ADDICTION CIRCUITRY IN THE HUMAN BRAIN

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“When you can stop you don't want to....
and when you want to stop, you can't...”

Wine boy at a Greek symposium

A study in 2010 asked drug-harm experts to rank various illegal and legal drugs.

These measures include damage to health, drug dependency, economic costs and crime.

Source: Drug harms in the UK: a multicriteria decision analysis, D J Nutt

DEFINITIONS

- ***Addiction:*** The repeated and increased use of a substance, the deprivation of which gives rise to symptoms of distress and an irresistible urge to use the agent again and which leads also to physical and mental deterioration. This term is not applied as a diagnostic term.

- ***Abuse:*** Use of any drug, usually by self-administration, in a manner that deviates from approved social or medical patterns.

- ***Dependence:*** The repeated use of a drug or chemical substance, with or without physical dependence.

DSM- IV, APA, 1994

DEFINITIONS (DSM- V)

- **Substance Use Disorders**: The essential feature of a substance use disorder is a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues using the substance de-spite significant substance-related problems.

- **Substance-induced disorder**: It includes intoxication, withdrawal, and other substance/medication-induced mental disorders (e.g., substance-induced psy-chotic disorder, substance-induced depressive disorder).

American Psychiatric Association; May 18, 2013

DSM 5 CRITERIA FOR SUBSTANCE USE DISORDER

These symptom criteria must be present within the past 12 months and lead to “clinically significant impairment or distress.”

1. _____ is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control _____ use.
3. A great deal of time is spent in activities necessary to obtain _____, use _____, or recover from its effects.
4. Craving, or a strong desire or urge to use ____.
5. Recurrent _____ use resulting in a failure to fulfil major role obligations at work, school, or home.
6. Continued _____ use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of _____.

DSM 5 CRITERIA FOR SUBSTANCE USE DISORDER ….CONT.

7. Important social, occupational, or recreational activities are given up or reduced because of ____ use
8. I
9. r
   o
10.
11.

Mild Substance Use Disorder	**2 – 3 Symptoms**
Moderate Substance Use Disorder	**4-5 Symptoms**
Severe Substance Use Disorder	**>6 Symptoms**

of

II. _____ is taken to relieve or avoid withdrawal symptoms.

IMPORTANT SUBSTANCE FOR ABUSE (DSM V)

TABLE 1 Diagnoses associated with substance class

	Psychotic disorders	Bipolar disorders	Depressive disorders	Anxiety disorders	Obsessive-compulsive and related disorders	Sleep disorders	Sexual dysfunctions	Delirium	Neurocognitive disorders	Substance use disorders	Substance intoxication	Substance withdrawal
Alcohol	I/W	I/W	I/W	I/W		I/W	I/W	I/W	I/W/P	X	X	X
Caffeine				I		I/W					X	X
Cannabis	I			I		I/W		I		X	X	X
Hallucinogens												
Phencyclidine	I	I	I	I				I		X	X	
Other hallucinogens	I*	I	I	I				I		X	X	
Inhalants	I		I	I				I	I/P	X	X	
Opioids			I/W	W		I/W	I/W	I/W		X	X	X
Sedatives, hypnotics, or anxiolytics	I/W	I/W	I/W	W		I/W	I/W	I/W	I/W/P	X	X	X
Stimulants**	I	I/W	I/W	I/W	I/W	I/W	I	I		X	X	X
Tobacco						W				X		X
Other (or unknown)	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W/P	X	X	X

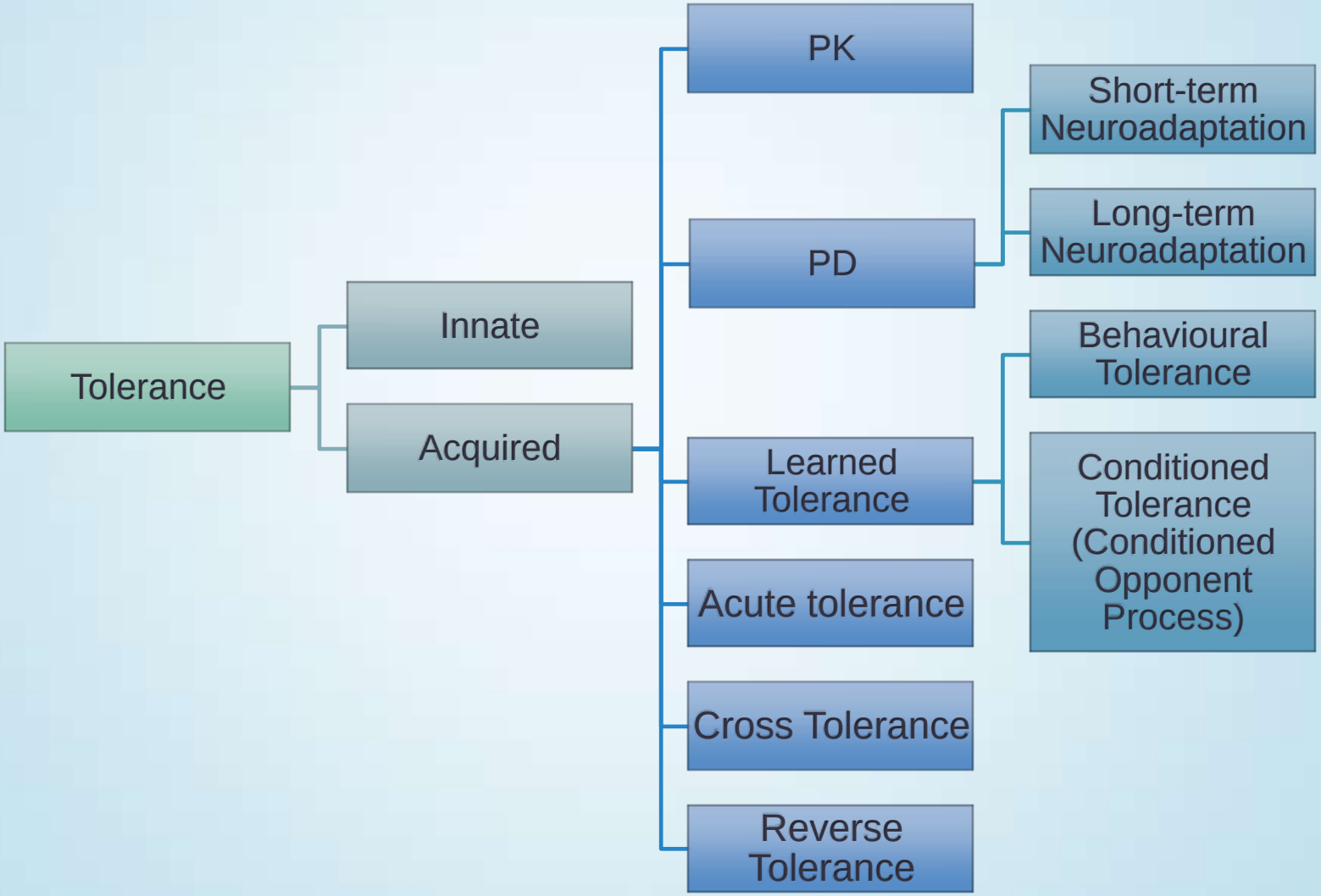
Note. X = The category is recognized in DSM-5.
I = The specifier "with onset during intoxication" may be noted for the category.
W = The specifier "with onset during withdrawal" may be noted for the category.
I/W = Either "with onset during intoxication" or "with onset during withdrawal" may be noted for the category.
P = The disorder is persisting.
*Also hallucinogen persisting perception disorder (flashbacks).
**Includes amphetamine-type substances, cocaine, and other or unspecified stimulants.

