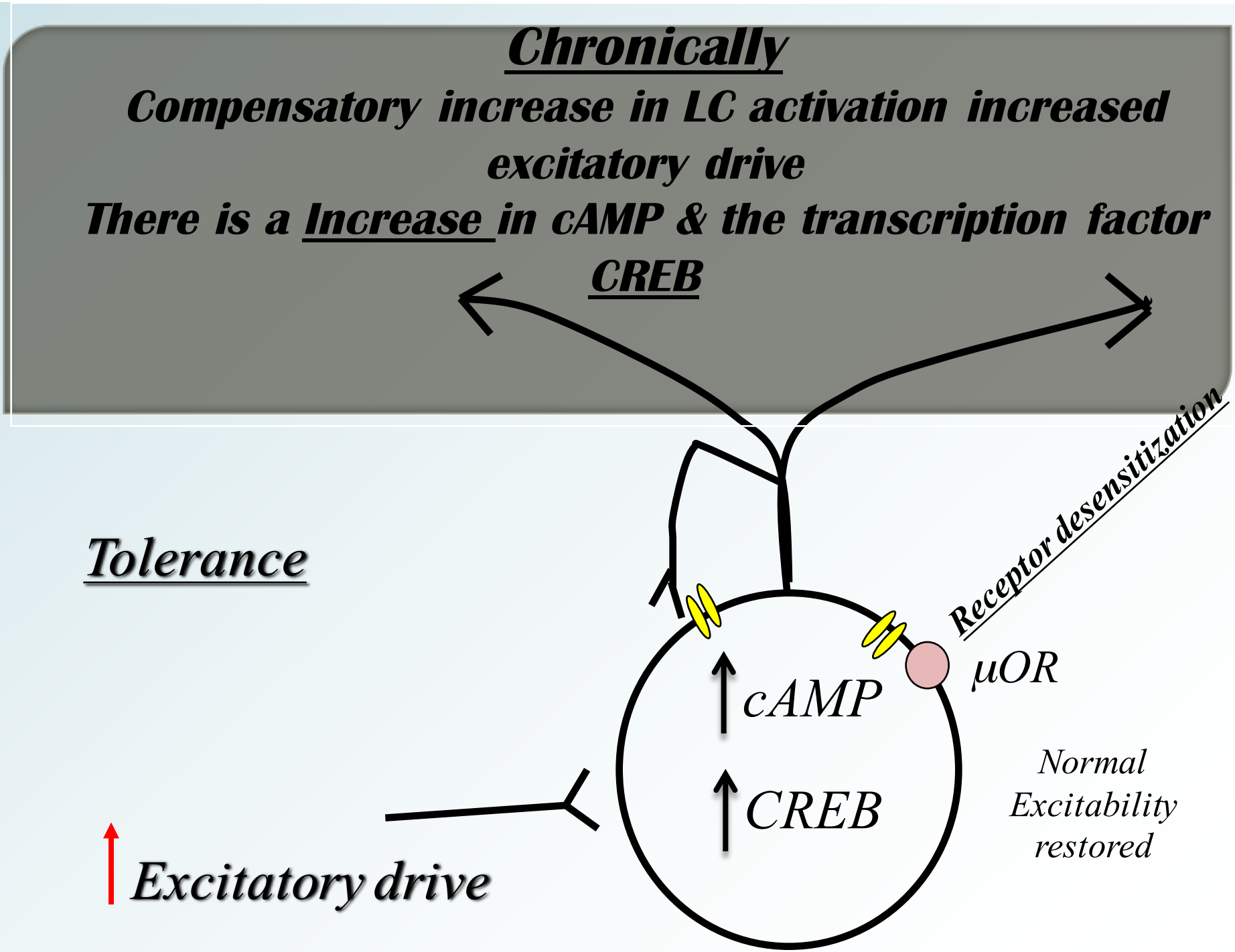
Morphine inhibits LC firing – sedation

There is a Decrease in cAMP



Noradrenergic neuron in the locus coeruleus

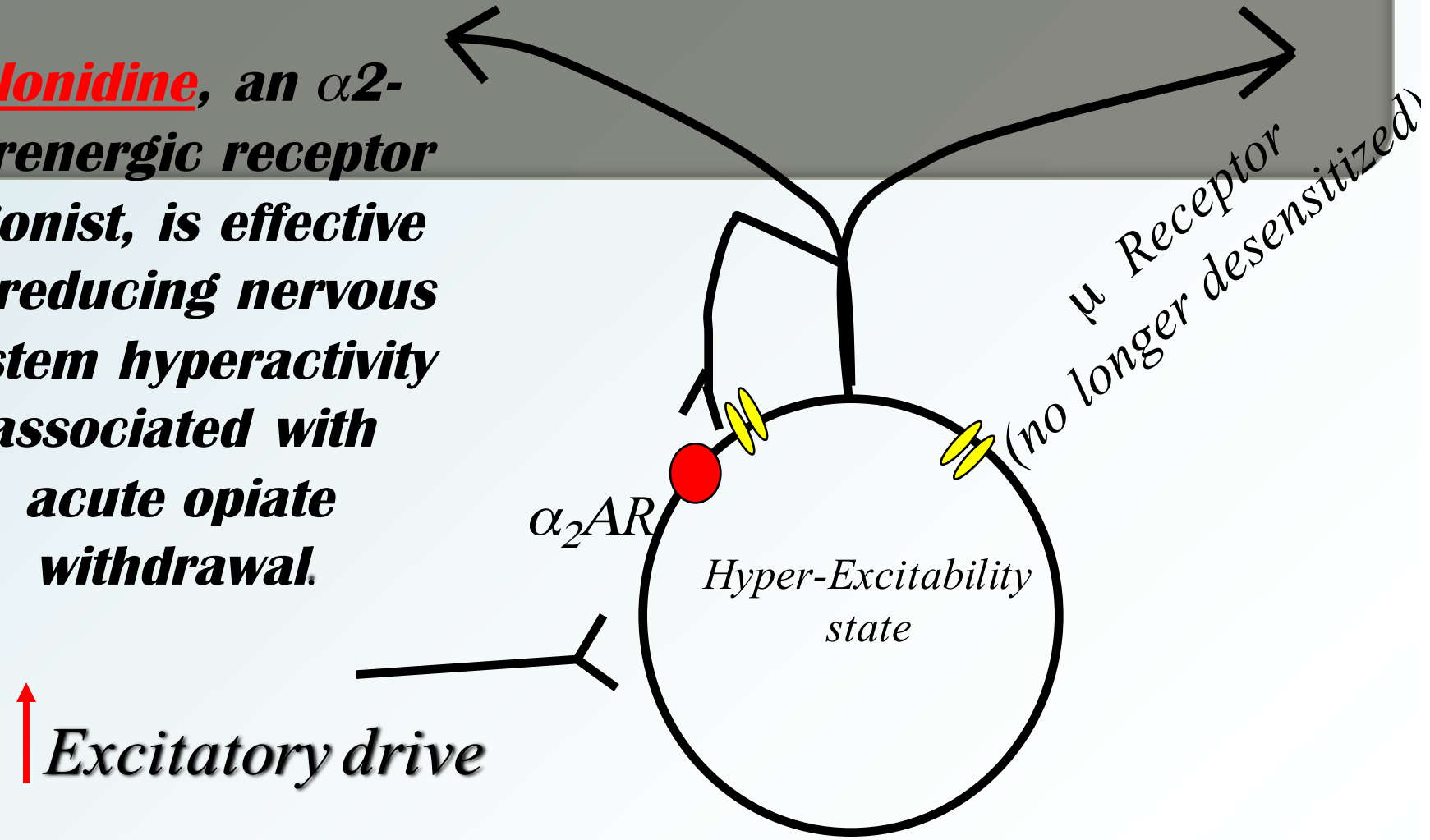
Modified from C. Chavkin University of Washington



Modified from C. Chavkin University of Washington

Withdrawal

Clonidine, an α2-adrenergic receptor agonist, is effective at reducing nervous system hyperactivity associated with acute opiate withdrawal.



