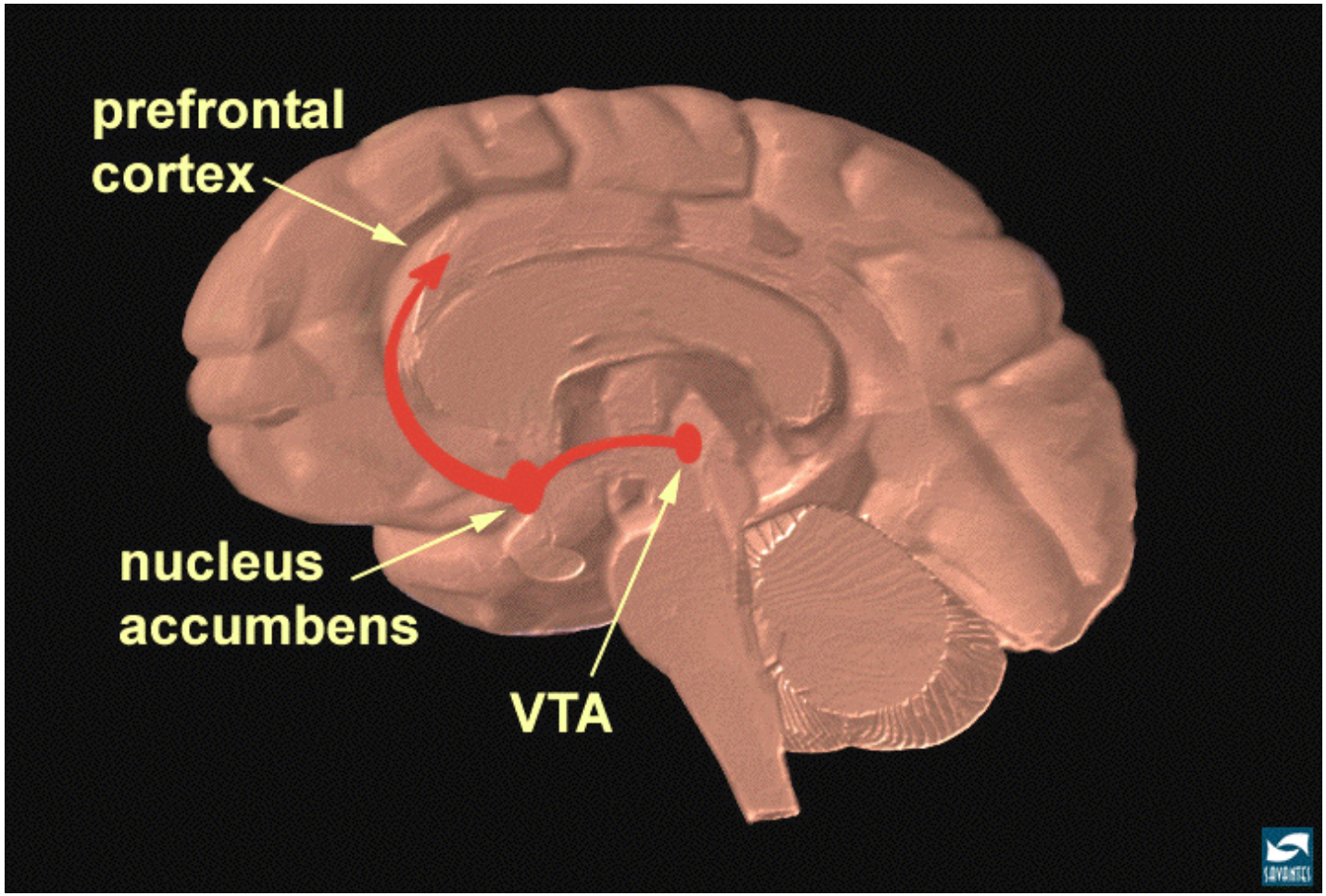
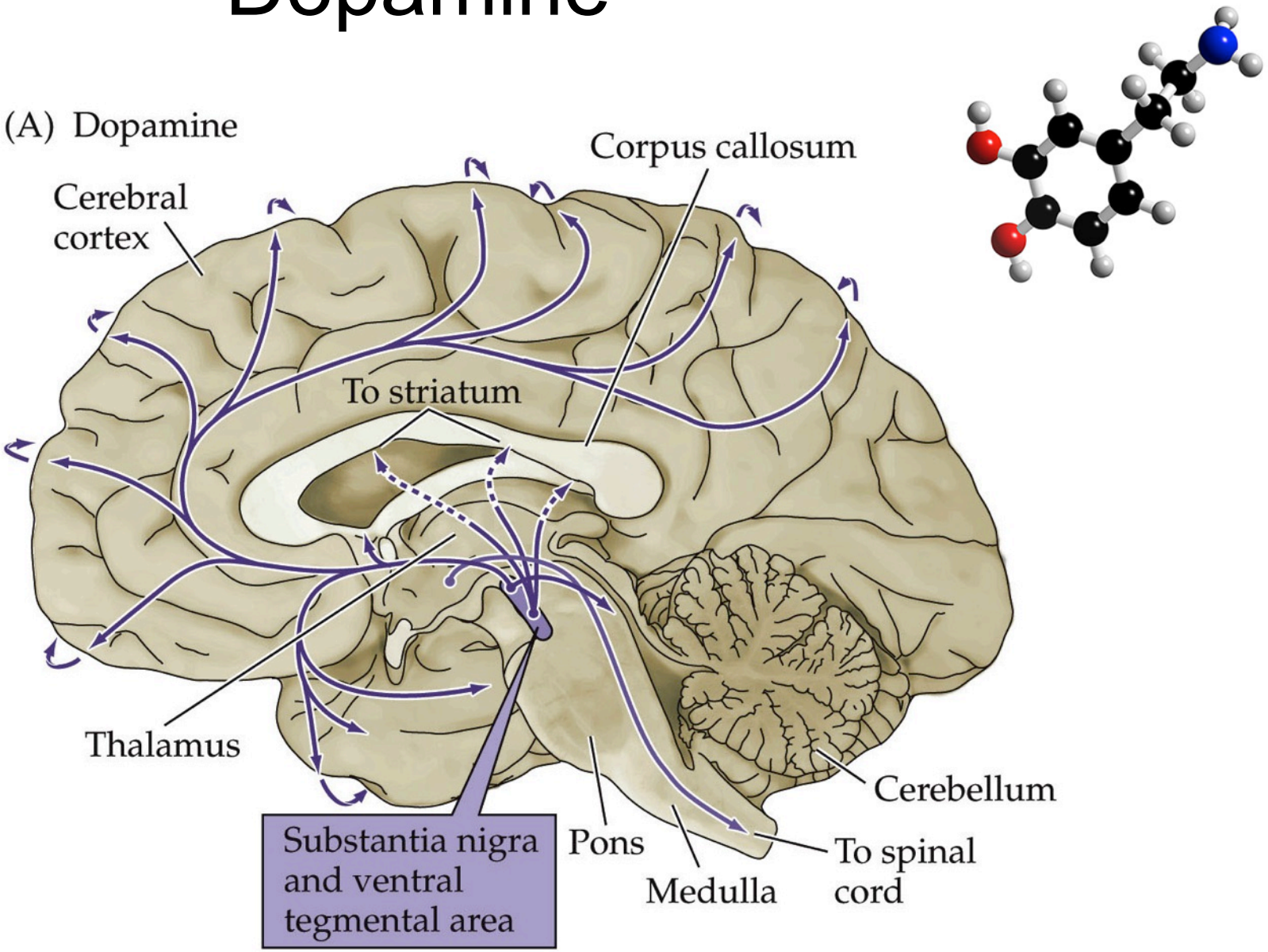
Reward and Learning

