Drug addiction and Epigenetic

What is Addiction? AS a Disease

"Chronically relapsing disorder that is characterized by 3 major elements:

I) Compulsion to seek and take the drug

II) Loss of control in limiting intake

III) Emergence of a negative emotional state when access to drug is prevented"

Kinds of Addiction?

- • Heroin addiction
- • Cocaine addiction
- • Alcohol addiction (“alcoholism”)
- • Marijuana addiction
- • Amphetamines addiction
- • Nicotine addiction

Other Kinds of addiction?

- • Sex addiction??
- • Gambling addiction??
- • Food addiction??
- • Shopping addiction????
- • Internet addiction????
- • Cell phone addiction????

Drug Abuse and Addiction are Among the Most Serious Public HealthProblems Facing Our Society

- and Frequently Coexist with Other Mental and Physical Disorders

Factors initiated Drug Abuse

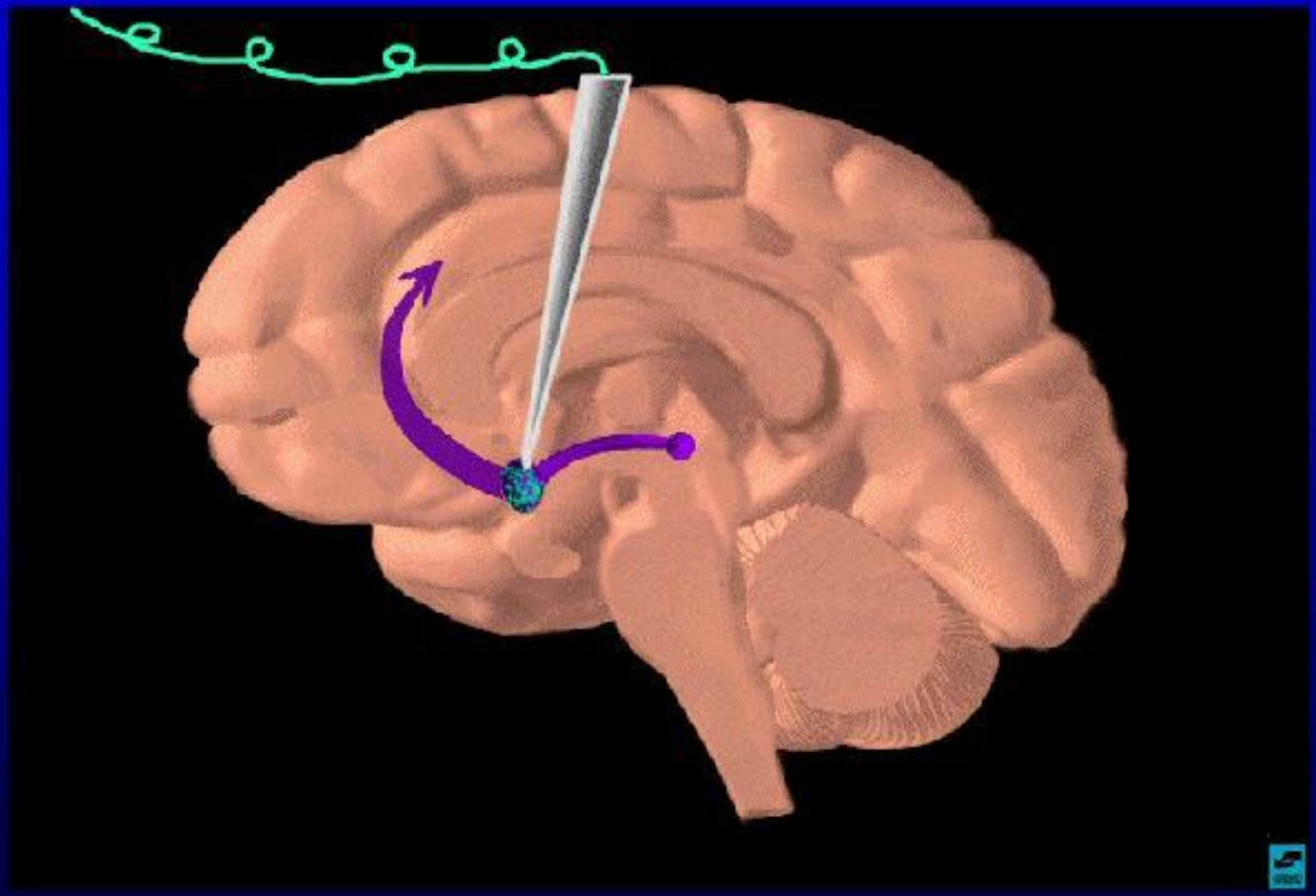
- **Reward & Pleasure**
- **Diseases (Pain, Depression, Anxiety &….)**
- **Genetic**

REWARD

History

- James Olds (1954)
- Pleasure is a distinct neurobiological function that is linked to a complex reward & reinforcement system
- Biochemical & Biological studies

James Olds (1954)



Drug Reward

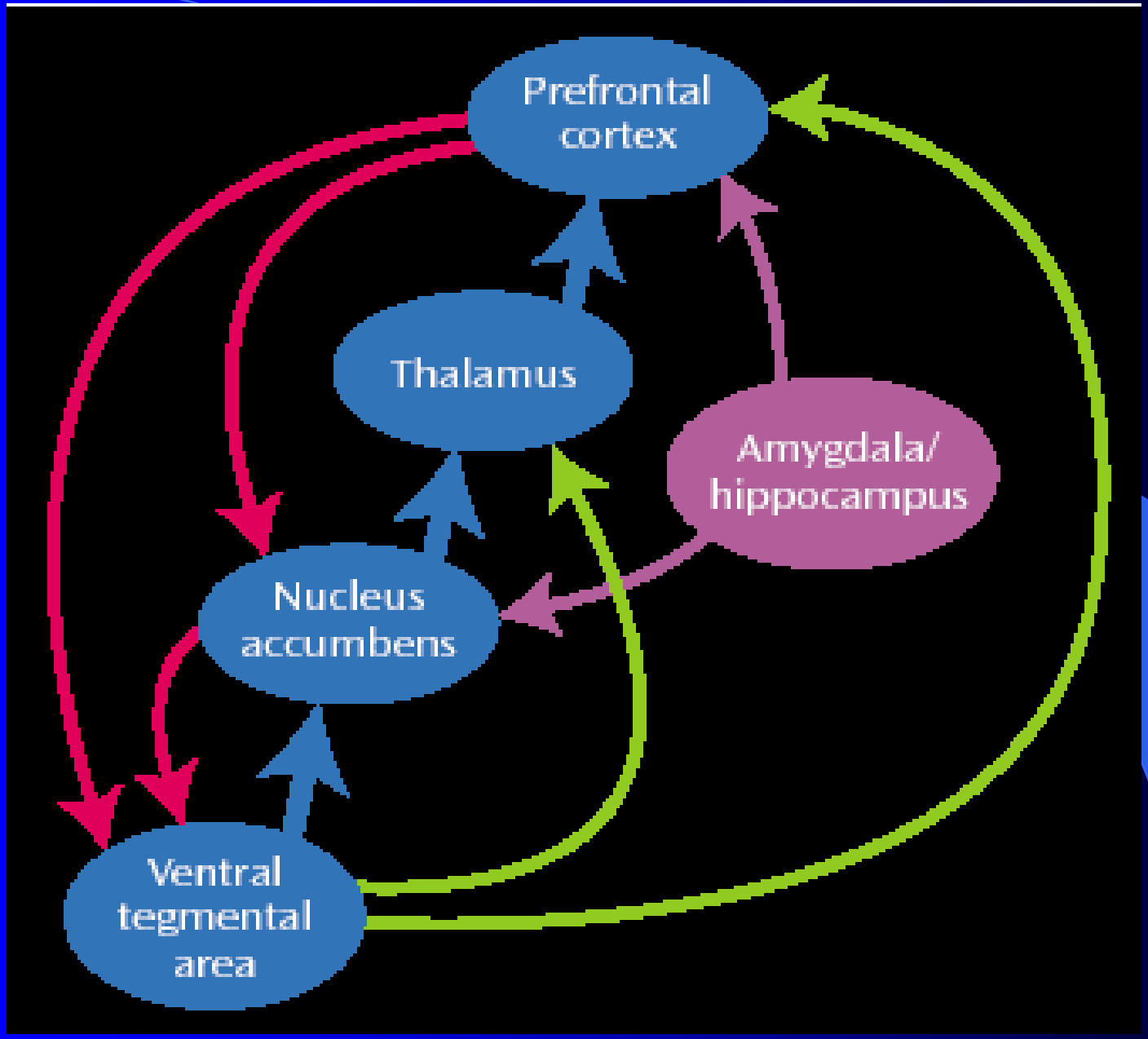
- **Reward: A response to a stimulus which causes pleasure; natural reward (food, liquids, sex) as well as electrical stimulation and many drugs**
- **Reinforcement: Continuing an action which has been shown reward previously**