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Effects of Opioids

Acute effects	Acute toxic dose	Chronic use	Withdrawal	Treatment
Euphoria	Pinpoint-size pupil	Risk of overdose	Irritability	Methadone
Well-being	Slow respiration	Malnutrition	Dysphoria	Naltrexone
Near stuporous state	Death	Reduced immunity	Nausea and vomiting	Naloxone
sweating		Risks due to IV injections	Muscles aches	
Nausea-vomiting		Reduced pain	Runny nose	
			Dilated pupils	
			Diarrhea	
			Yawning	
			Fever	
			Insomnia	

Opiate Tolerance

receptor desensitization compensatory adaptations in neuronal circuit learning mechanisms

Physical Dependence

compensatory adaptations in neuronal circuit

Drug Withdrawal

removal of opiate unmasks compensatory adaptations

Drug Addiction

(rare during treatment of pain)

Opioid withdrawal/abstinence syndrome

Severity depends on dose used and rate of elimination.

Rhinorrhea
Lacrimation
Chills
Goose flesh
**Muscle aches*
**Diarrhea*
Yawning
**Anxiety*
Hostility

Precipitated withdrawal by a partial agonist or antagonist administration

Opioid Antagonists

- Naloxone (Narcan®)
- *Naloxone is specifically used to counteract life-threatening depression of the central nervous system and respiratory system*
- Naltrexone
- *Naltrexone hydrochloride is a pure opioid antagonist*
- *markedly attenuates or completely blocks the subjective effects of intravenously administered opioids.*
- *When co-administered with morphine, on a chronic basis, Naltrexone hydrochloride blocks the physical dependence to morphine, heroin and other opioids.*

Heroin/opiate addiction		
FDA approved[72]	Naltrexone	Mu opioid receptor (antagonist)
	Methadone	Mu opioid receptor (substitution with different pharmacokinetics)
	Buprenorphine	Mu opioid receptor (substitution)

Psychostimulants

Large class of diverse compounds

- Stimulate alertness, arousal ("psycho-")
- Stimulate motor activity ("-motor")

Major Psychostimulants:

- Amphetamines and related compounds
- Cocaine

Mechanisms of Action

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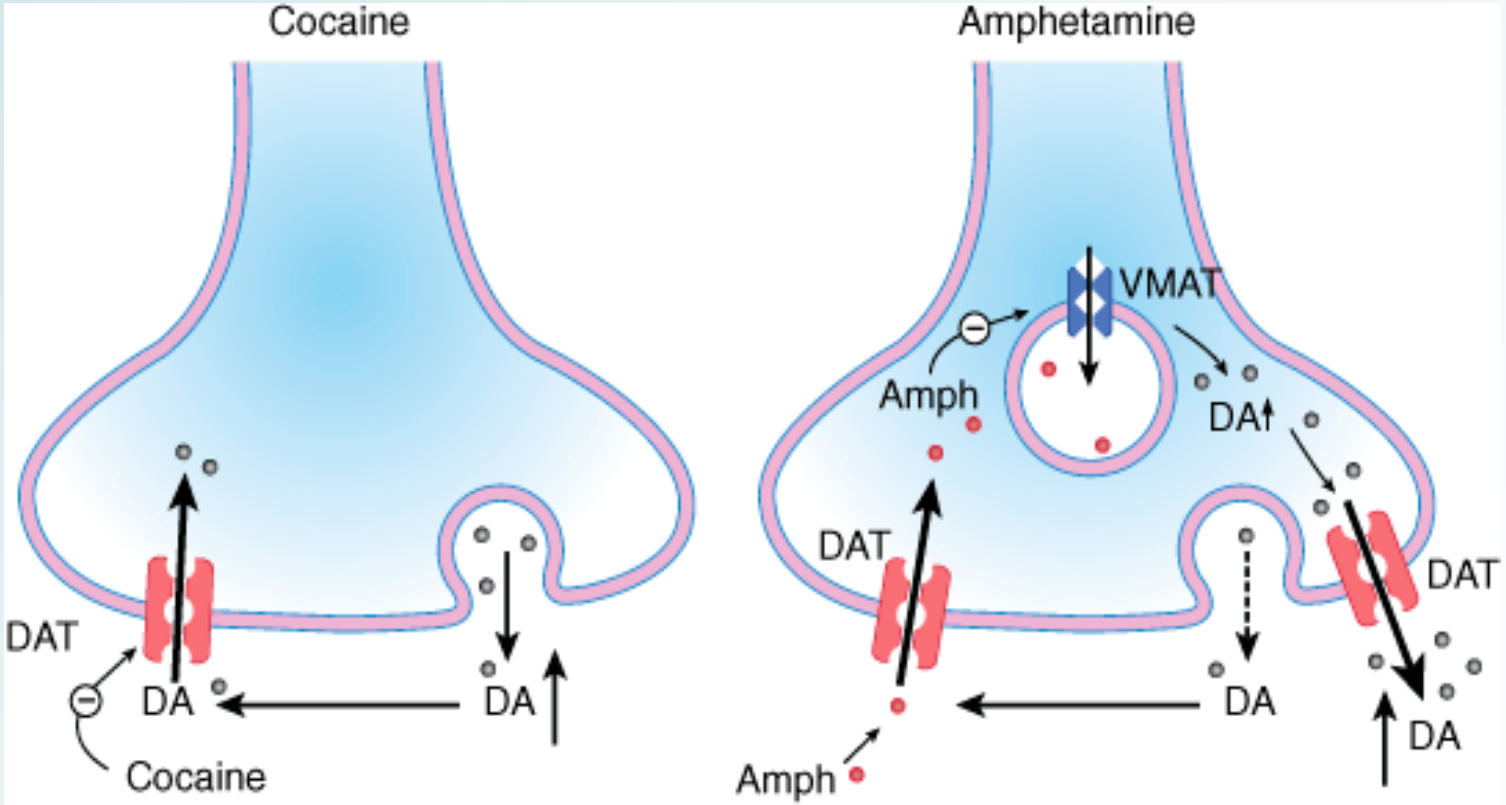
Cannabinoids	Agonist at CB_1 and CB_2 cannabinoid receptors¶	G_i
Phencyclidine (PCP)	Antagonist at NMDA glutamate receptors	Ligand-gated channels
Hallucinogens	Partial agonist at $5\text{-}HT_{2A}$ serotonin receptors	G_q
Inhalants	Unknown	