The reward pathway



Dopamine



NEUROSCIENCE, Fourth Edition, Figure 6.11 (Part 1)

Neurobiology of Addiction

Degrees of Substance Use

- Occasional, controlled, or social use
- Abuse or harmful use
- Addiction

Drug Addiction

A chronic relapsing syndrome that moves from an impulse control disorder involving positive reinforcement to a compulsive disorder involving negative reinforcement

Why do people use?

- Feel Good (Sensation Seeking)
- Feel Better (Self Medication)

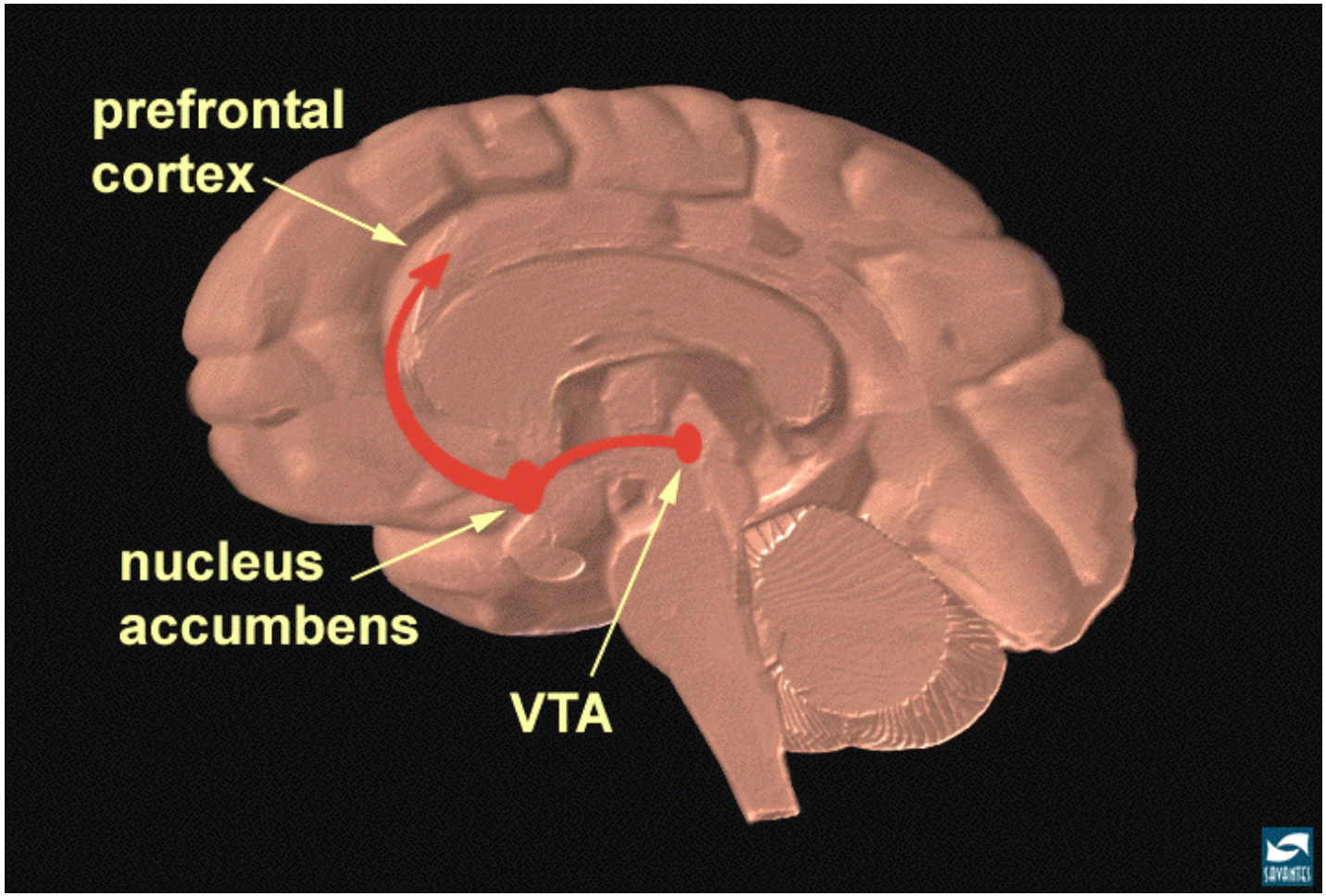
What is driving addiction?