TOLERANCE AND WITHDRAWAL

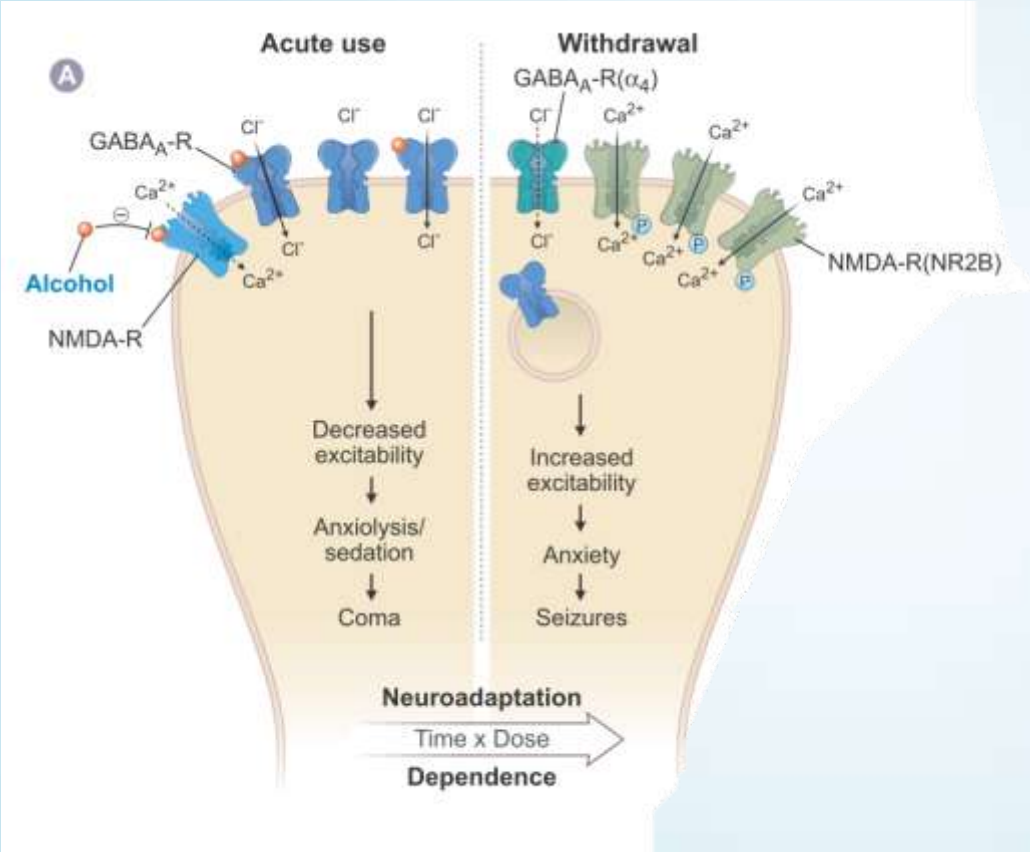
- **Tolerance** : Phenomenon in which, after repeated administration, a given dose of drug produces a decreased effect or increasingly larger doses must be administered to obtain the effect observed with the original dose.

- **Withdrawal** : A syndrome that occurs when blood or tissue concentra-tions of a substance decline in an individual who had maintained prolonged heavy use of the substance.

TOLERANCE


Tolerance
Innate
Acquired
PK
PD
Short-term Neuroadaptation
Long-term Neuroadaptation
Learned Tolerance
Behavioural Tolerance
Conditioned Tolerance (Conditioned Opponent Process)
Acute tolerance
Cross Tolerance
Reverse Tolerance

MECHANISM OF DEPENDENCE & WITHDRAWAL



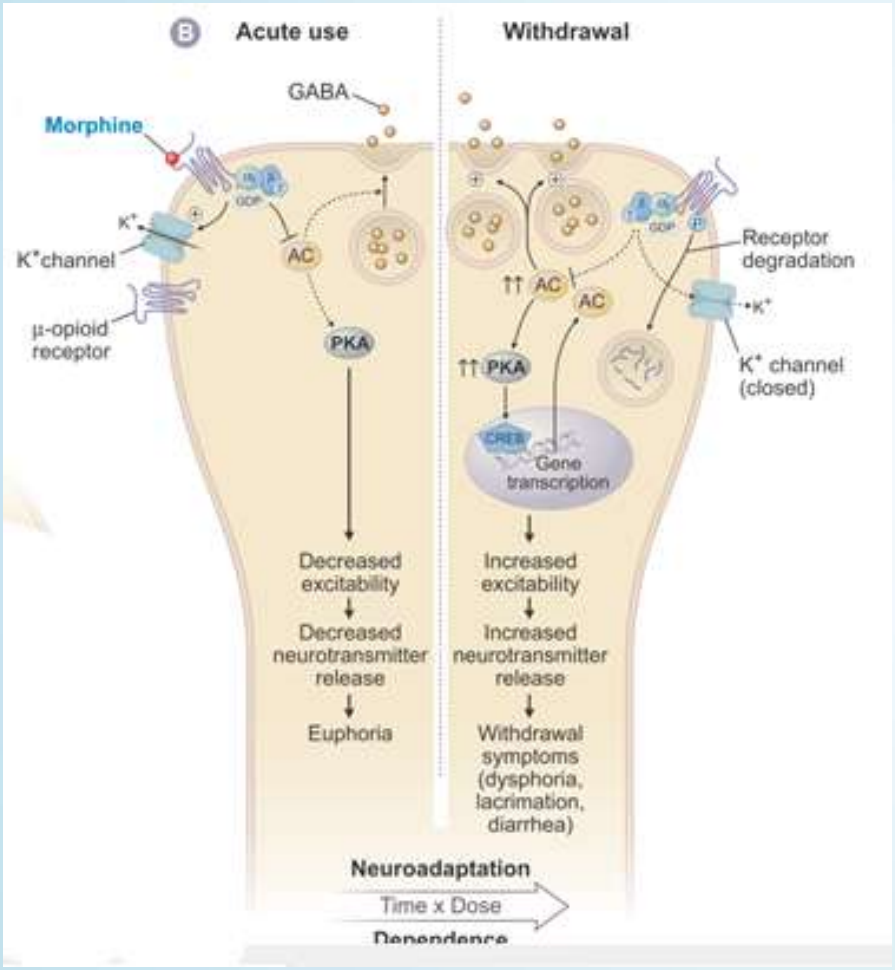
ALCOHOL Dependance

(1) internalization and decreased surface expression of "normal" α1 subunit-containing GABA$_A$ receptors

(2) increased surface expression of "low alcohol sensitivity" α4 subunit-containing GABA$_A$ receptors

(3) increased phosphorylation of NMDA receptors containing "high conductance" NR2B subunits.

MECHANISM OF DEPENDENCE & WITHDRAWAL



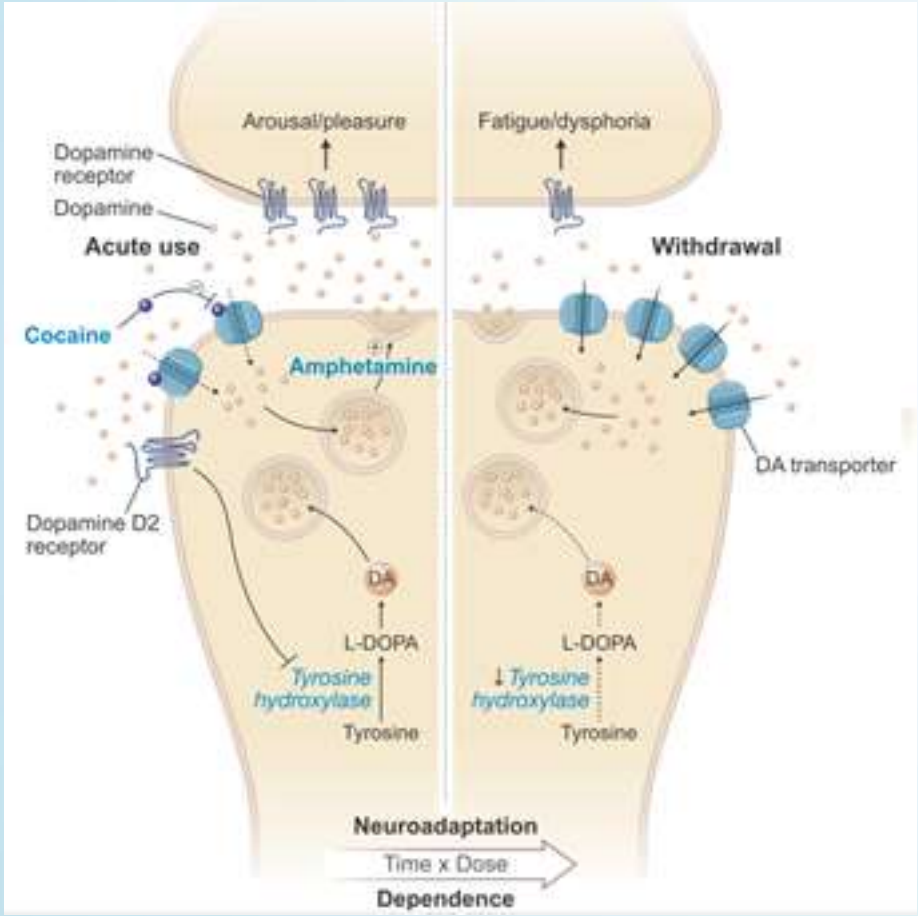
(1) Increased μ-opioid receptor internalization and degradation.