Nestler EJ. Nature



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Dopamine transporter (DAT)

(amphetamine reverses DAT and VMAT direction; cocaine blocks DAT)

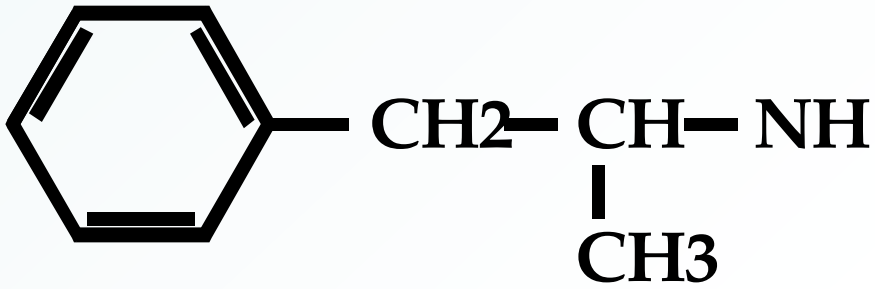
AMPHETAMINE

Amphetamine (racemic)

- mixture of d- and l- isomers
- Benzedrine®
- “speed”

d-Amphetamine

- dextroamphetamine
- Dexedrine®



Amphetamine

Amphetamine related drugs

Methylphenidate

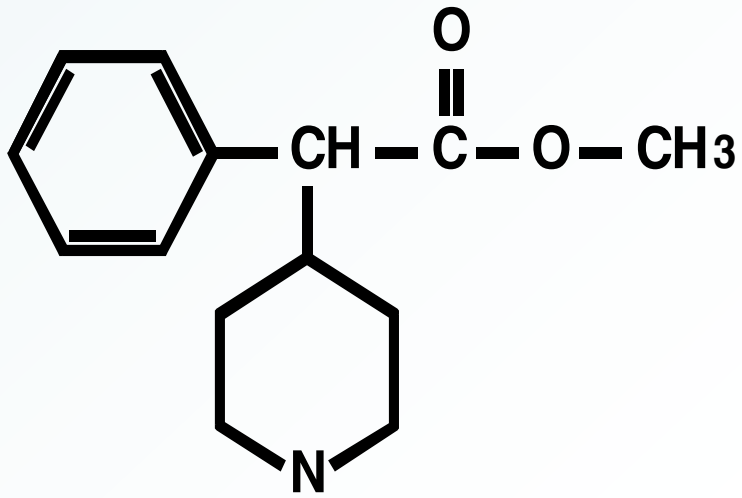
- Ritalin®
- attention deficit disorder

Fenfluramine

- Redux®
- anorectic

Phenmetrazine

- Preludin®
- anorectic



Methylphenidate

Amphetamine

Acute dose	Acute toxic dose	Chronic use	Withdrawal	Treatment
Euphoria	Chest Pain	Cardiac damage	Depression	Treat aspects of withdrawal
Increased self-esteem	Unconsciousness	Liver Damage	Decreased energy	
Increased self-confidence	Psychotic reaction	Weight loss	Increased appetite	
Hyperactivity		Paranoid states	Low self-esteem	
Immunity to fatigue		Amphetamine psychosis	Decreased libido	
Sterotyped behavior		Depression	Paranoia	
Chills		IV related illnesses	Paranoid schizophrenia	
Nausea and vomiting				
Decreased appetite				

Cocaine

Naturally-occurring alkaloid in leaves of shrub
Erythroxylon coca