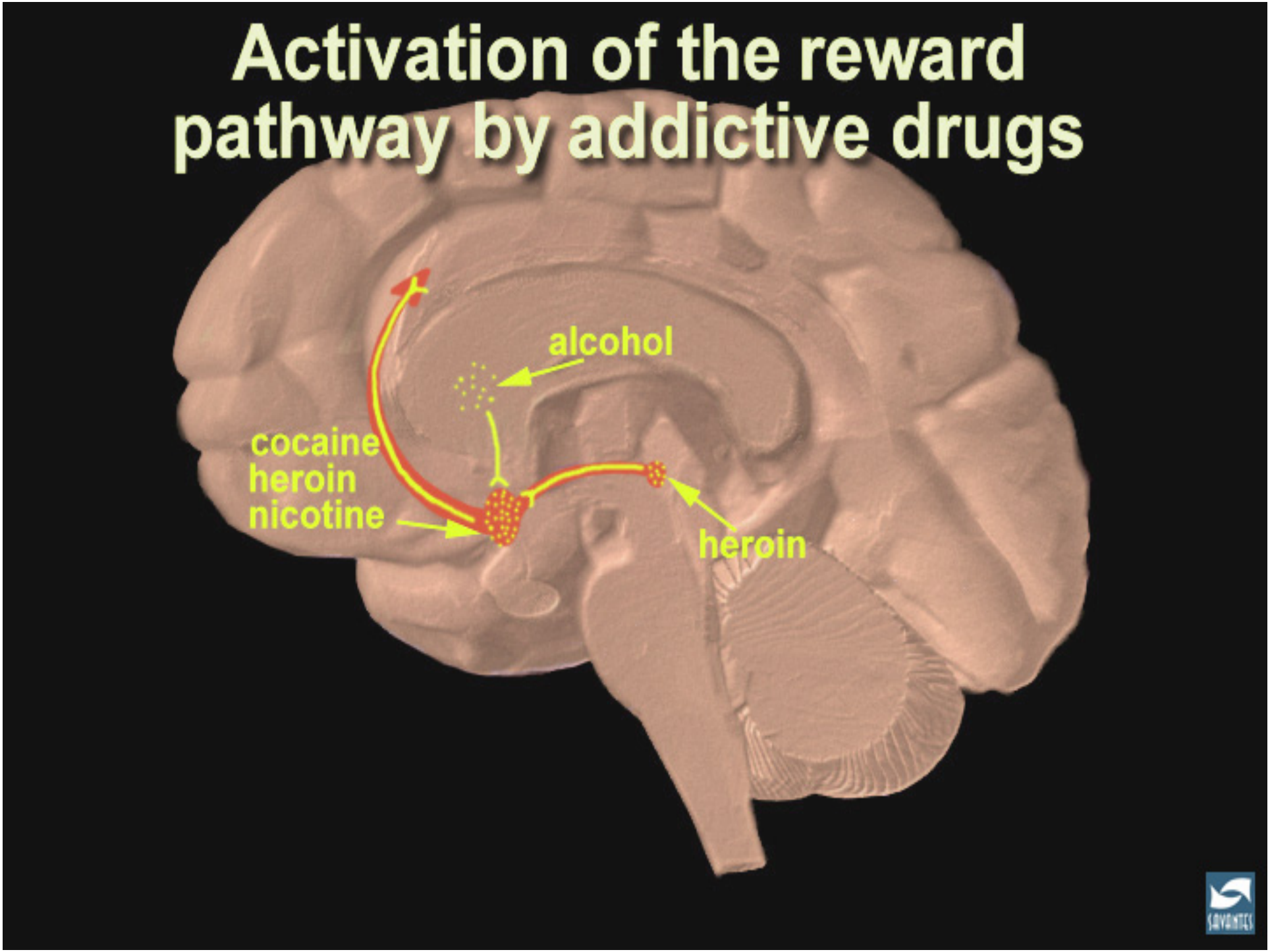
- Positive Reinforcement - rewards that strengthen a conditioned response after it has occurred, such as the feeling of euphoria after taking a hit

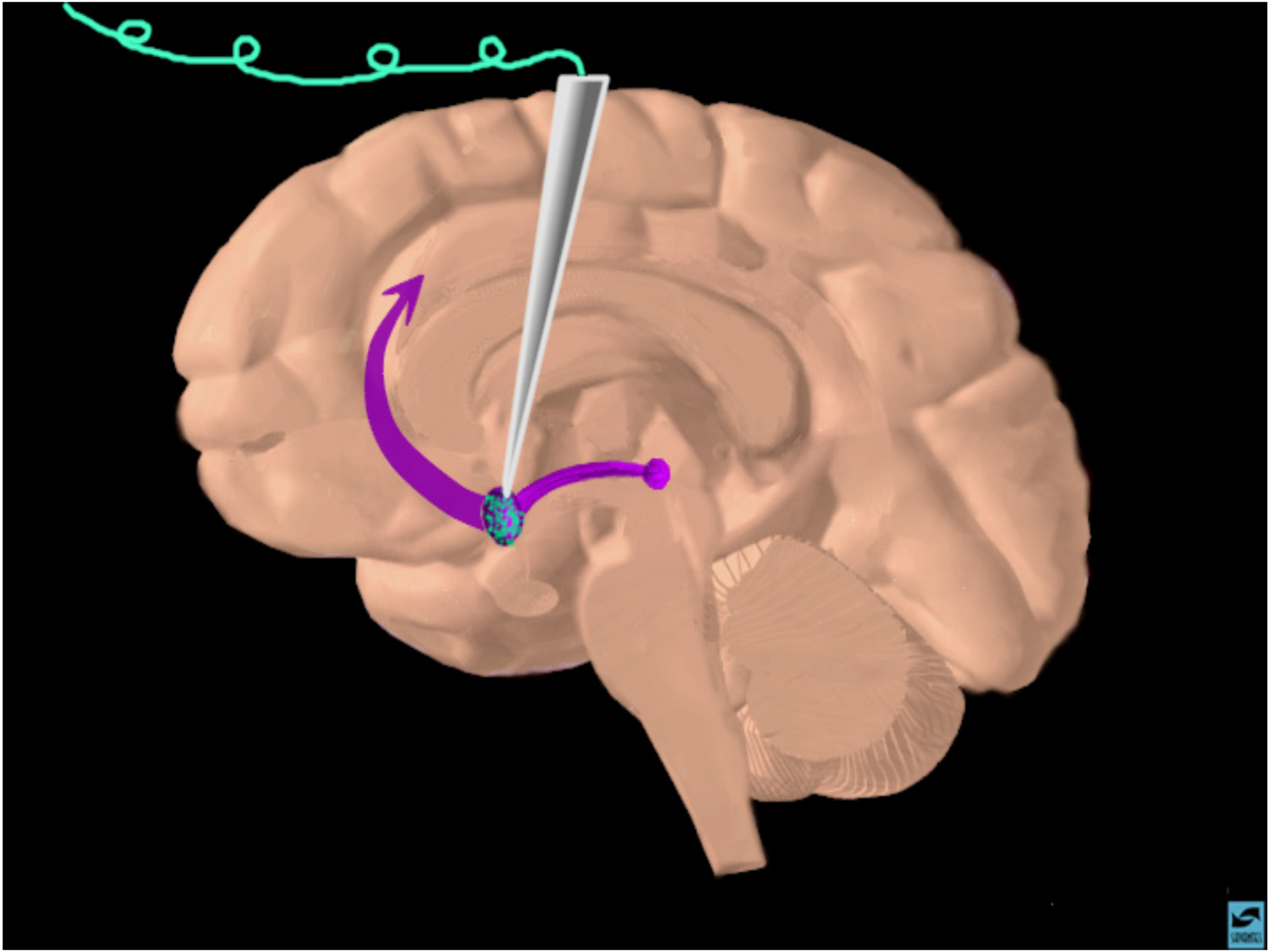
- Negative Reinforcement – stimuli (e.g., stress) that are removed when the desired response (e.g., drug use) has been obtained
  - Escape conditioning - learning to escape an unpleasant or aversive stimulus (using drugs to reduce stress)
  - Avoidance conditioning – Learning to avoid an aversive stimulus (e.g., stress) before it occurs (e.g., using drugs before going to a stressful mtg)