(2) Decreased efficacy of μ-opioid signal transduction.

(3) Hyperactivation of adenylyl cyclase signaling, leading to enhanced GABA release and to increased gene transcription via activation of transcription factors

Opioid Dependence

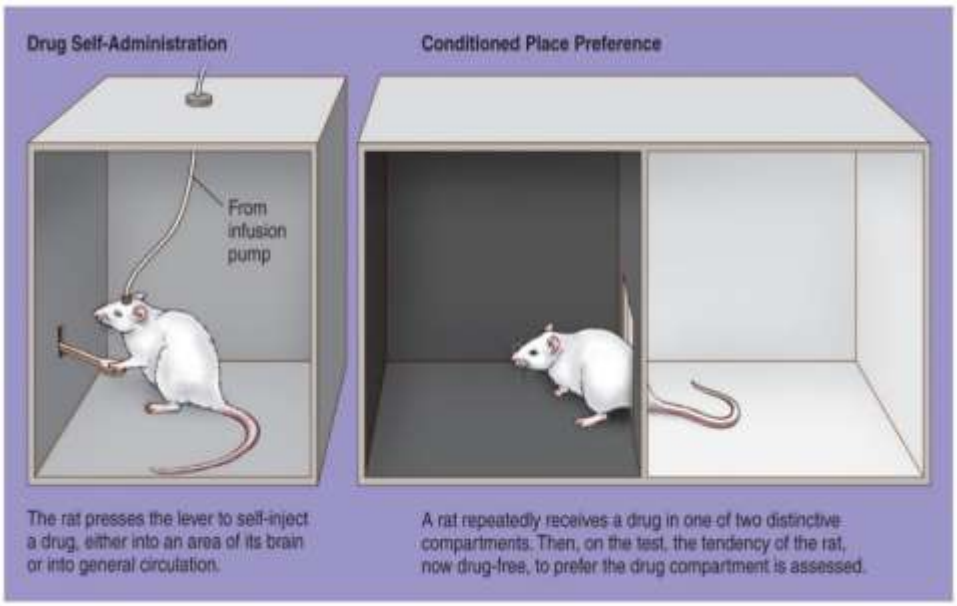
MECHANISM OF DEPENDENCE & WITHDRAWAL



1. DAT expression increases
2. The number of postsynaptic dopamine receptors decreases
3. Presynaptic dopamine is depleted

COCAINE and STIMULANT Dependance

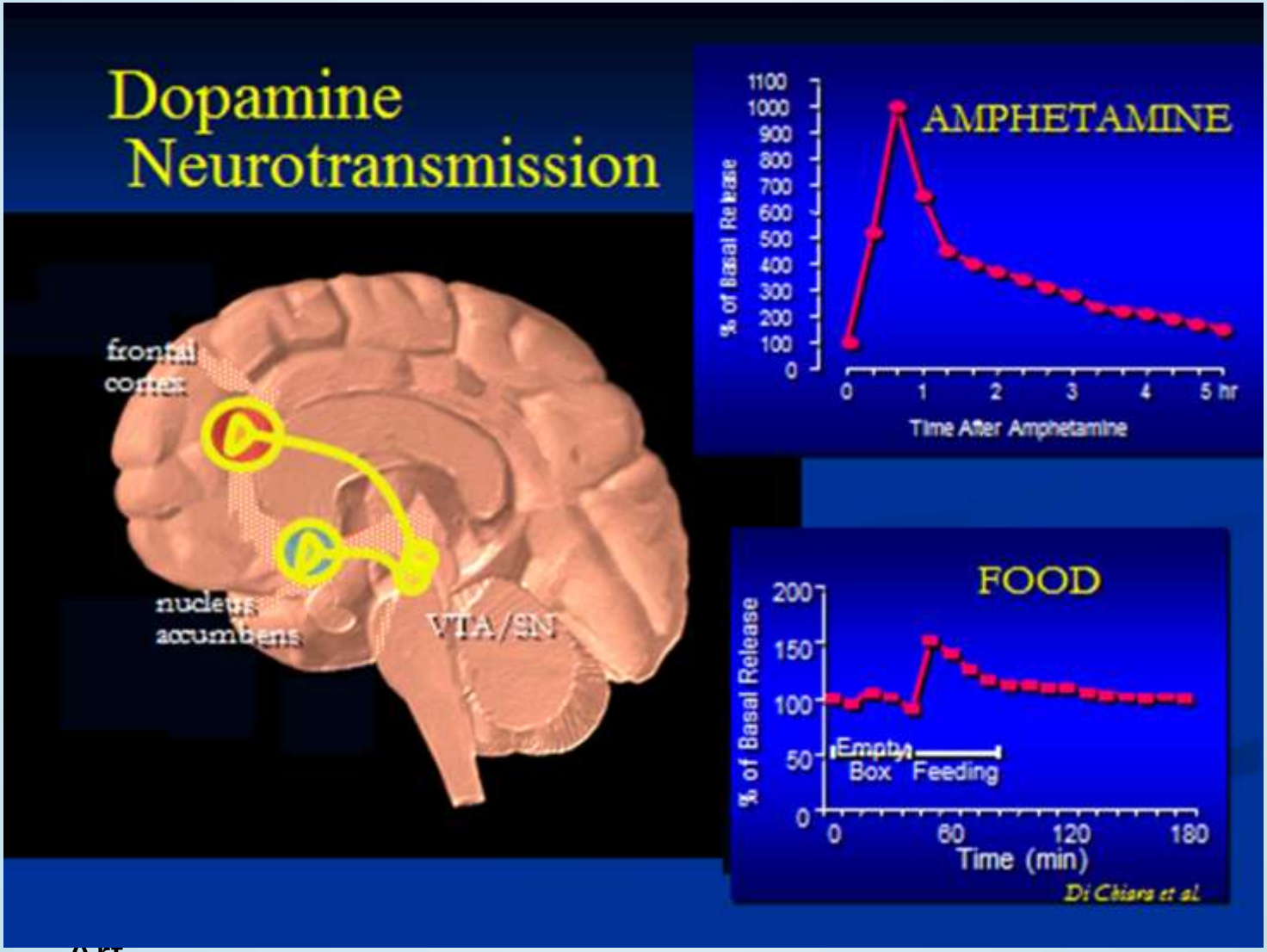
DISCOVERY OF REWARD CIRCUIT



In the 1950s, Olds and Milner implanted electrodes in various regions of the rat brain to systematically determine which neuroanatomic areas could reinforce self-stimulation.