Systems involves in biology of REWARD

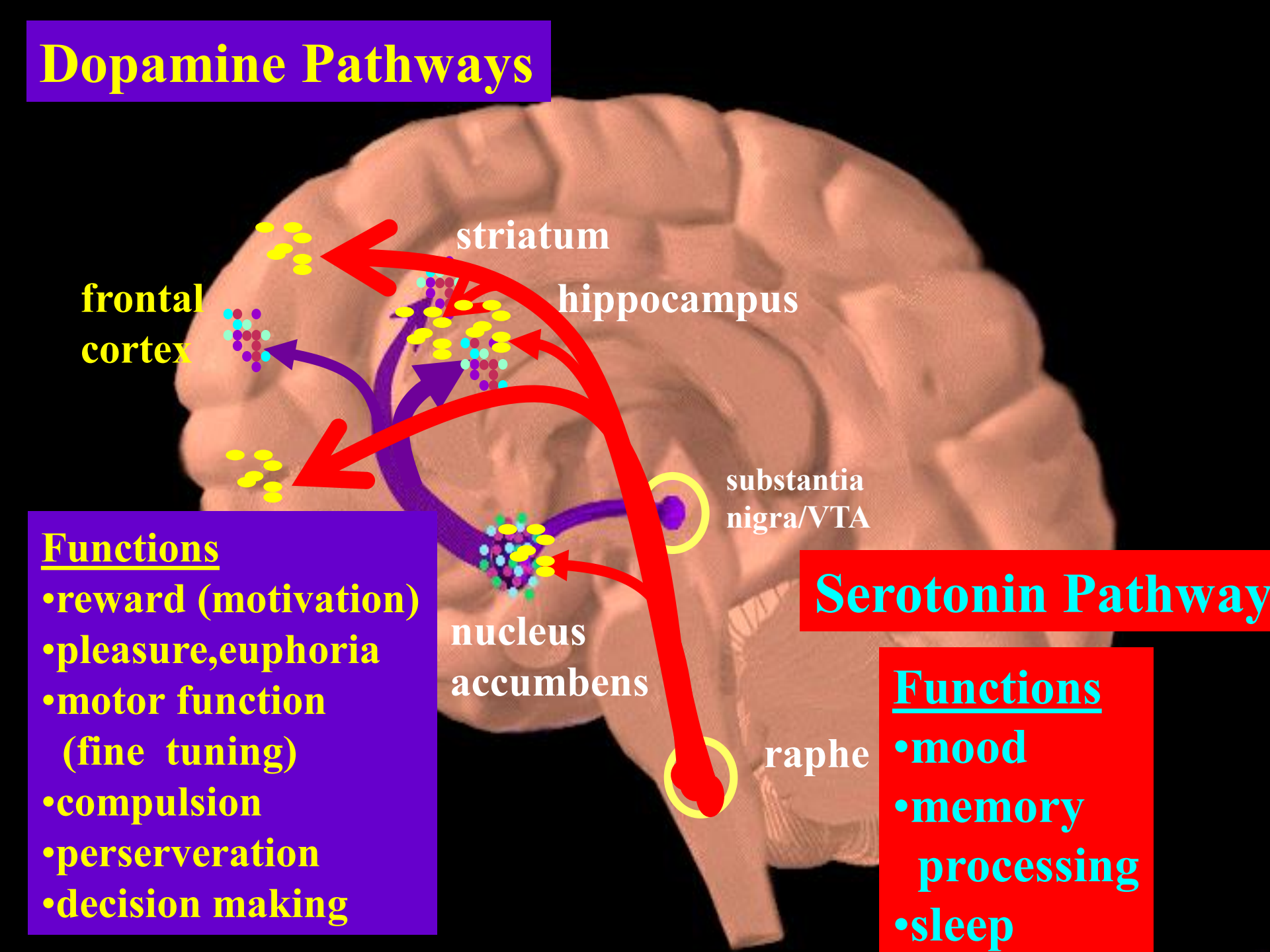
- Serotonin in Hypothalamus
- Enkephalins (opioid peptide) in VTA & Nucleus accumbens
- GABA in VTA & Nucleus accumbens
- NE (Release of NE in Hyppocampus from neuronal fibers that originate in the LC)

Importance of Reward

- Reinforcement (Reward) leads to more drug administration
- Which may lead to drug tolerance
- To gain the previous drug effect after tolerance induction, Higher doses of drug is needed which may cause dependence


Prefrontal cortex
Thalamus
Amygdala/ hippocampus
Nucleus accumbens
Ventral tegmental area

Dopamine Pathways



Functions

- reward (motivation)
- pleasure,euphoria
- motor function (fine tuning)
- compulsion
- perserveration
- decision making