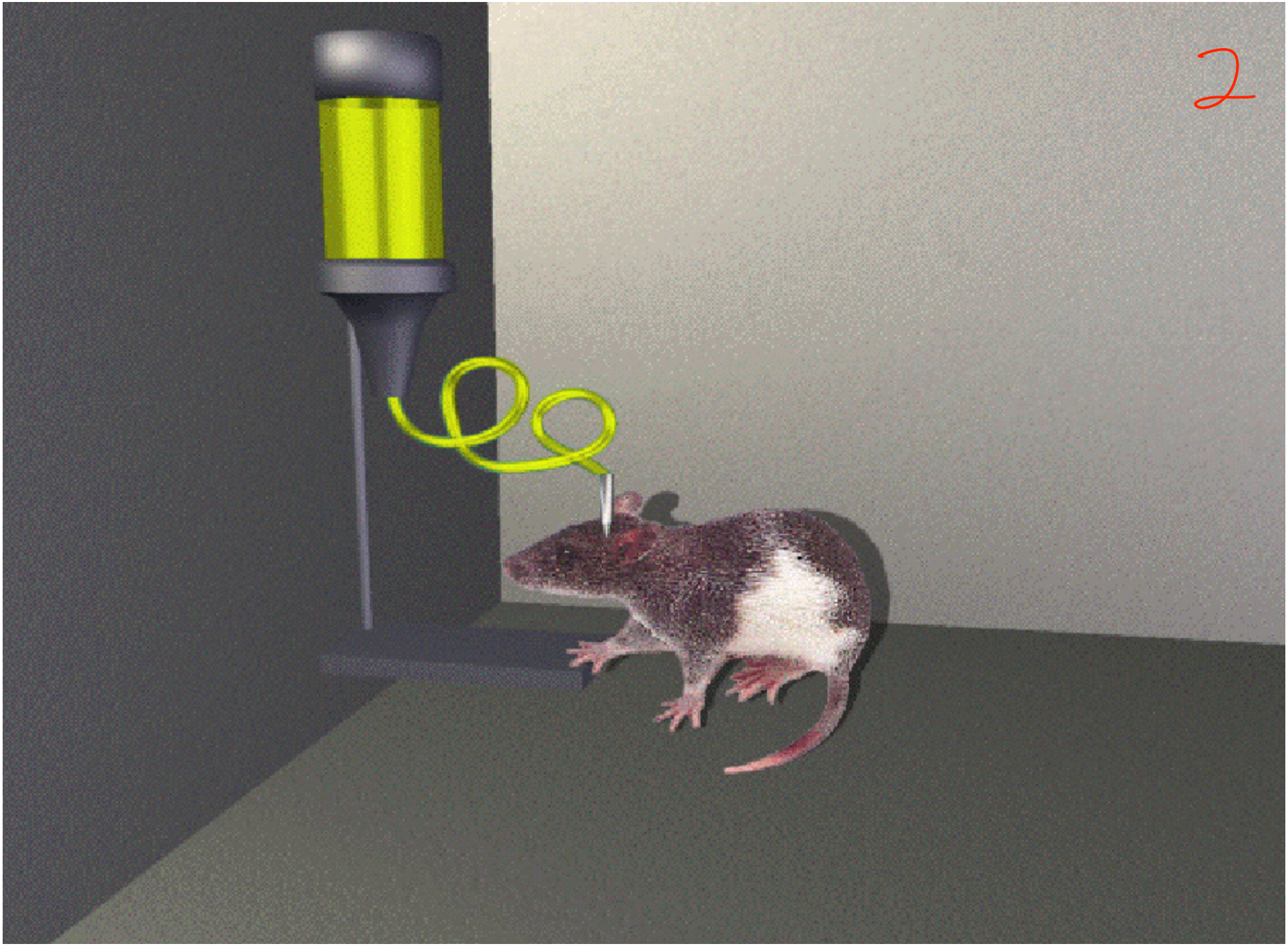
A Major Reason People Take a Drug is They Like What it Does to Their Brains

The reward pathway




Activation of the reward pathway by addictive drugs
alcohol
cocaine
heroin
nicotine
heroin