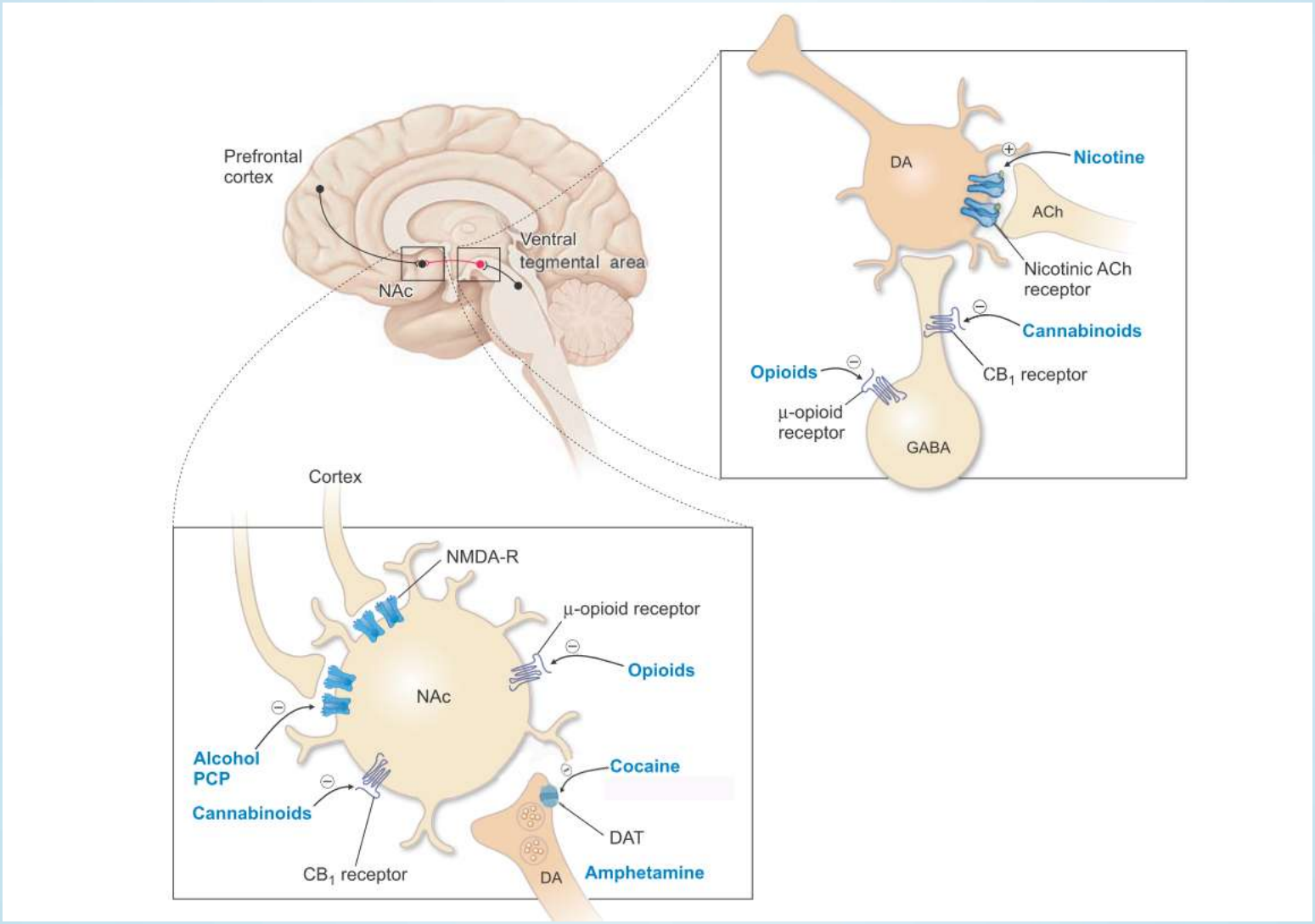
The medial forebrain bundle and **ventral tegmental area (VTA)** in the midbrain were found to be particularly effective sites. These sites have been termed "pleasure centers"

REWARD CIRCUIT IN BRAIN AND ITS FUNCTIONS

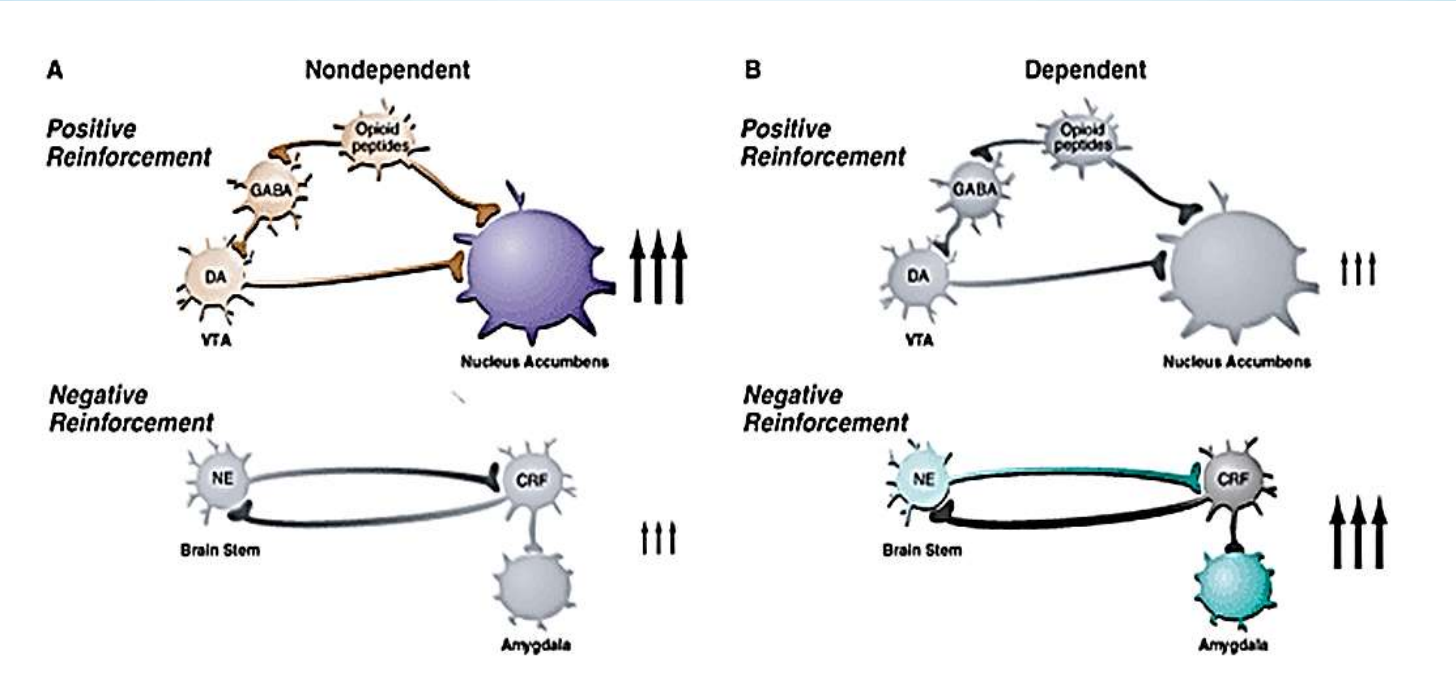


Art

PSYCHOACTIVE DRUGS "HIJACK" REWARD CIRCUIT



NEUROADAPTIVE CHANGES IN REWARD CIRCUIT DURING DEVELOPMENT OF DEPENDENCE



DA and opioid peptide neurons on **VTA** and the **nucleus Accumbens** and which are activated during initial alcohol use and <u>early stages</u> of the progression to dependence
(i.e.. The binge/intoxication stage)

Corticotropin releasing factor (CRF) and norepinephrine (NE)-releasing neurons that converge on GABA interneurons in the central nucleus of the **amygdala** and which are activated during the <u>development of dependence</u>.