Serotonin Pathway

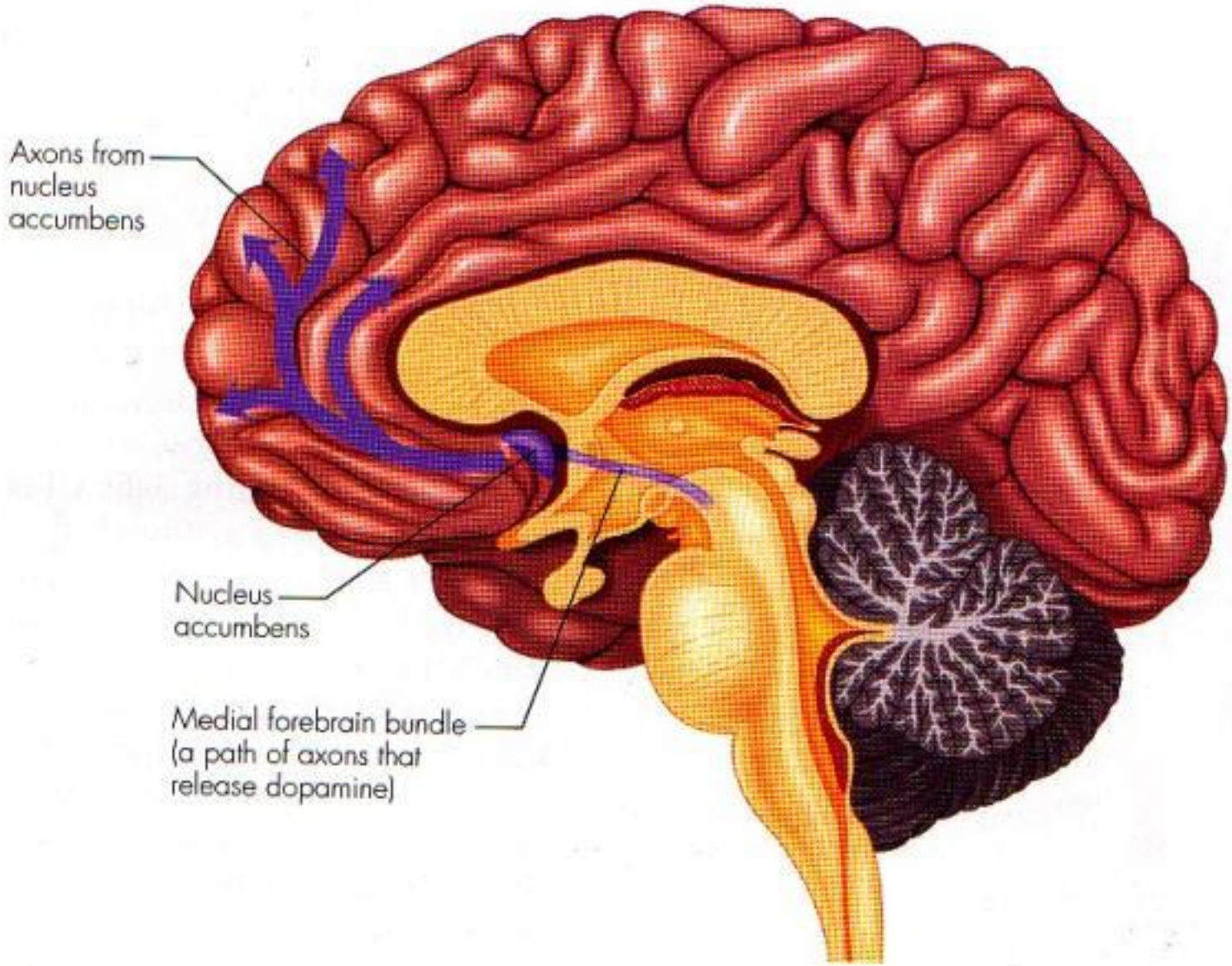
Functions

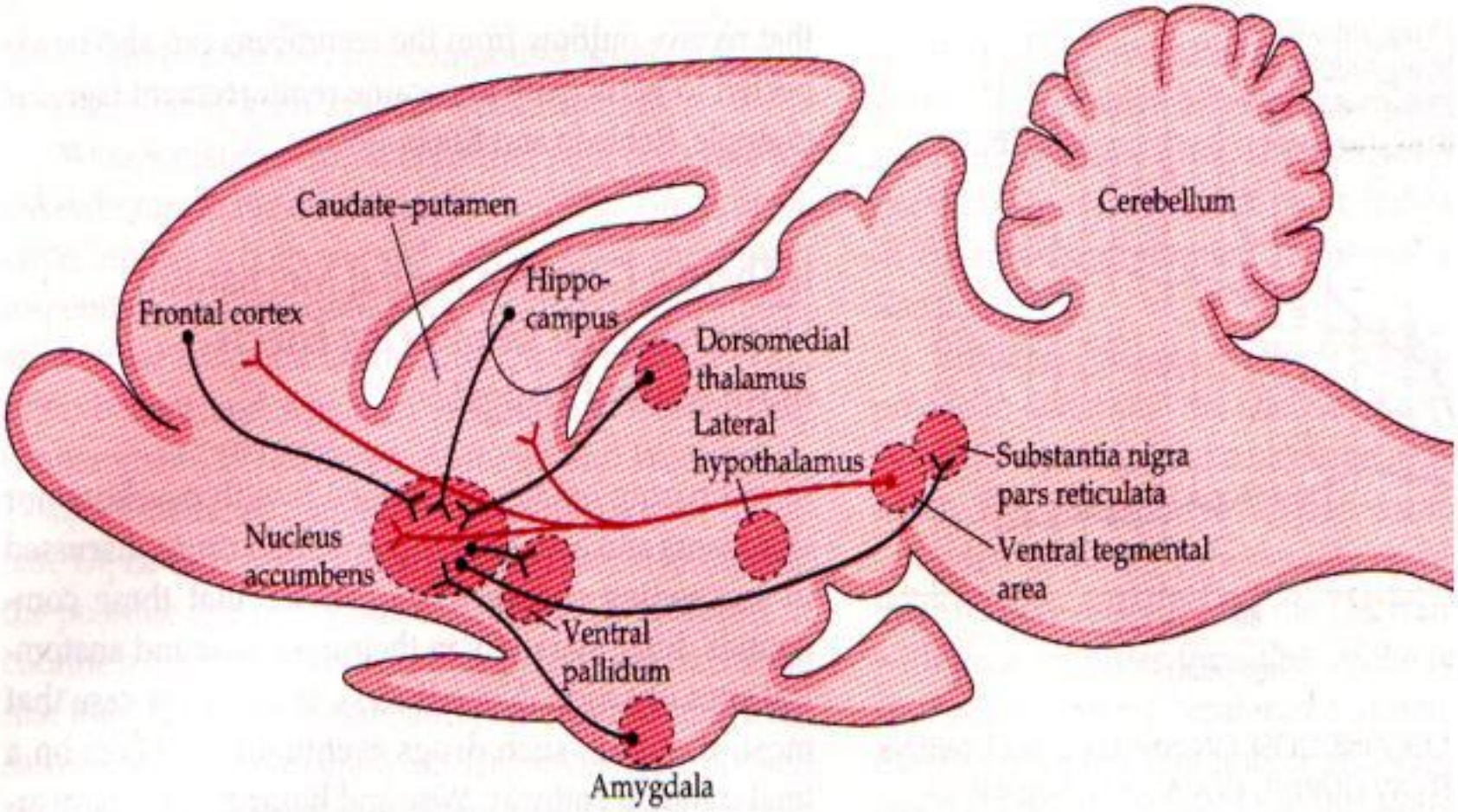
- mood
- memory processing
- sleep

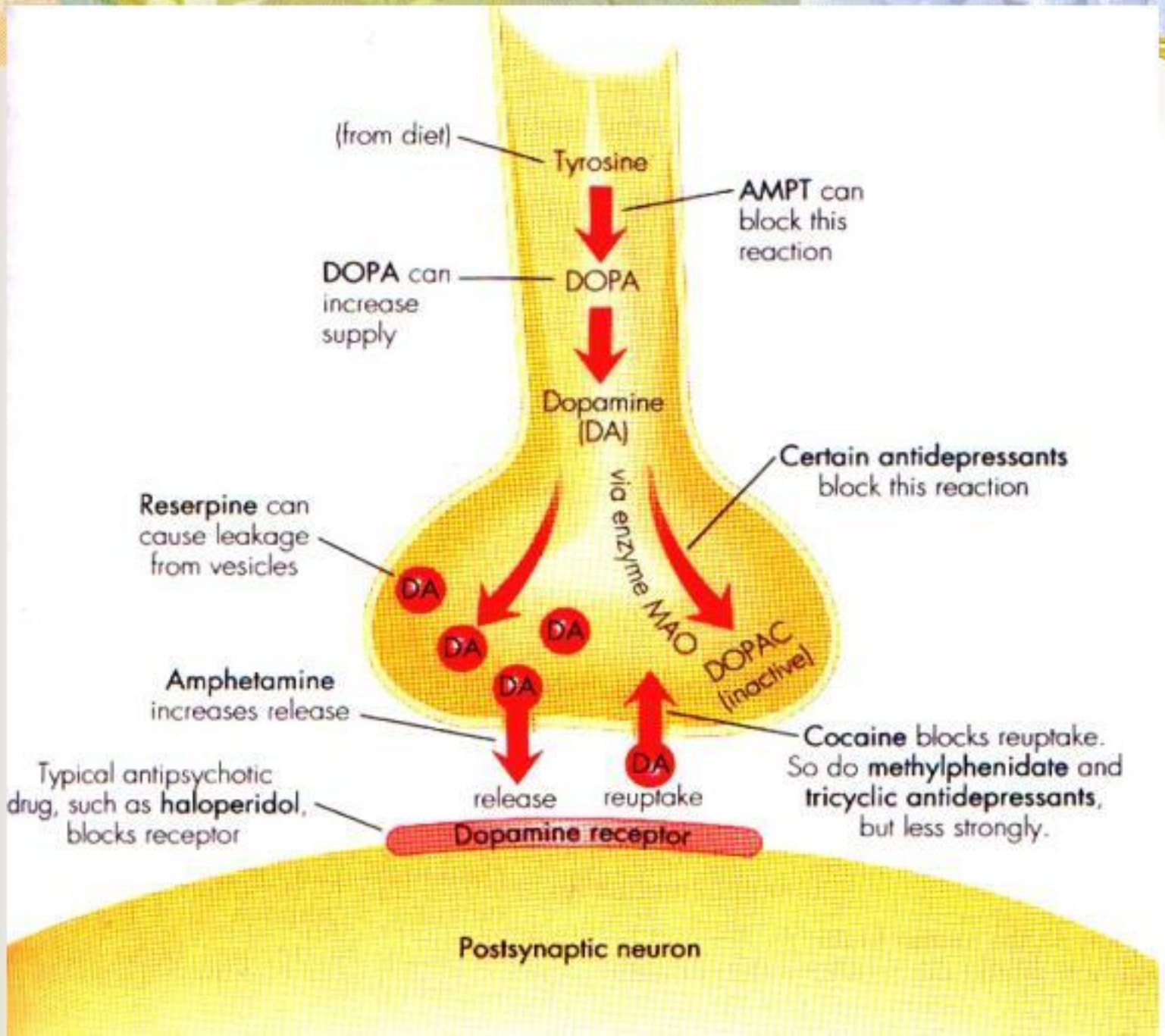
Dopaminergic System

Is

the final common pathway


Axons from nucleus accumbens
Nucleus accumbens
Medial forebrain bundle (a path of axons that release dopamine)


Caudate–putamen
Cerebellum
Hippo-
campus
Frontal cortex
Dorsomedial
thalamus
Lateral
hypothalamus
Substantia nigra
pars reticulata
Nucleus
accumbens
Ventral tegmental
area
Ventral
pallidum
Amygdala


(from diet)
Tyrosine
AMPT can block this reaction
DOPA can increase supply
DOPA
Dopamine (DA)
Certain antidepressants block this reaction
Reserpine can cause leakage from vesicles
via enzyme MAO
DA
DA
DA
DA
DOPAC (inactive)
Amphetamine increases release
Cocaine blocks reuptake. So do methylphenidate and tricyclic antidepressants, but less strongly.
Typical antipsychotic drug, such as haloperidol, blocks receptor
release
reuptake
Dopamine receptor
Postsynaptic neuron

Dopamine receptors

- D_1 type (D_1 & D_5) increase cAMP
- D_2 type (D_2, D_3 & D_4) decrease cAMP

Reward Pathway

The following neurotransmitters act on the reward pathway:

Dopamine • Receptors: D1, D2 • Function: pleasure, euphoria, mood, motor function	**Serotonin** • Receptors: 5HT3 • Function: mood, impulsivity, anxiety, sleep, cognition
Cannabinoids • Receptors: CB1, CB2 • Function: Pain, appetite, memory	**Opioid peptides (Endorphins, Enkephalins)** • Receptors: Kappa, Mu, Delta • Function: pain