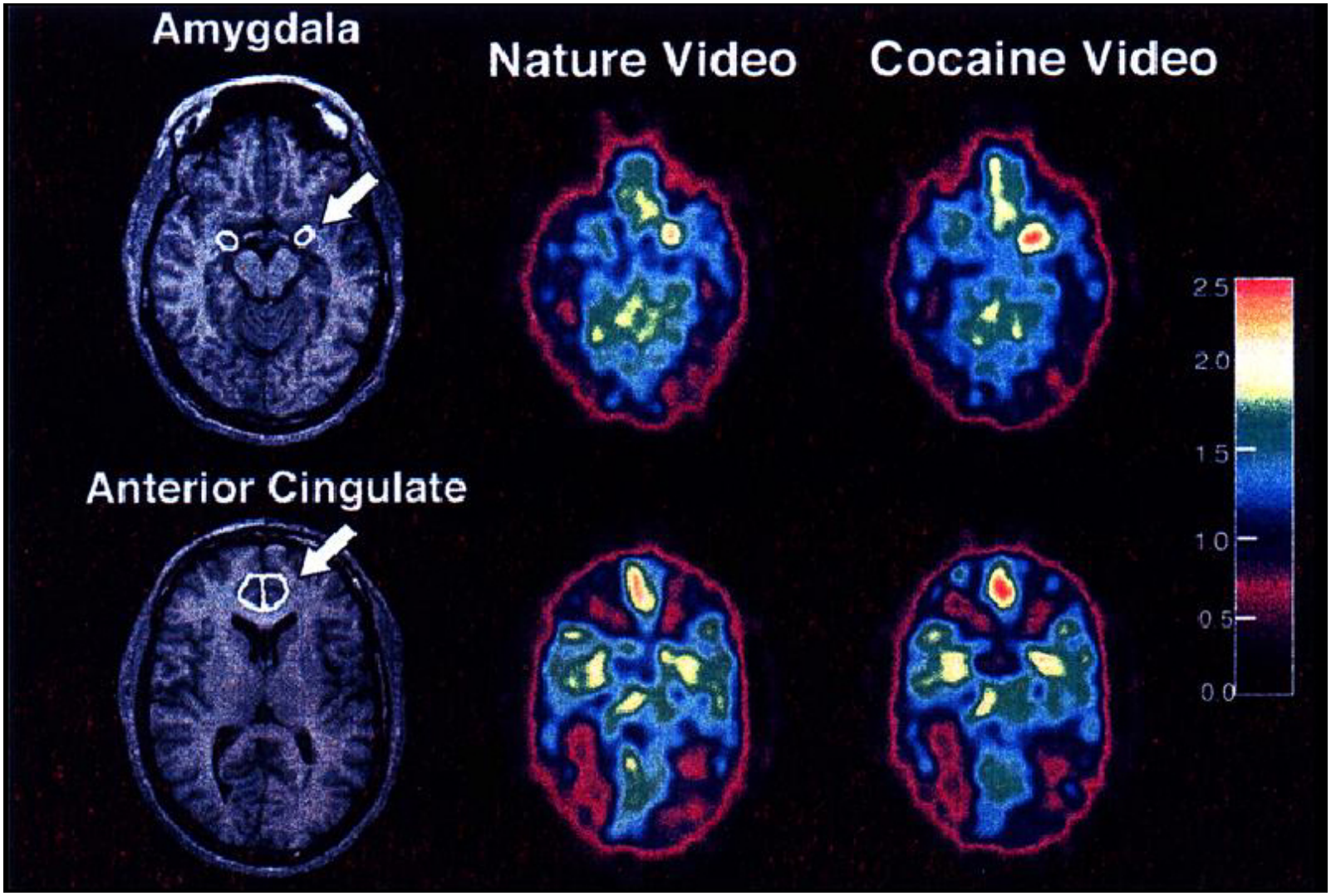

2

Positive Reinforcement

“Go!” System

PET/fMRI of Cocaine Craving

Childress et al., 1999; Am.J.Psychiat



Cocaine Cue Reactivity

- Drug Cues can trigger a strong, affect-positive state of drug desire (GO!)
- Cues can be used to study brain substrates of "GO!" in the imaging setting
- Brain substrates: Limbic Activation
  - Anterior cingulate
  - Amygdala
  - Insula
  - Ventral Striatum (NAc)
  - Orbitofrontal Cortex

Same processes present in…

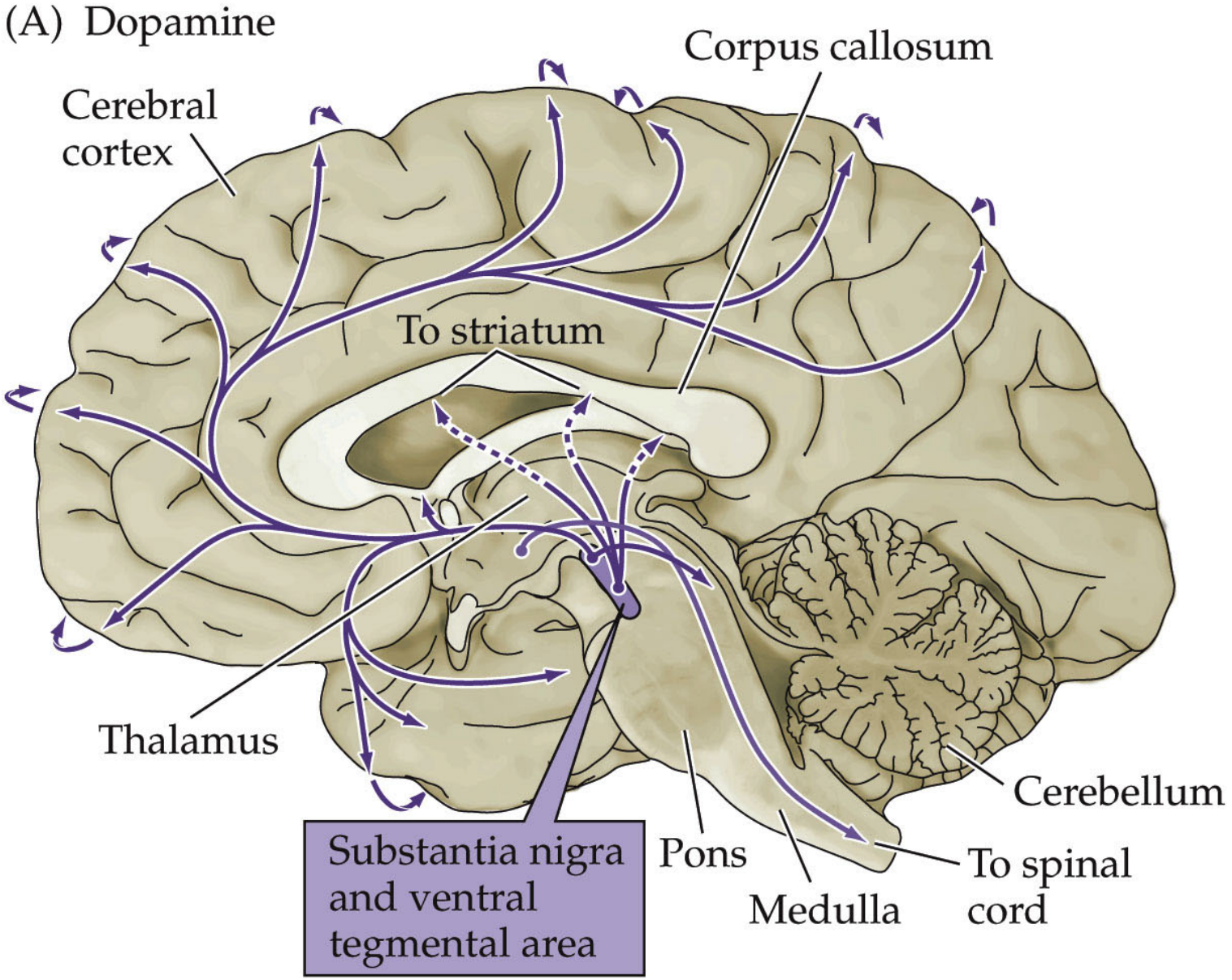
- Opiates – heroin craving correlated with inferior frontal lobe, prefrontal cortex, insula
- Nicotine – smoking videos correlated with OFC, insula, anterior cingulate, DLPFC
- Sex – arousal correlated with anterior cingulate, mPFC, OFC, insular, amygdala, ventral striatum