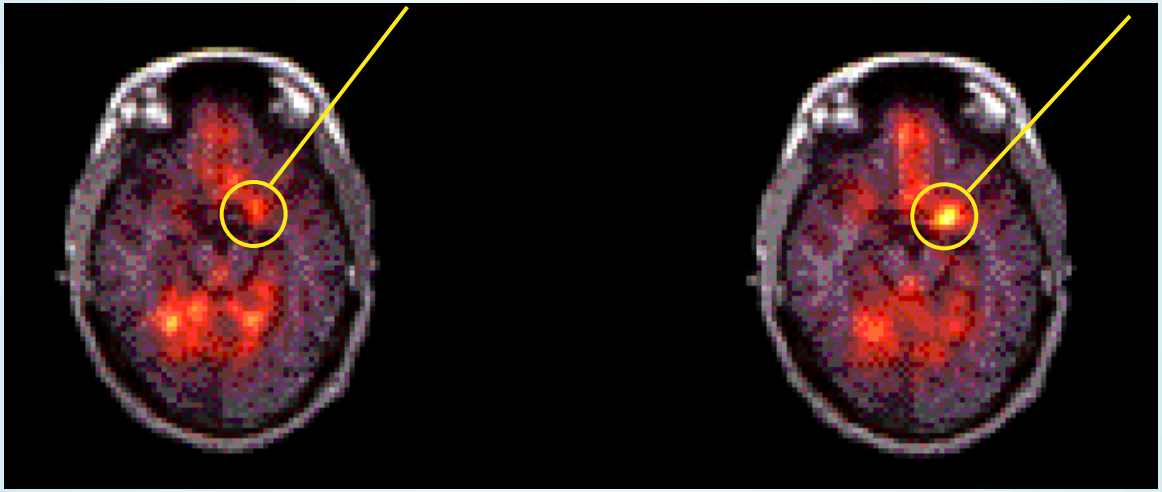
SOURCE: Nestler et al. 2005

PET IMAGES OF D2 AVAILABILITY

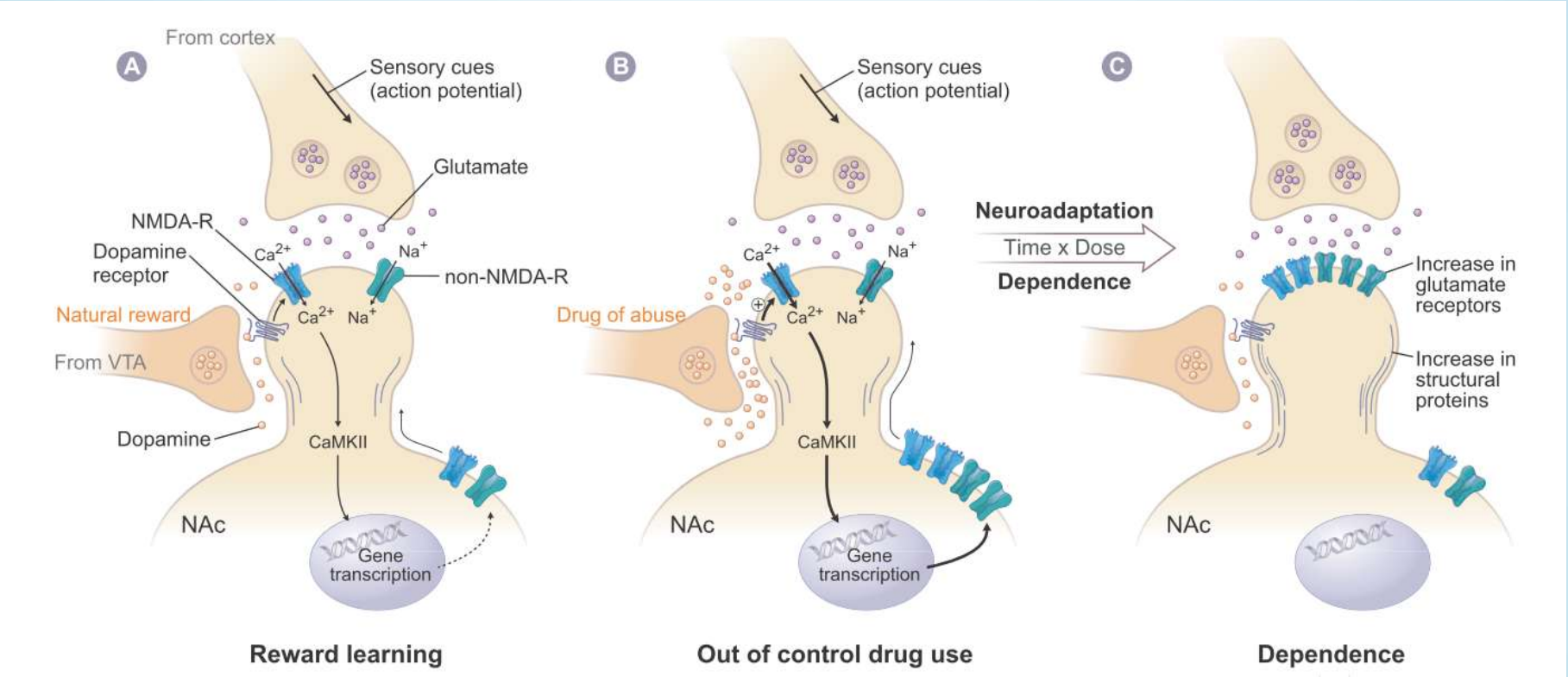
- Differential adaptation in D1R versus D2R signaling pathways with repeated drug administration is likely to underlie neuroplastic changes in addiction.

- Overall in animal studies, the increases in D1R signalling are associated with sensitized responses to drugs, and the decreases in D2R signaling with compulsive drug intake

DRUG MEMORY


Amygdala not lit up
Amygdala activated
Front of Brain
Back of Brain
Nature Video
Cocaine Video

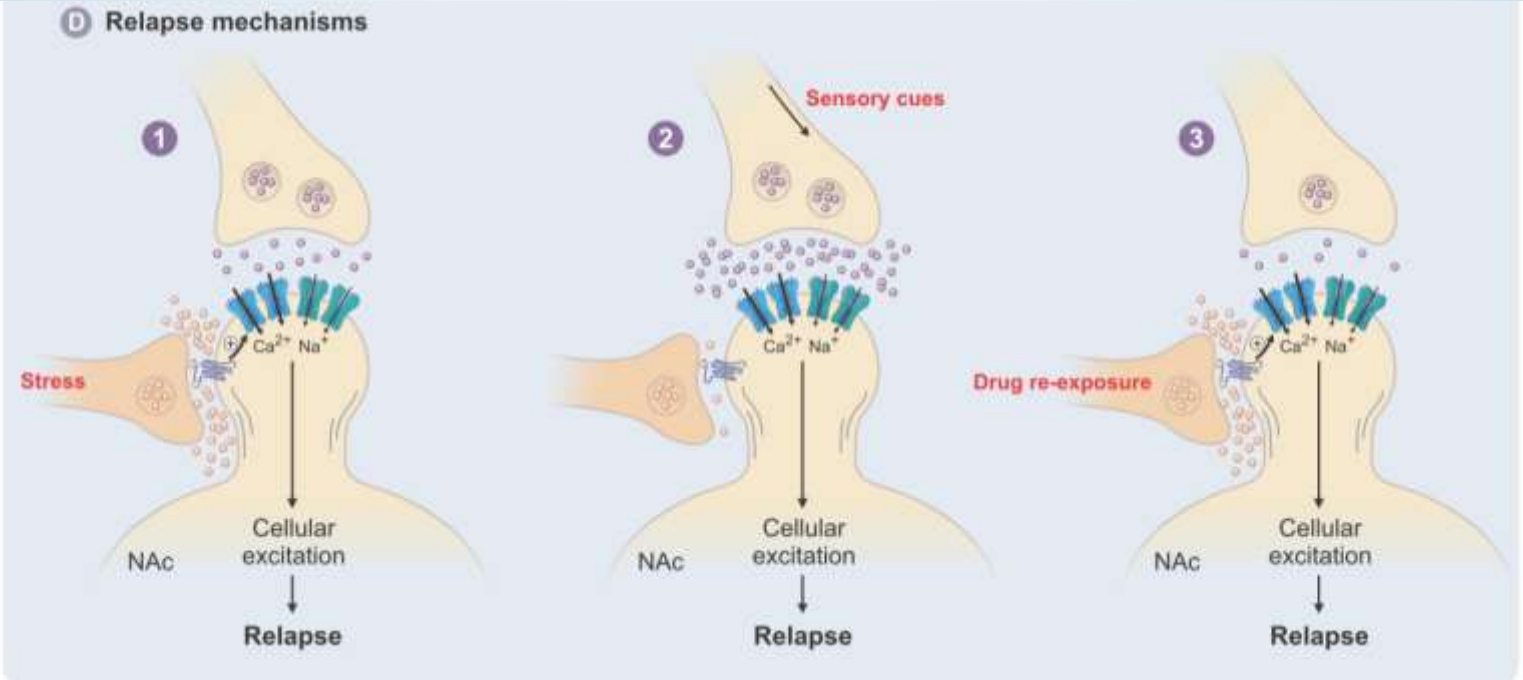
NEUROPLASTIC CHANGES AND ALLOSTASIS



Synaptic changes linking environmental stimuli, drug effects, and reward learning in drug dependence

Source: Principles of Pharmacology, E. Golan, 3-rd Ed.