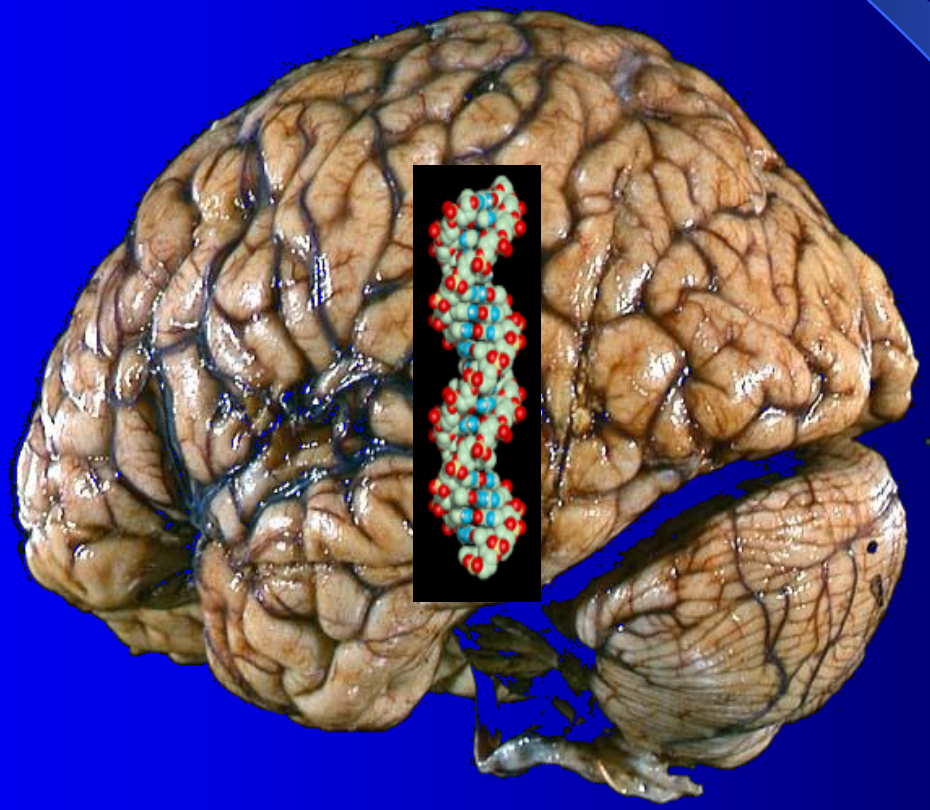
In all rewards, dopamine is the final activation chemical

Reward Pathway

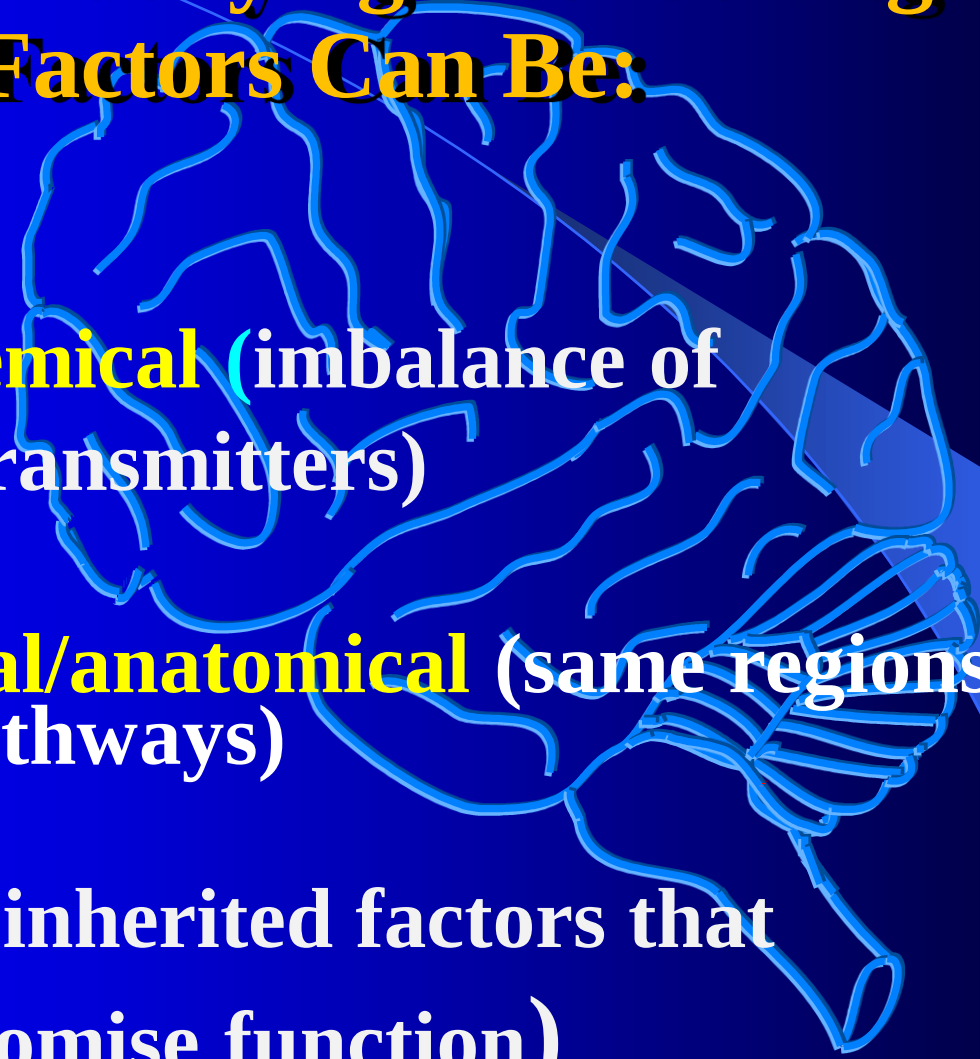
Neurotransmitters and anatomical sites involved in the acute reinforcing effects of drugs of abuse

Dopamine Ventral tegmental area, nucleus accumbens	**Opioid Peptides** Nucleus accumbens, amygdala, ventral tegmental area
GABA Amygdala, bed nucleus of stria terminalis	**Glutamate** Nucleus accumbens

Drug addiction and Epigenetic

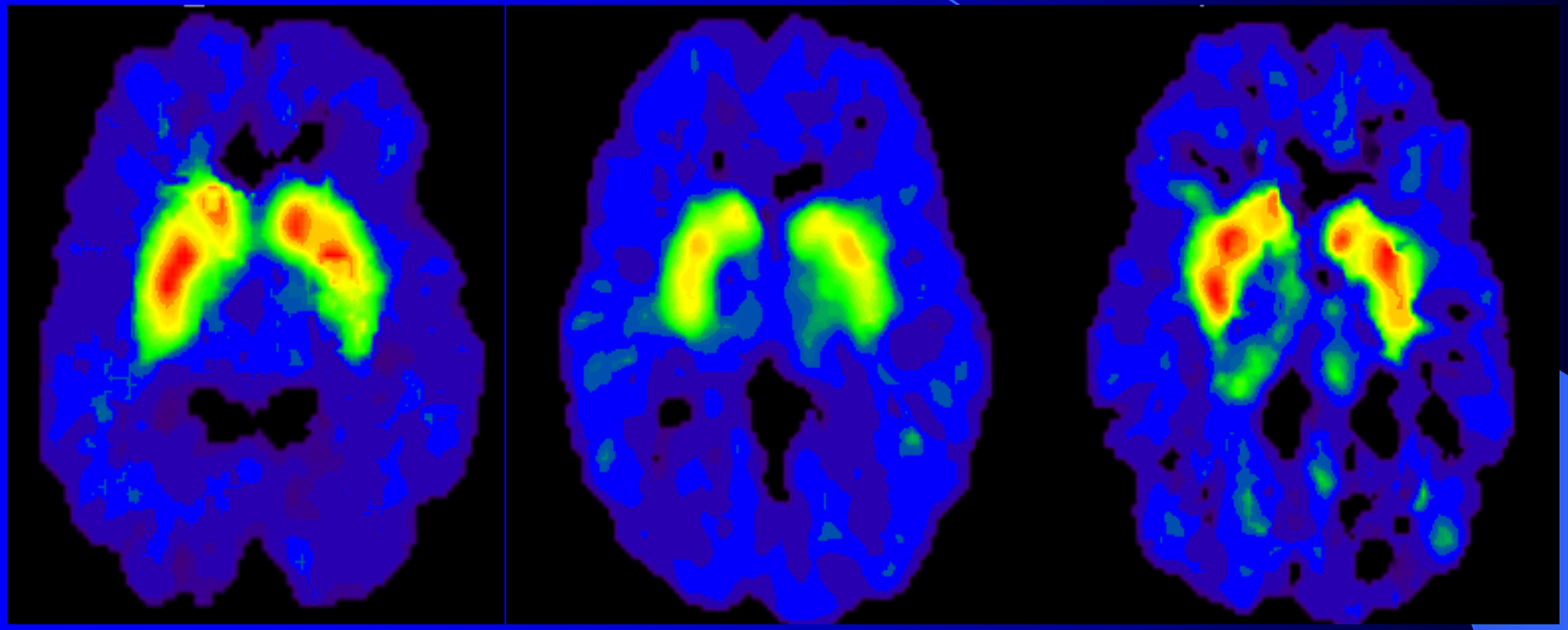


Common Underlying Neurobiological Factors Can Be:



- **Neurochemical** (imbalance of neurotransmitters)
- **Structural/anatomical** (same regions and pathways)
- **Genetic** (inherited factors that compromise function)

Why is Continued Treatment Critical?