But “GO!” isn’t the whole story…

STOP System

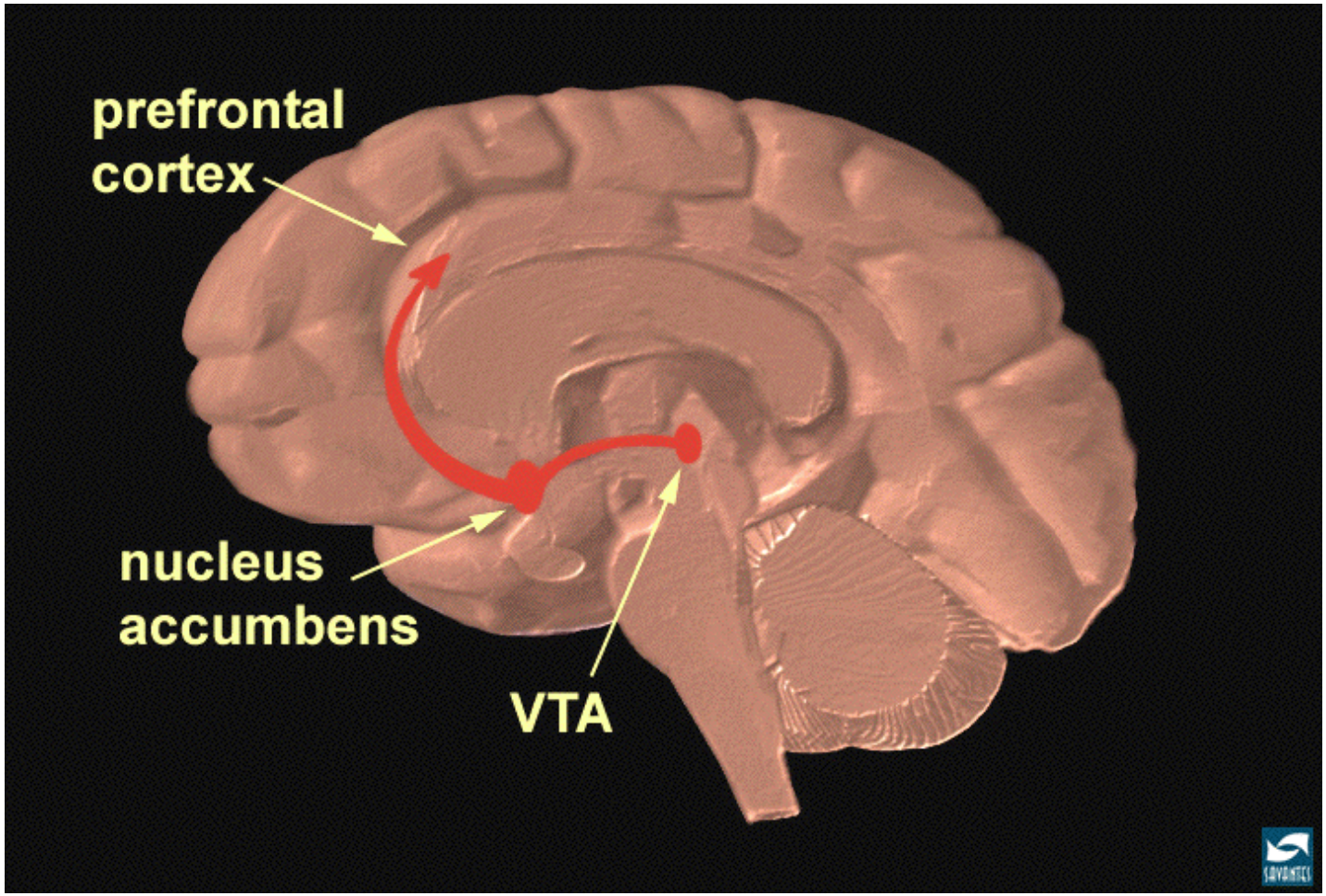
- Frontal Lobes
  - Critical for good decision making
    - **disinhibition**
  - Lower activity (blood flow and glucose metabolism) in cocaine users

Addictive drugs have wide spread effects



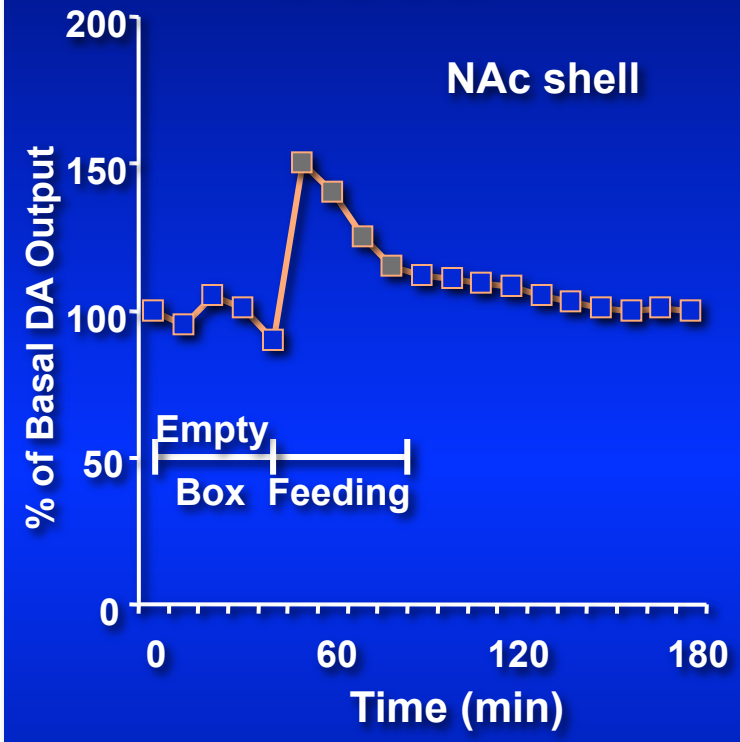
NEUROSCIENCE, Fourth Edition, Figure 6.11 (Part 1)

What is happening at the synapse?