Raw leaves

- chew
- alkaloid content low (0.6 - 1.8 %)
- not stable

Coca paste

- initial extraction
- smoked
- around 80% cocaine

Forms of cocaine

Cocaine HCl

- purified and converted to HCl salt
- crystalline form, water soluble
- pure if not diluted
- snorted or i.v.

Cocaine free base: crack

- extract
- smoked

Cocaine

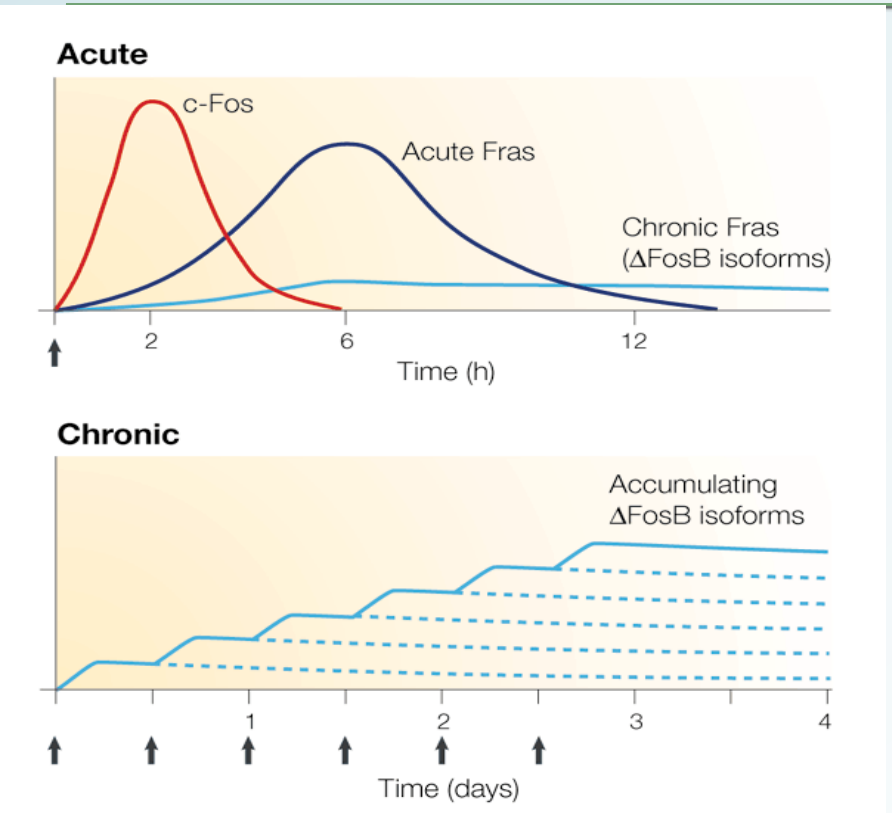
Acute mild dose	Acute high dose	Acute toxic dose	Chronic use	Withdrawal	Treatment
Euphoria	Stereotyped behavior	Restlessness	Weight loss	The crash	
Increased self-esteem	Impaired judgement	Agiatation	Sleep disorders	Withdrawal	treat aspects of withdrawal
Increased self-confidence	Chills	Intense anxiety	Memory impairment	Extinction	
Improved mental performance	Nausea and vomiting	Tremors	Attention deficit		
Immunity to fatigue	Chest pains	Muscular twitching	Irritability and mood swings		
Improved sexual performance	Cardiac arrythmias	Delirium and hallucination	Social isolation		
	Increased heart rate	Death	Paranoia		
	Elevated BP		Loss of interest in pleasure		
	Dilated pupils		Diminished libido		
	Constriction of blood vessels		Depression		
	Increased respiration				
	Decreased appetite				
	Increased metaboloc rate				