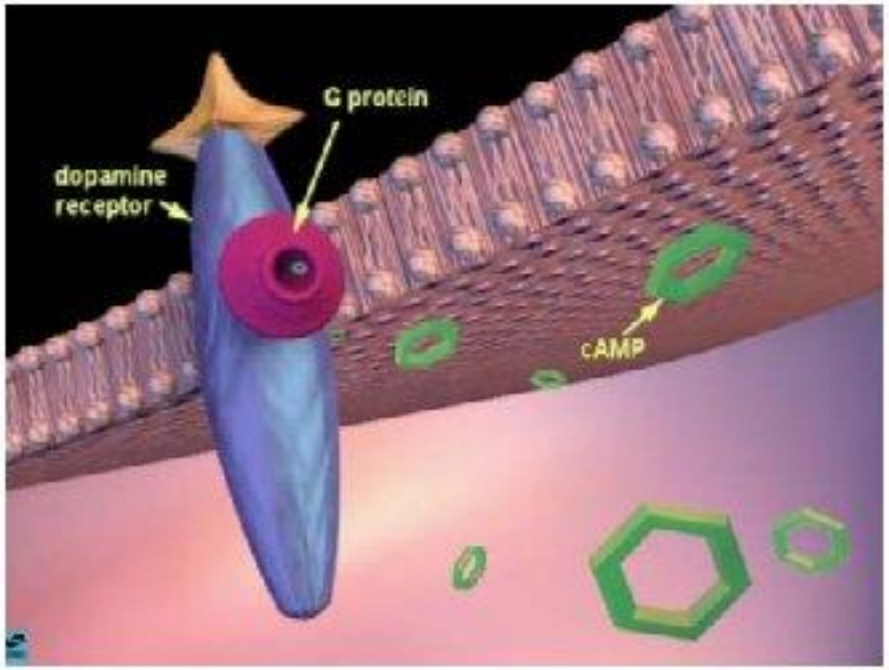
Normal Control

Meth user
(1 month abstinent)

Meth user
(36 months abstinent)

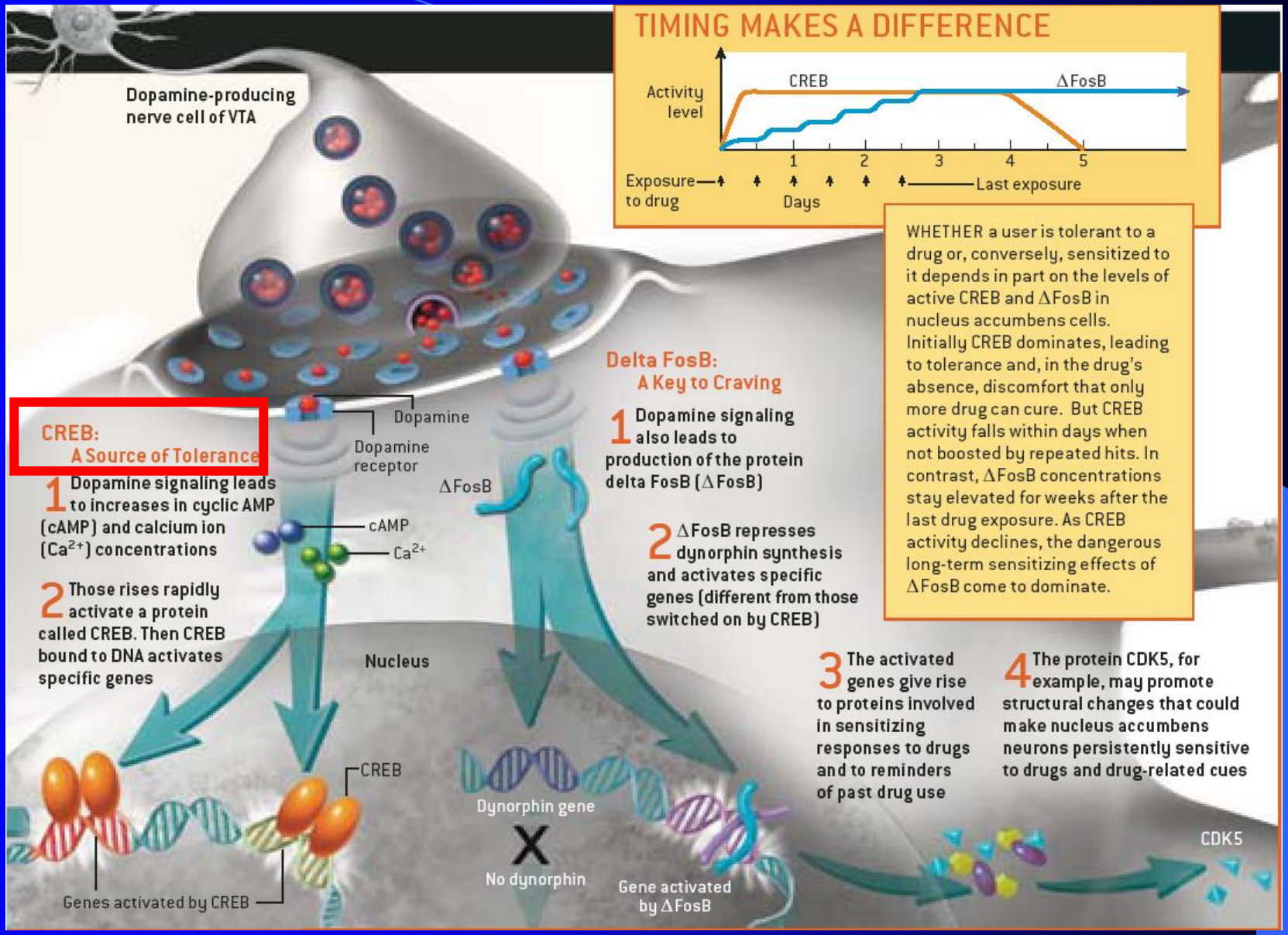
Partial Recovery of Dopamine Transporters After Prolonged Abstinence

Dopamine & cAMP



- activation of dopamine receptors causes
  - **increased** production of **cAMP** inside the post-synaptic cell.
  - many changes inside neuronal cells lead to **abnormal firing** patterns
  - there are **increased impulses** leaving the **nucleus accumbens** to activate the **reward system**

NIDA: www.drugabuse.gov/pubs/Teaching/


TIMING MAKES A DIFFERENCE
Activity level
CREB
ΔFosB
1
2
3
4
5
Exposure to drug
Days
Last exposure
WHETHER a user is tolerant to a drug or, conversely, sensitized to it depends in part on the levels of active CREB and ΔFosB in nucleus accumbens cells. Initially CREB dominates, leading to tolerance and, in the drug's absence, discomfort that only more drug can cure. But CREB activity falls within days when not boosted by repeated hits. In contrast, ΔFosB concentrations stay elevated for weeks after the last drug exposure. As CREB activity declines, the dangerous long-term sensitizing effects of ΔFosB come to dominate.
Dopamine-producing nerve cell of VTA
CREB: A Source of Tolerance
1 Dopamine signaling leads to increases in cyclic AMP (cAMP) and calcium ion (Ca^{2+}) concentrations
2 Those rises rapidly activate a protein called CREB. Then CREB bound to DNA activates specific genes
Dopamine
Dopamine receptor
ΔFosB
cAMP
Ca^{2+}
Nucleus
CREB
Genes activated by CREB
Delta FosB: A Key to Craving
1 Dopamine signaling also leads to production of the protein delta FosB (ΔFosB)
2 ΔFosB represses dynorphin synthesis and activates specific genes (different from those switched on by CREB)
Dynorphin gene
X
No dynorphin
Gene activated by ΔFosB
3 The activated genes give rise to proteins involved in sensitizing responses to drugs and to reminders of past drug use
4 The protein CDK5, for example, may promote structural changes that could make nucleus accumbens neurons persistently sensitive to drugs and drug-related cues
CDK5

Common Molecular Changes Associated with Dependence

- **Dopamine D-2 receptor binding**

  decreased in human imaging studies in dependent subjects

- **CREB (cyclic adenosine monophosphate response element binding protein) transcription factor**

  decreased in nucleus accumbens and extended amygdala during the development of dependence

- **Delta-FosB transcription factor**

  changed during protracted abstinence to drugs of abuse

Definition

Drug Addiction can be viewed as a stable form of drug-induced neural plasticity, whereby long-lasting changes in gen expression mediate some of the stable behavioral abnormalities that define an addicted state.