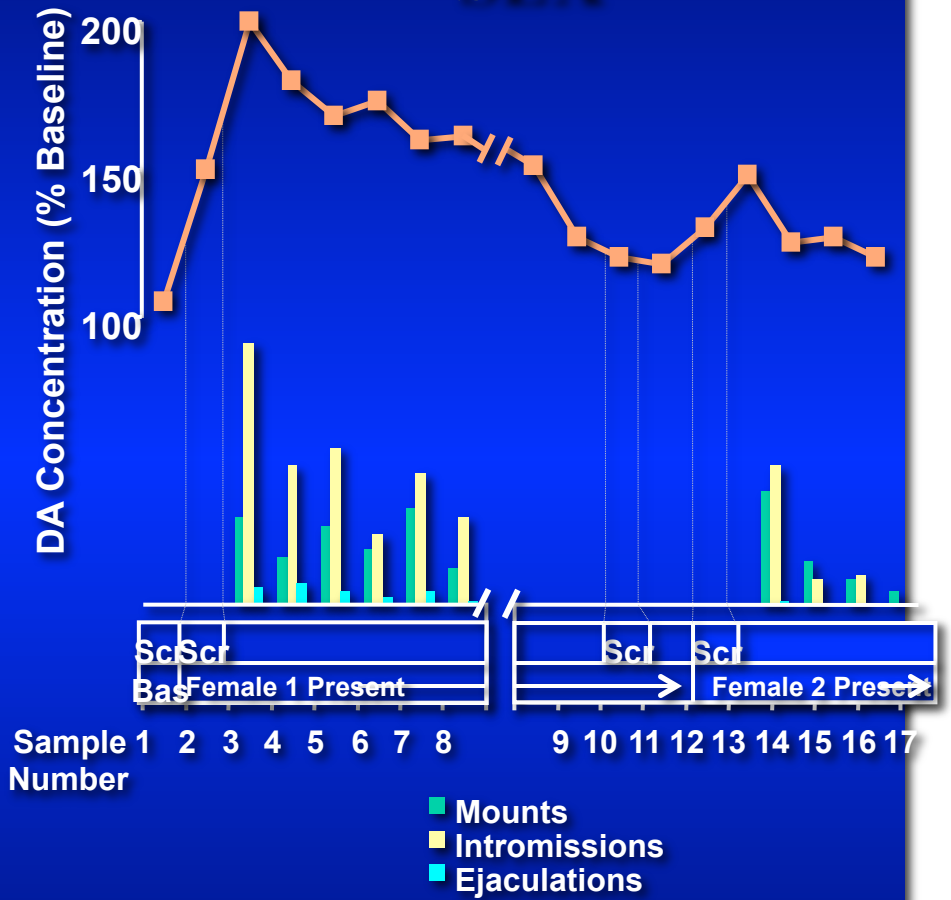
Natural Rewards Elevate Dopamine Levels

FOOD



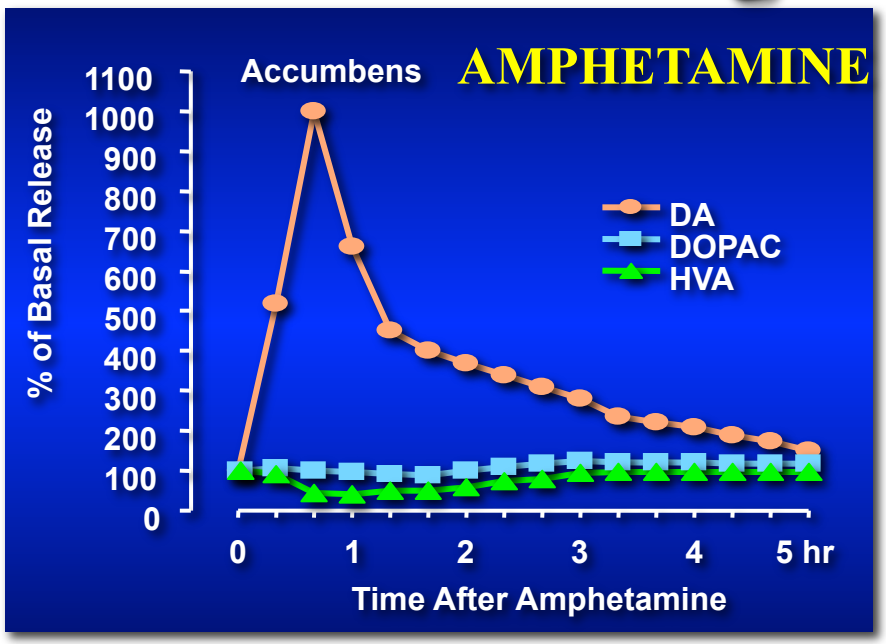
Source: Di Chiara et al.