Cocaine addiction-pharmacotherapy

Clinical target	Medication	Biological target
Alcoholism		
FDA approved[60]	Disulfiram (Antabuse; Wyeth-Ayerst)	Aldehyde dehydrogenase (triggers aversive response)
	Naltrexone	Mu opioid receptor (antagonist; interferes with reinforcement)
	Acamprosate	Glutamate related
	†Topiramate[61] (Topamax; Ortho-McNeil)	GABA/glutamate
Under investigation	†Valproate[62]	GABA/glutamate
	Ondansetron[63]	5-HT_3 receptor
	Nalmefene[64]	Mu opioid receptor (antagonist)
	Baclofen[65] (Lioresal; Novartis)	$GABA_B$ receptor (agonist)
	Pyrrolopyrimidine compound[66] (Antalarmin; George Chrousos *et al.*)	CRF1 receptor (inhibits stress-triggered responses)
	Rimonabant (Acomplia; Sanofi-Synthelabo)[67]	CB1 receptor (antagonist)
Nicotine addiction		
FDA approved[68]	Nicotine replacement	Nicotinic receptor (substitution with different pharmacokinetics)
	Bupropion	DA transporter blocker (amplifies DA signals)
Under investigation	Deprenyl[69]	MAO-B inhibitor (inhibits metabolism of DA)
	Rimonabant (Acomplia; Sanofi-Synthelabo)[67]	CB1-receptor (antagonist)
	Methoxsalen[70]	CYP2A6 (inhibits nicotine metabolism)
	Nicotine conjugate vaccine[71] (NicVax; Nabi Biopharmaceuticals)	Blocks entry into brain
Heroin/opiate addiction		
FDA approved[72]	Naltrexone	Mu opioid receptor (antagonist)
	Methadone	Mu opioid receptor (substitution with different pharmacokinetics)
	Buprenorphine	Mu opioid receptor (substitution)
Cocaine addiction		
Under investigation	†Topiramate[73] (Topamax; Ortho-McNeil)	GABA (agonist)
	†γ-vinyl GABA (GVG)[74] (Sabril; Hoechst Marion Roussel)	GABA transaminase (inhibits GABA metabolism)
	†Gabapentin[75] (Neurontin; Parke-Davis)	GABA/glutamate (synthesis)
	†Tiagabine[76] (Gabitril; Abbott)	GABA transporter (inhibitor)
	Baclofen[77] (Lioresal; Novartis)	$GABA_B$ receptor (agonist)
	Modafinil[78]	Glutamate (?)
	Disulfiram[79] (Antabuse; Wyeth-Ayerst)	Unknown for cocaine
	Cocaine vaccine[71] (TA-CD; Xenova)	Blocks entry into brain

Volkow & Li, Nature Reviews

Delta FosB: a sustained molecular switch for addiction?