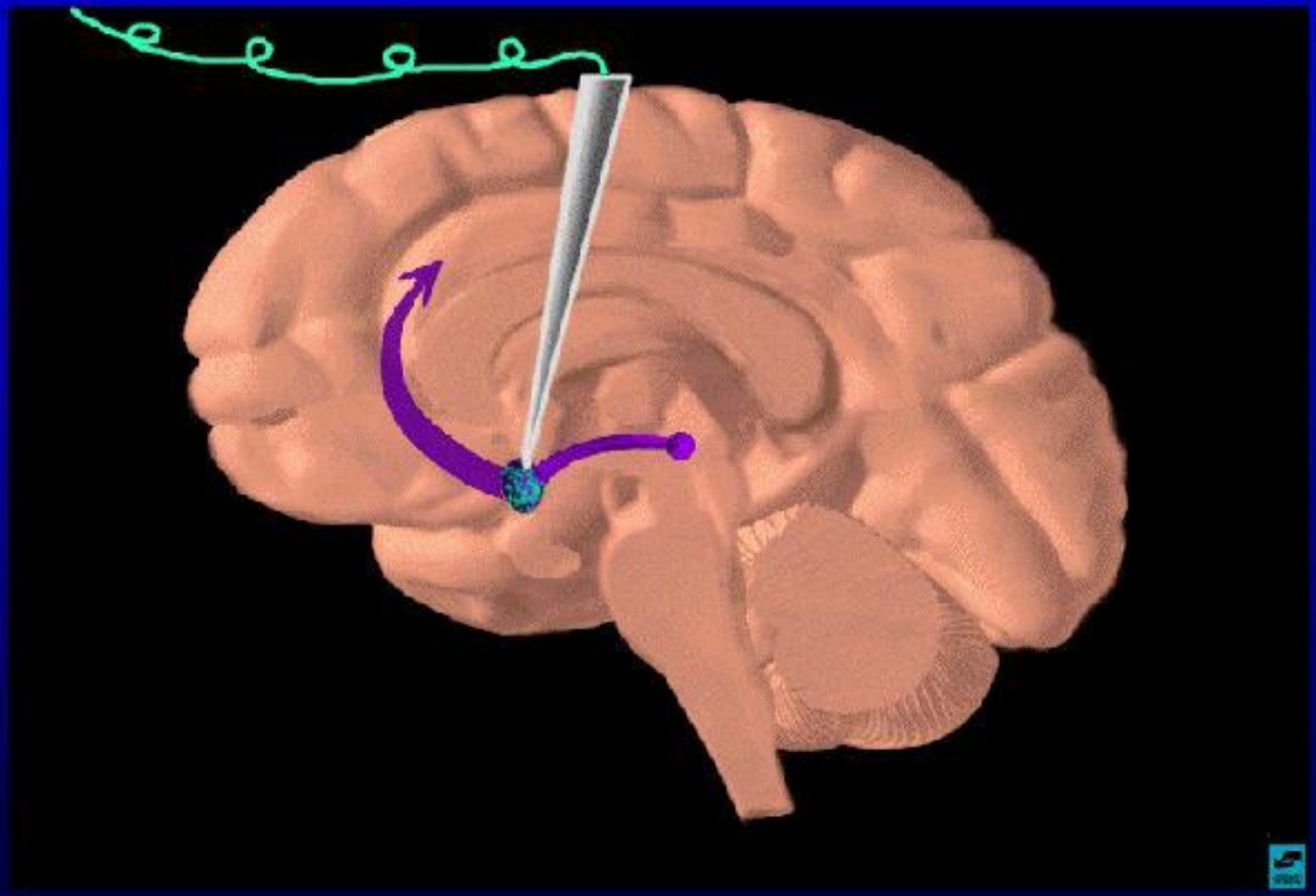
Epigenetic is interactions between genes and the environment that result in specific biological phenotypes.

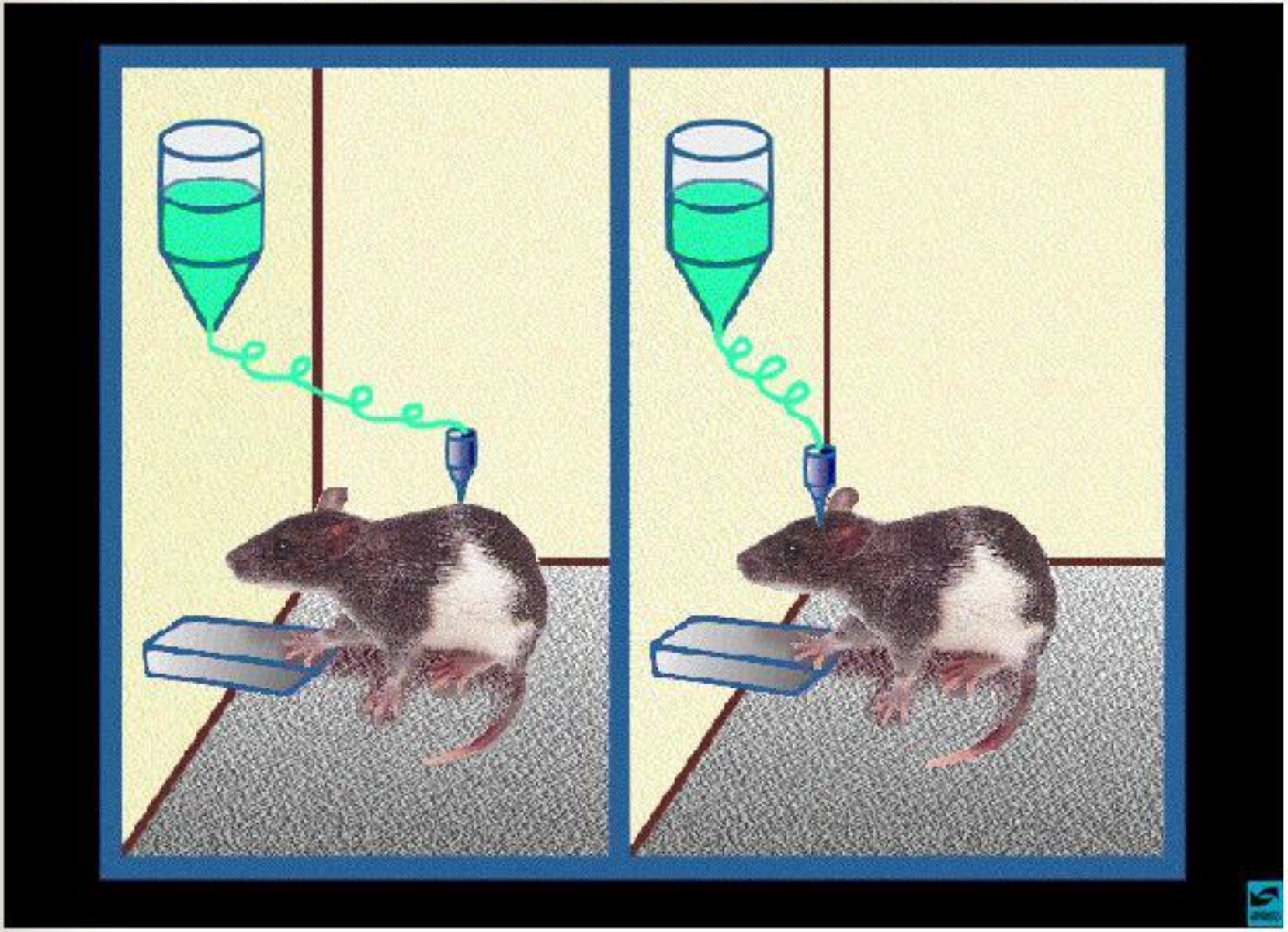
Animal Models

(Based on Conditioning)

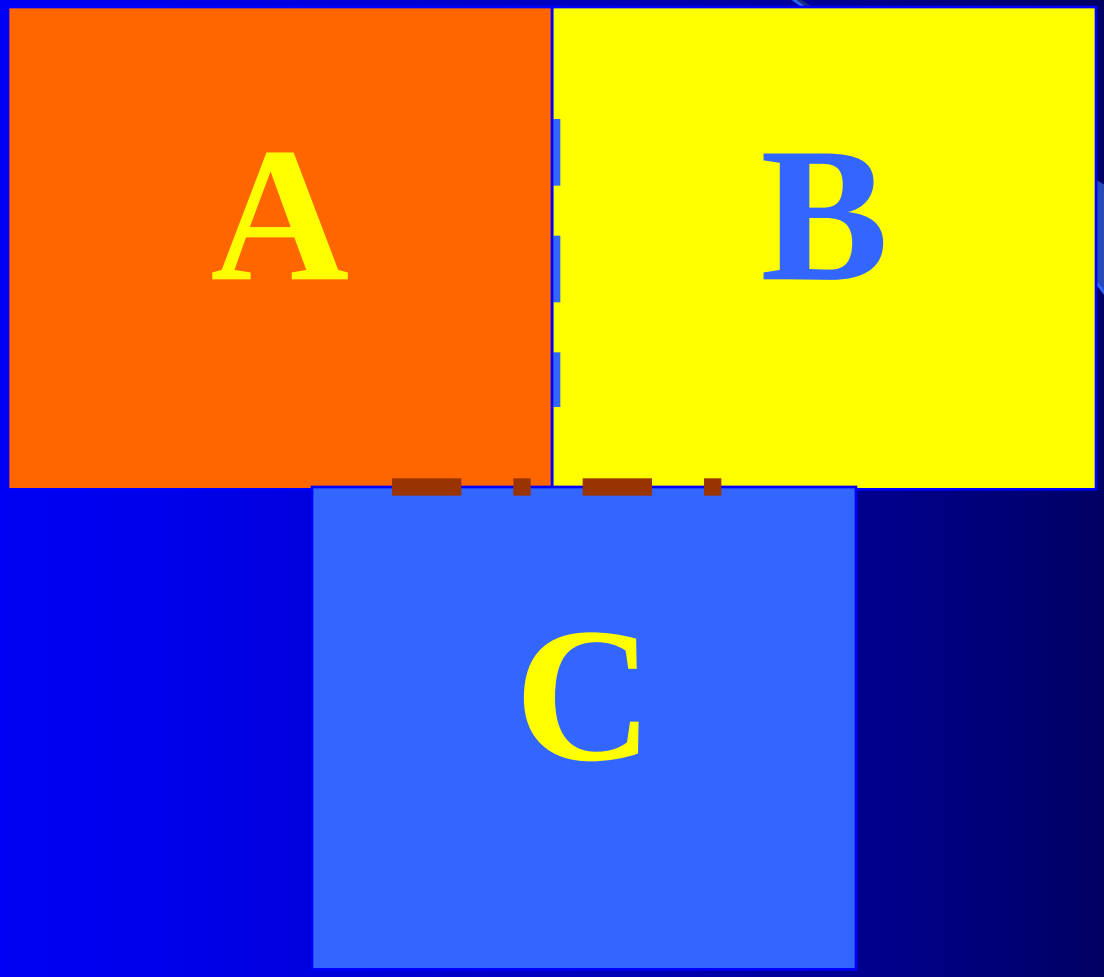
- Intracranial Self-stimulation
- Drug Self-administration
- Conditioning Place Preference