MECHANISM OF RELAPSE

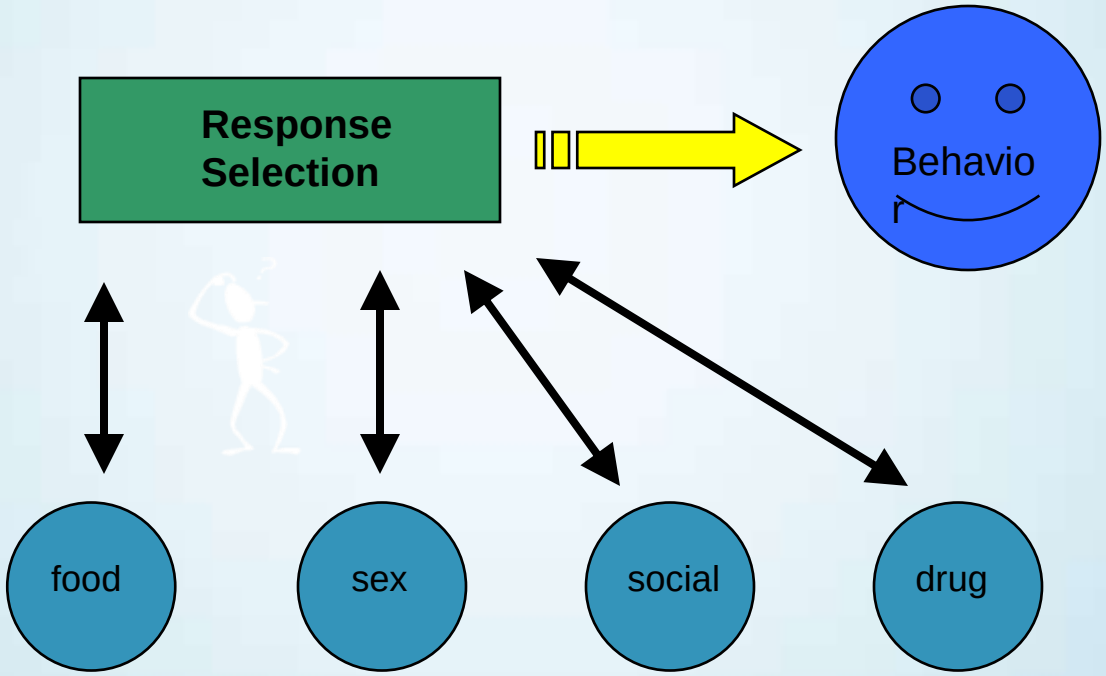


Stress induced relapse

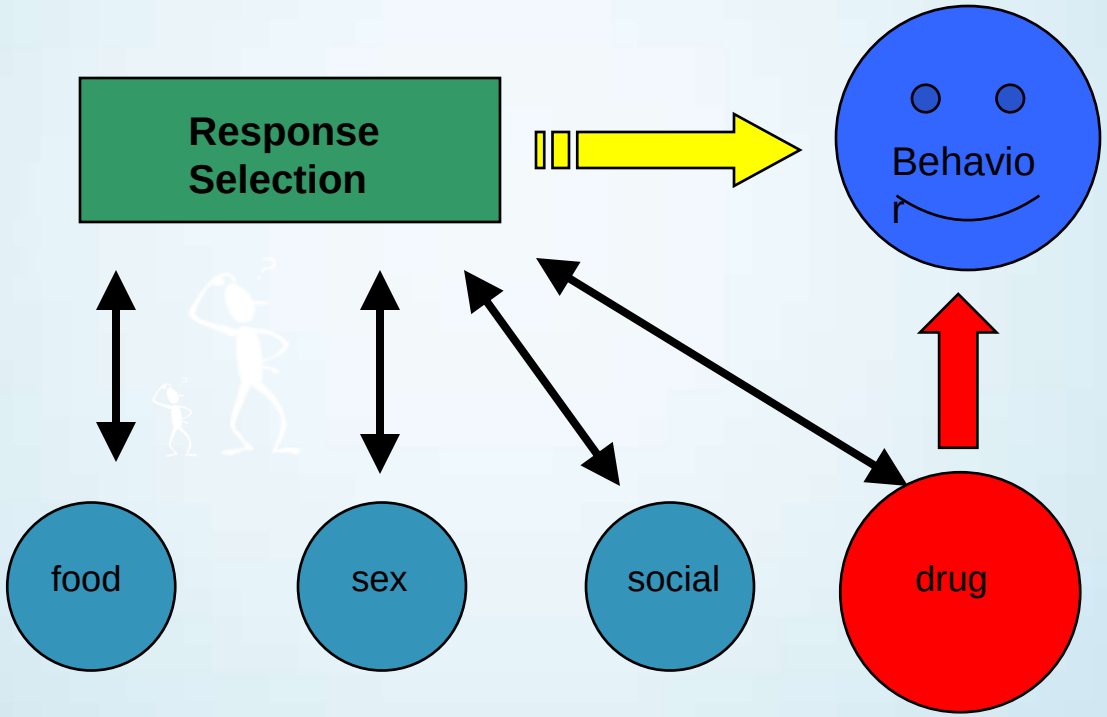
Sensory Cue induced relapse

Drug re-exposure

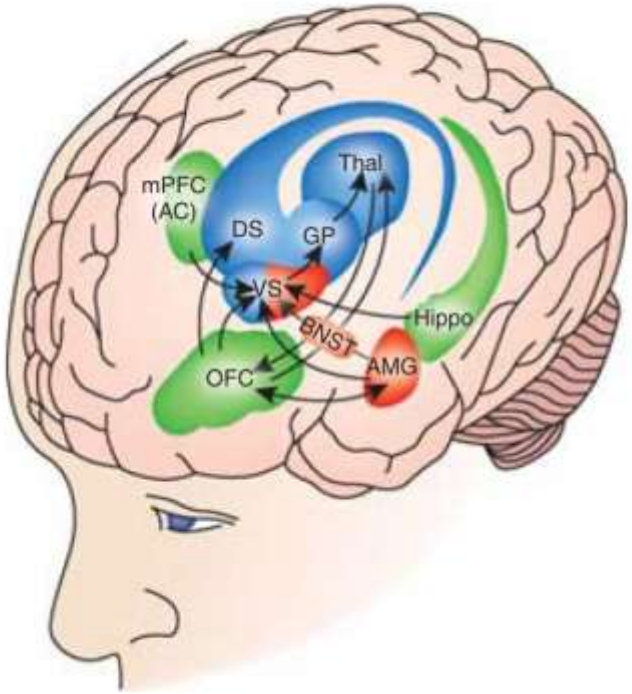
CHOICE BEHAVIOR AND THE NOTION OF "SELF-CONTROL"