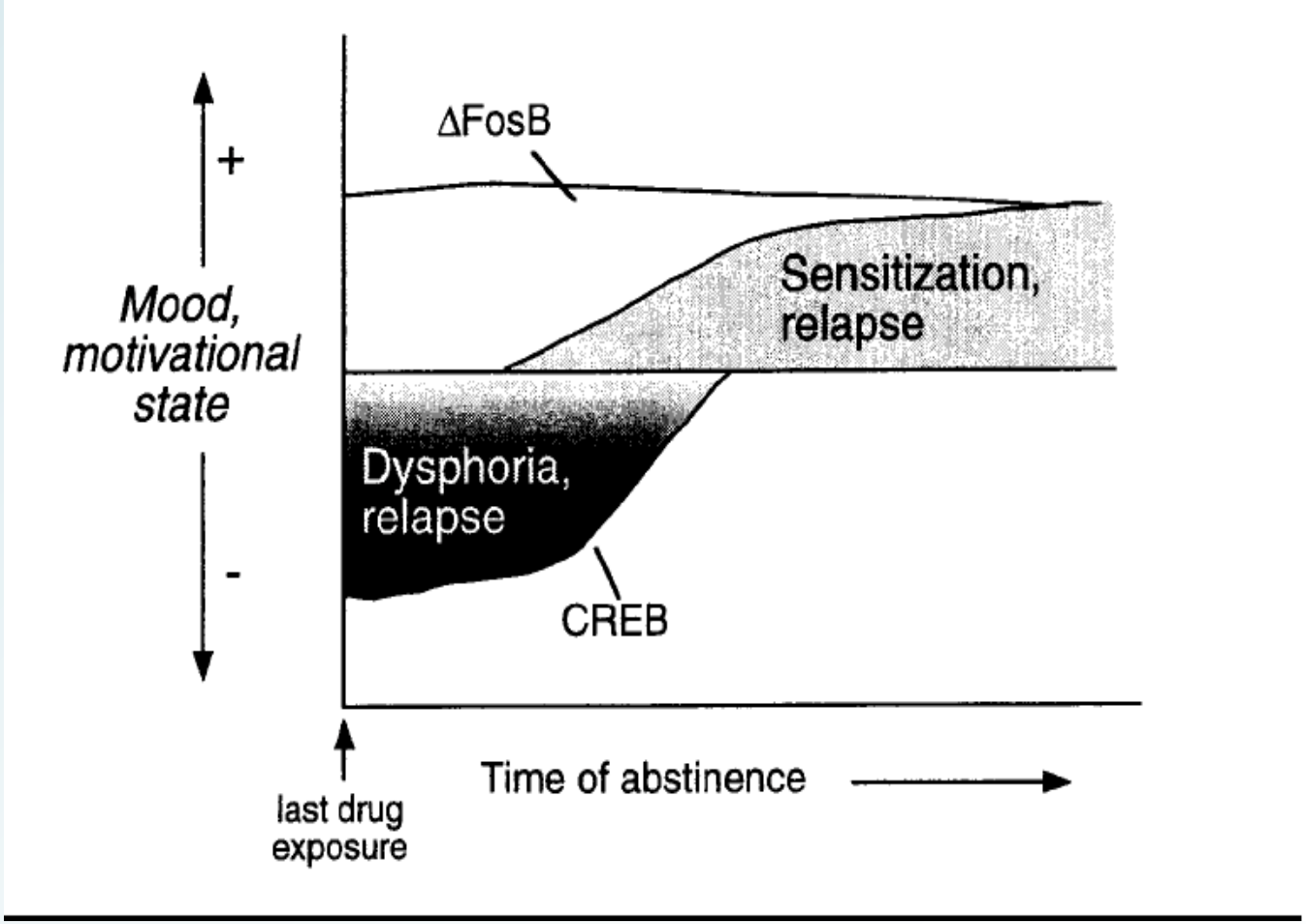


- *Increase rewarding properties of cocaine*
- *Increase in behavioral sensitization*
- *Increase in self administration of cocaine*

ΔFosB is known to directly regulate:

- *Cholecystokinin* ***(CCK)***
- *AMPA Glutamate subunits-* ***GluR2***
- ***Cry2***
- *Ca^{2+}/calmodulin-dependent protein kinases II* ***(CaMKII)***
- *Sirtuin* ***1 (Sirt1)***

Drug-Induced Molecular Adaptations



Epigenetic Regulation of Gene Expression Governs Long-Term Changes