James Olds (1954)

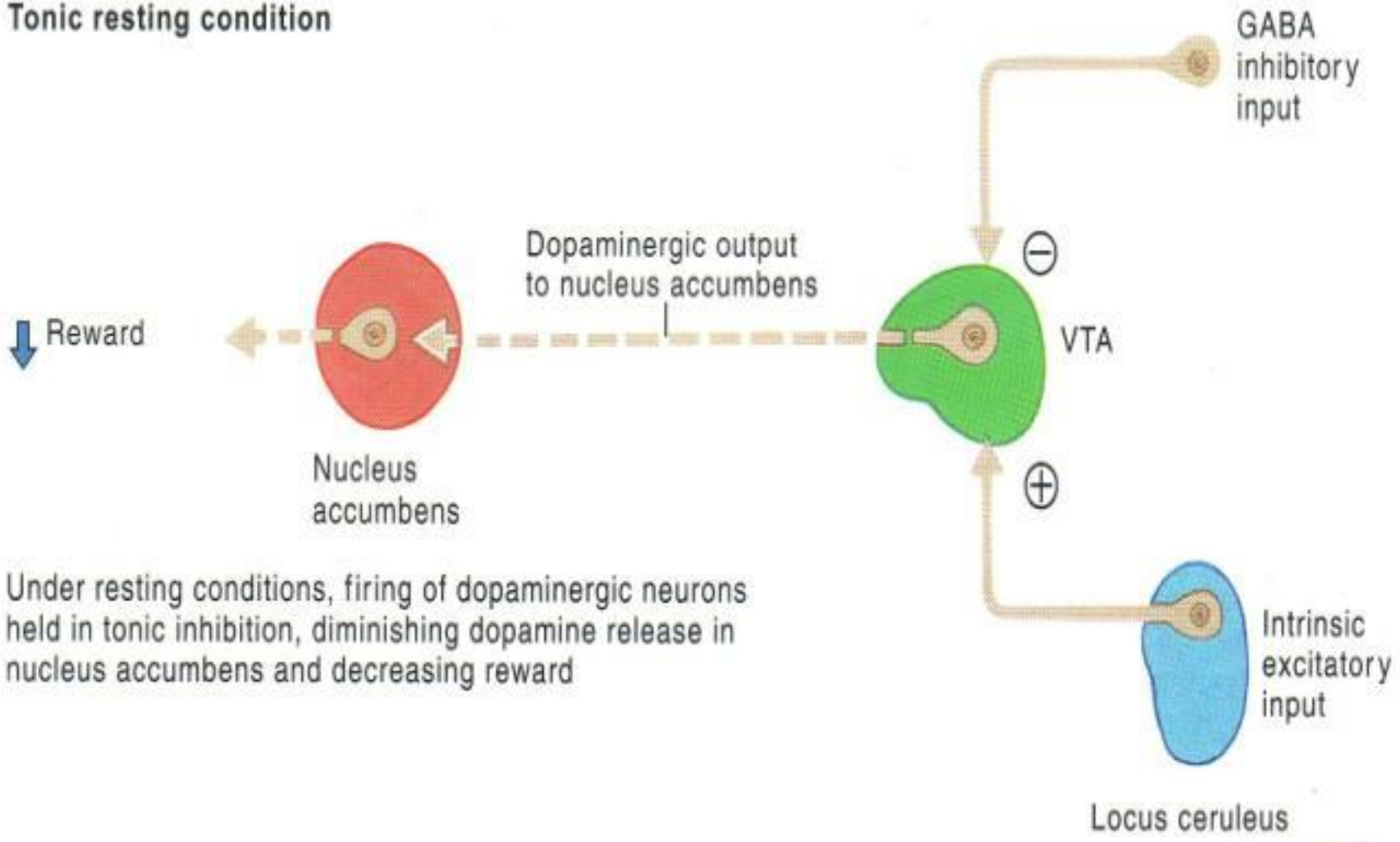




CPP Apparatus

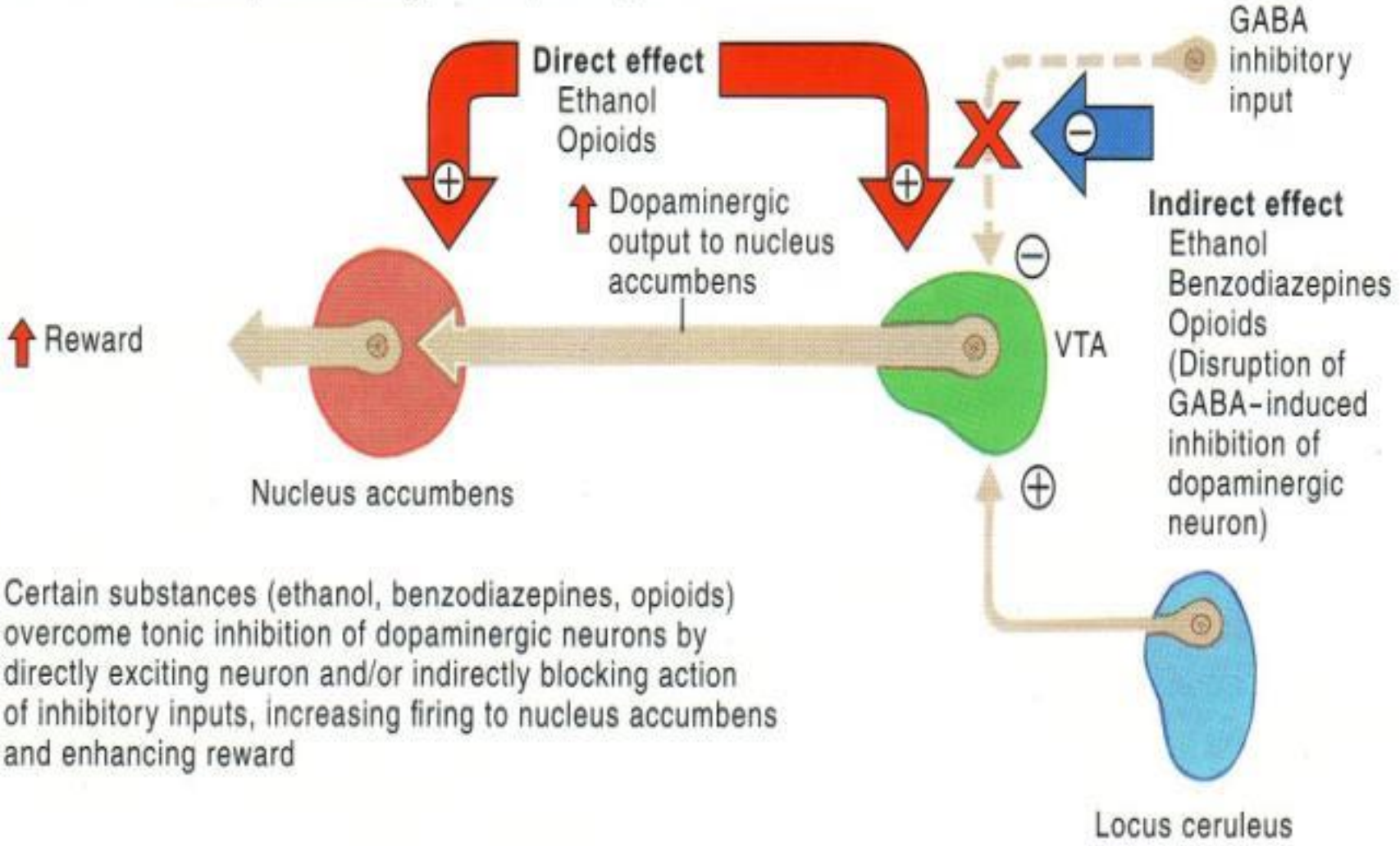


Drug Action Mechanisms in Brain Reward Circuit



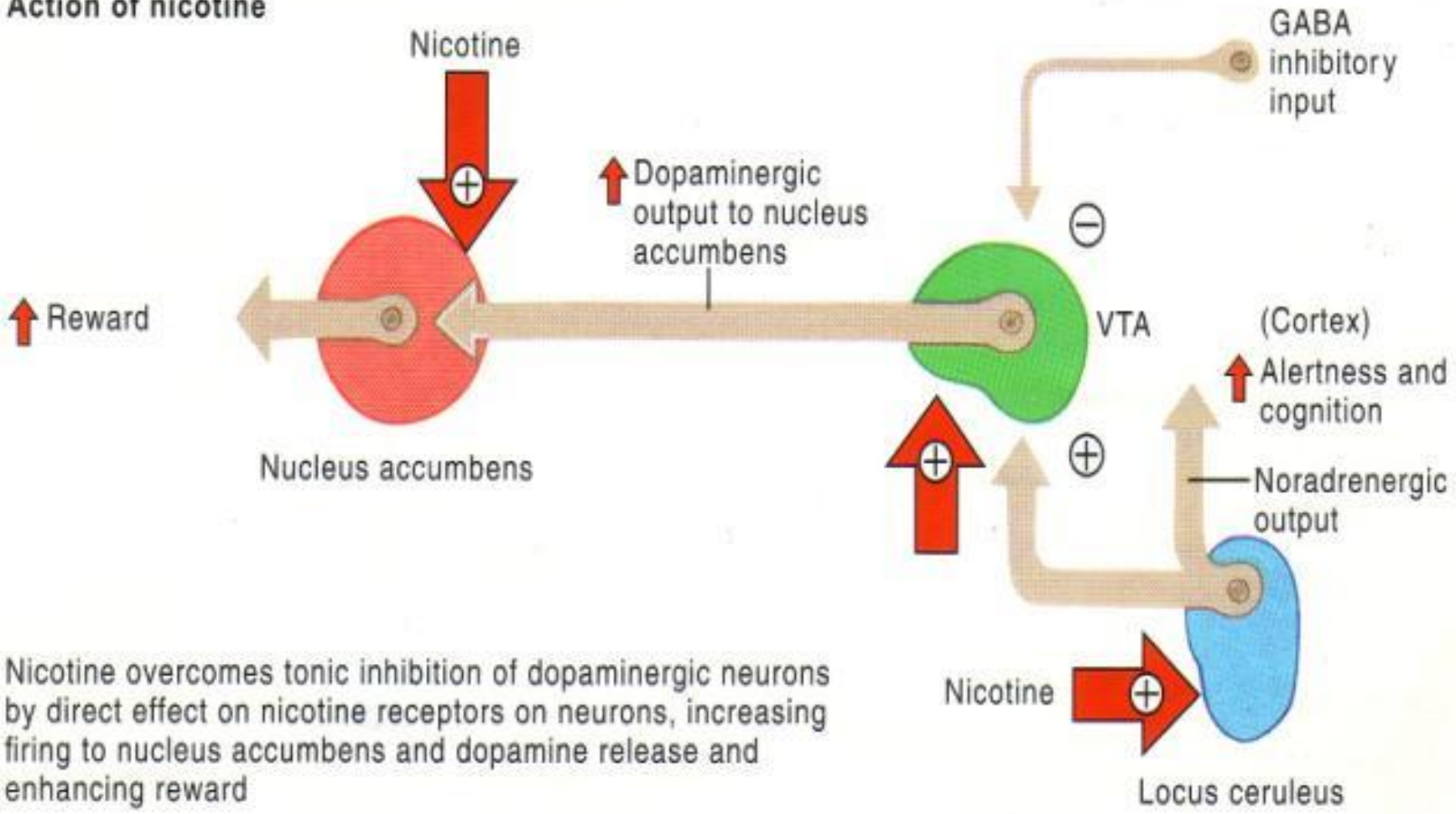
Under resting conditions, firing of dopaminergic neurons held in tonic inhibition, diminishing dopamine release in nucleus accumbens and decreasing reward

Action of alcohol, sedative/hypnotics, and opioids



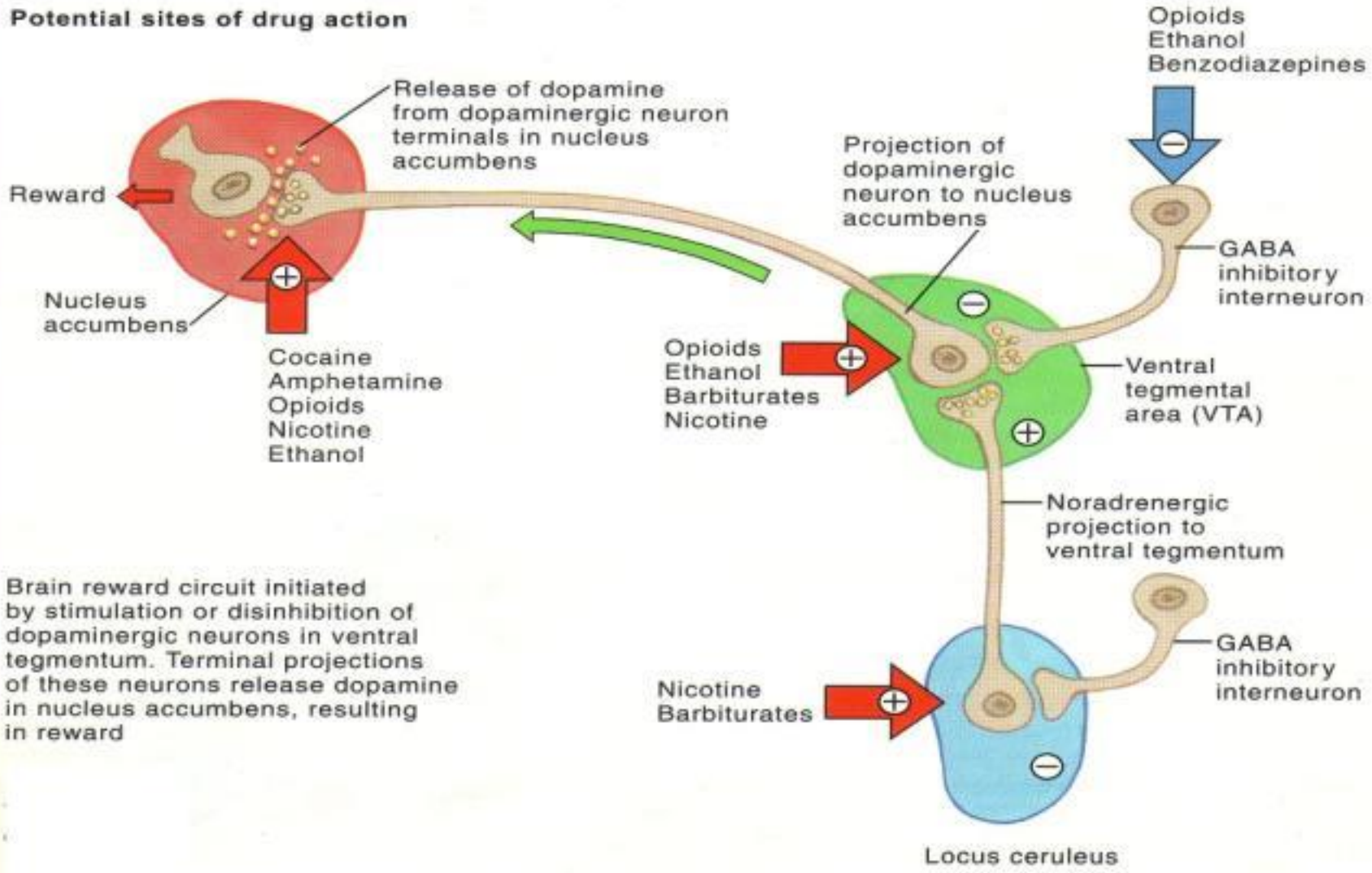
Certain substances (ethanol, benzodiazepines, opioids) overcome tonic inhibition of dopaminergic neurons by directly exciting neuron and/or indirectly blocking action of inhibitory inputs, increasing firing to nucleus accumbens and enhancing reward

Action of nicotine



Nicotine overcomes tonic inhibition of dopaminergic neurons by direct effect on nicotine receptors on neurons, increasing firing to nucleus accumbens and dopamine release and enhancing reward

Potential sites of drug action



Brain reward circuit initiated by stimulation or disinhibition of dopaminergic neurons in ventral tegmentum. Terminal projections of these neurons release dopamine in nucleus accumbens, resulting in reward