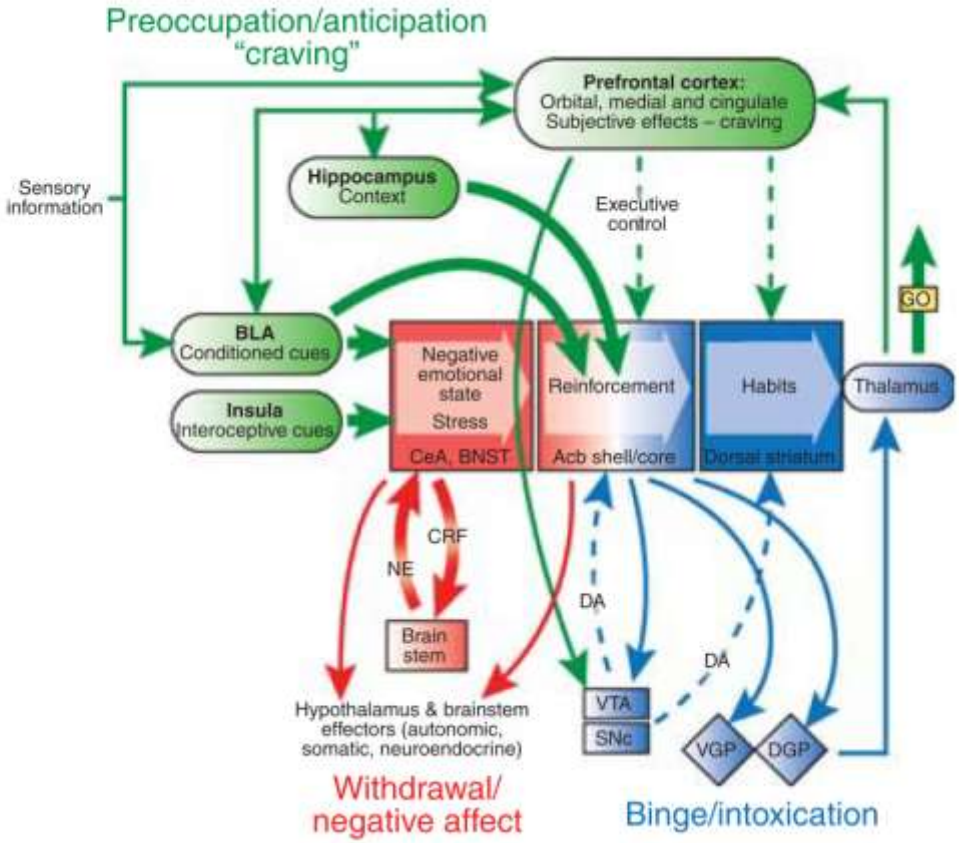


SELF-PERCEIVED “LOSS OF CONTROL”



ADDICTION AND HUMAN BRAIN …



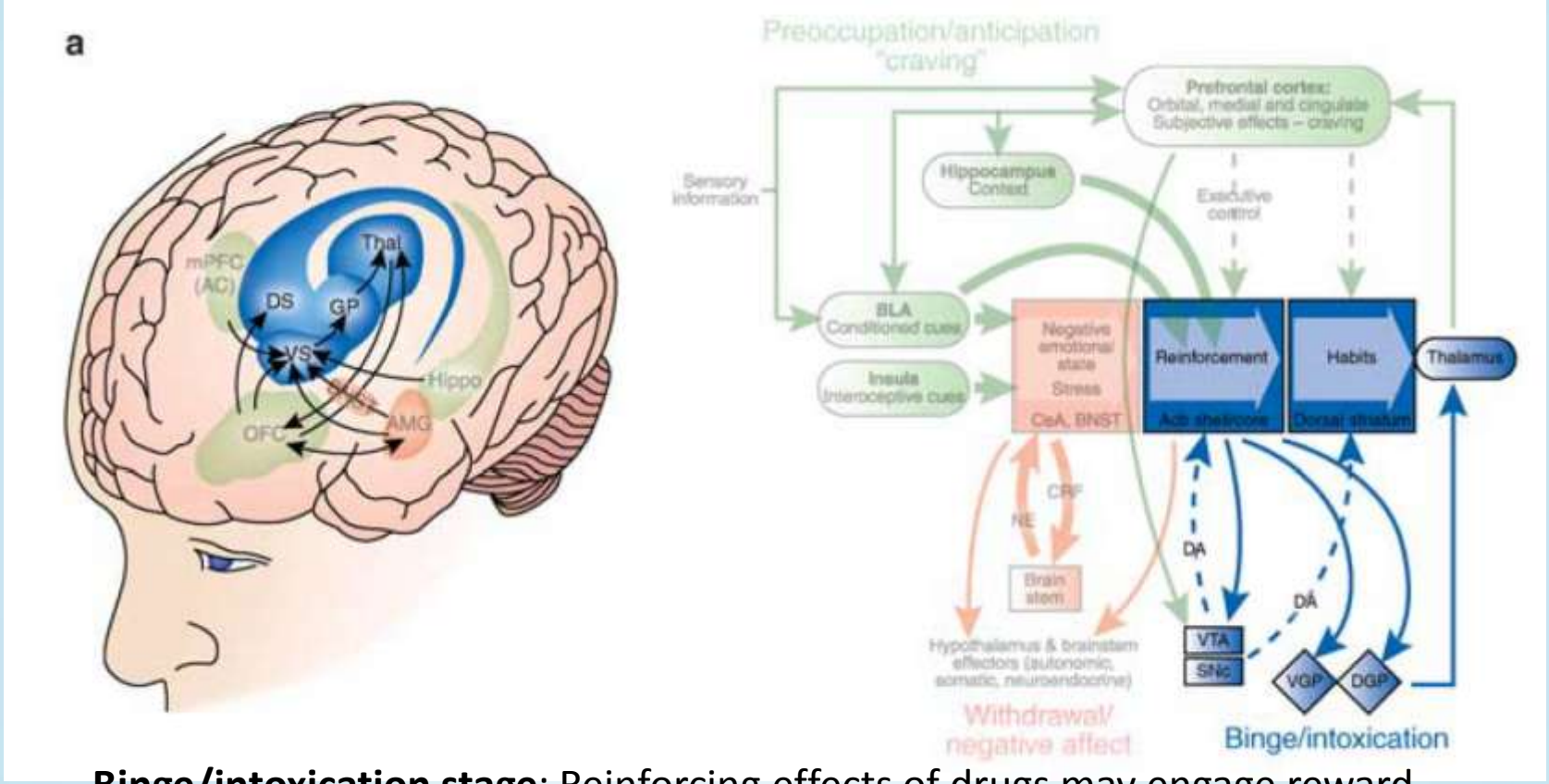


Acb nucleus accumbens
BLA basolateral amygdala
VTA ventral tegmental area
SNc substantia nigra pars compacta

VGP ventral globus pallidus
DGP dorsal globus pallidus
BNST bed nucleus of the stria terminalis

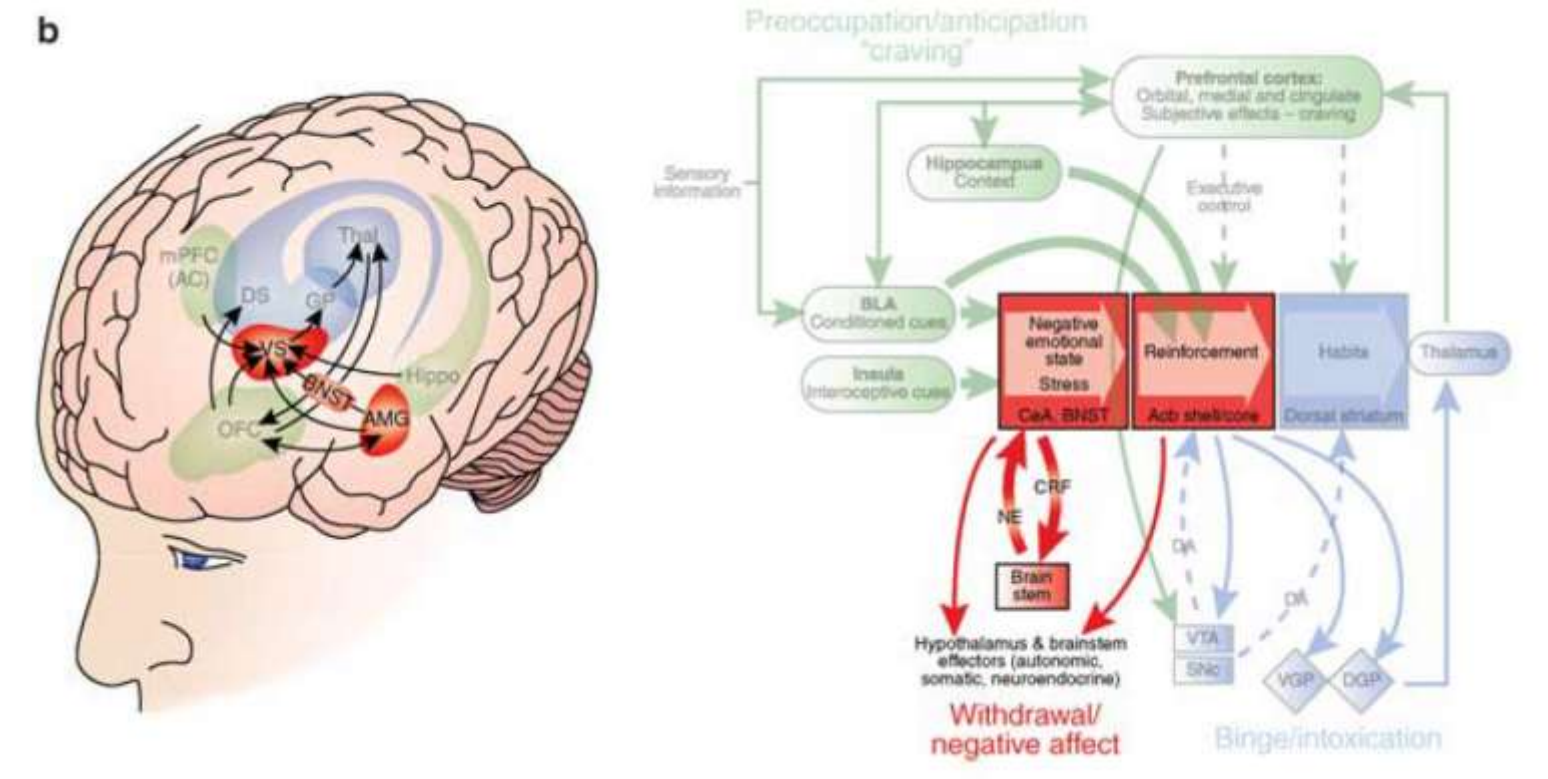
Source : Koob et al, 2008

ADDICTION AND HUMAN BRAIN …



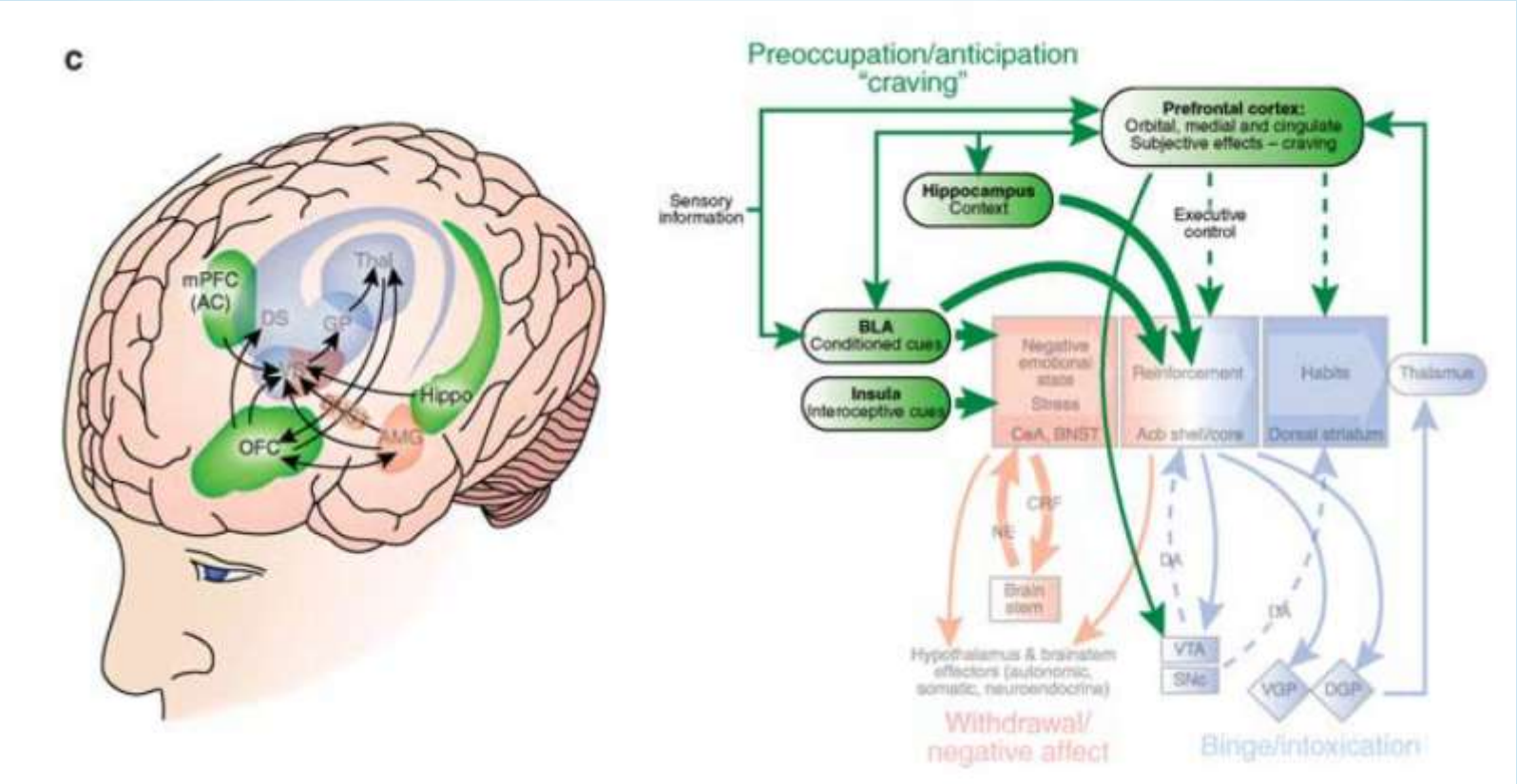
Binge/intoxication stage: Reinforcing effects of drugs may engage reward neurotransmitters and associative mechanisms in the Nucleus Accumbens shell and core and then engage stimulus–response habits that depend on the dorsal striatum. Two major neurotransmitters mediating the rewarding effects of drugs of abuse are dopamine and opioid peptides.

ADDICTION AND HUMAN BRAIN …



The negative emotional state of withdrawal may engage the activation of the **extended amygdala**. Major neurotransmitters in the extended amygdala hypothesized to have a function in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. Major projections of the extended amygdala are to the **hypothalamus** and **brainstem**.

ADDICTION AND HUMAN BRAIN …



This stage involves the processing of conditioned reinforcement in the **BLA** and the processing of contextual information by the **hippocampus**. Executive control depends on the **prefrontal cortex** and includes subjective states (ie, craving and, presumably, feelings) associated with drugs.

DOES EVERYBODY BECOME ADDICTED TO DRUGS?

GENETICS matters ….

- Genes either increase risk or are protective

  Htrlb receptor gene absence greater attraction to cocaine and alcohol

  Curl receptor gene presence makes less responsive to morphine

  ALDH*2 if two copies less likely to develop alcoholism

- Persistent drug use leads to gene transcription modification - part of neuroplasticity

“Every form of addiction is bad, no matter whether the narcotic be alcohol, morphine or idealism.”

Thank You