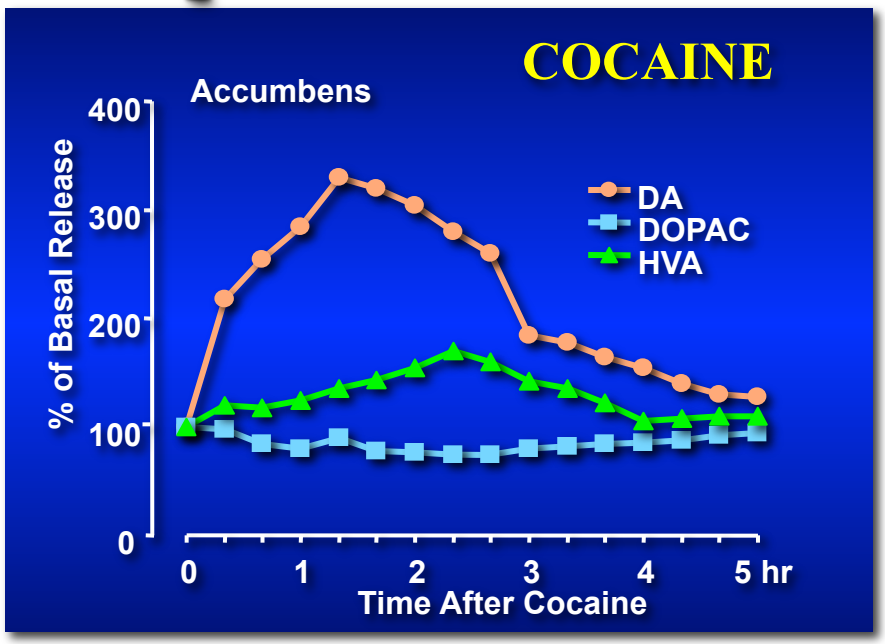
SEX

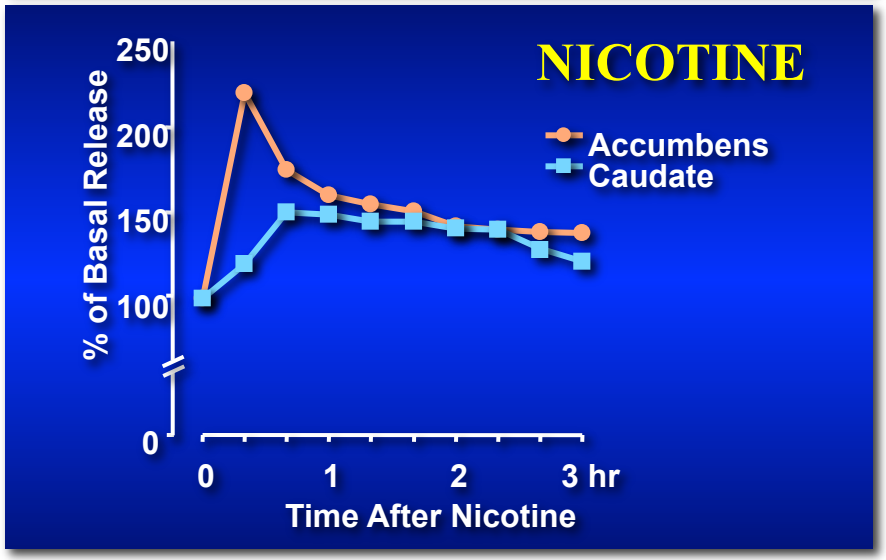


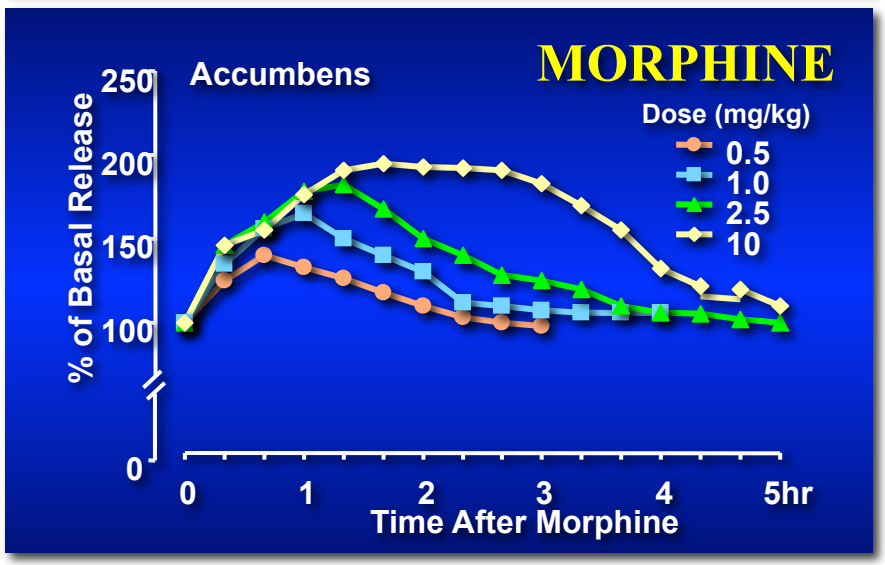
Source: Fiorino and Phillips

Effects of Drugs on Dopamine Levels





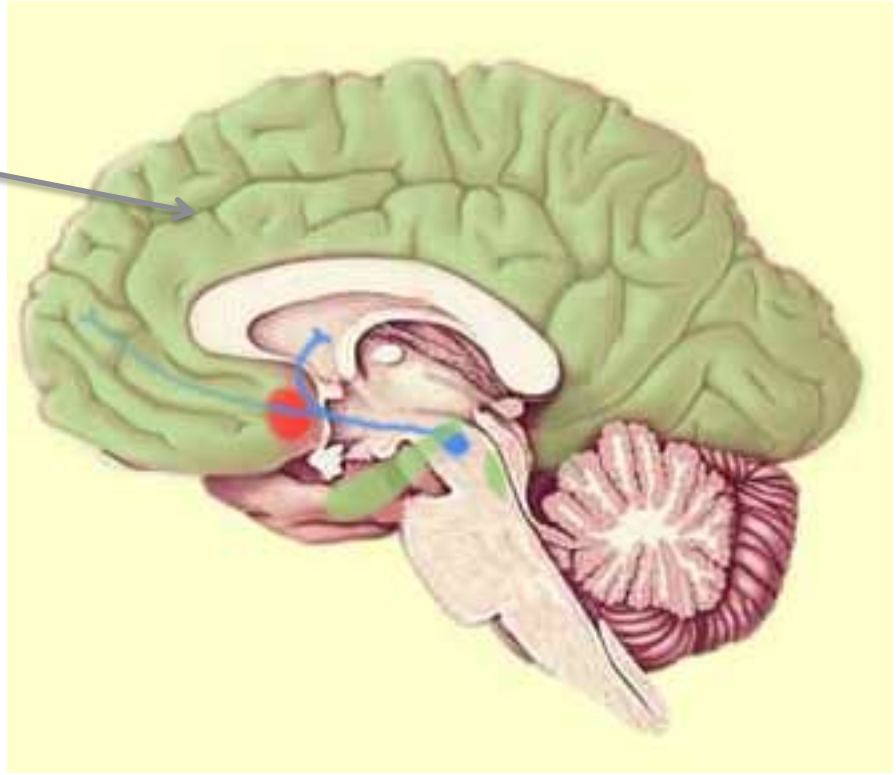




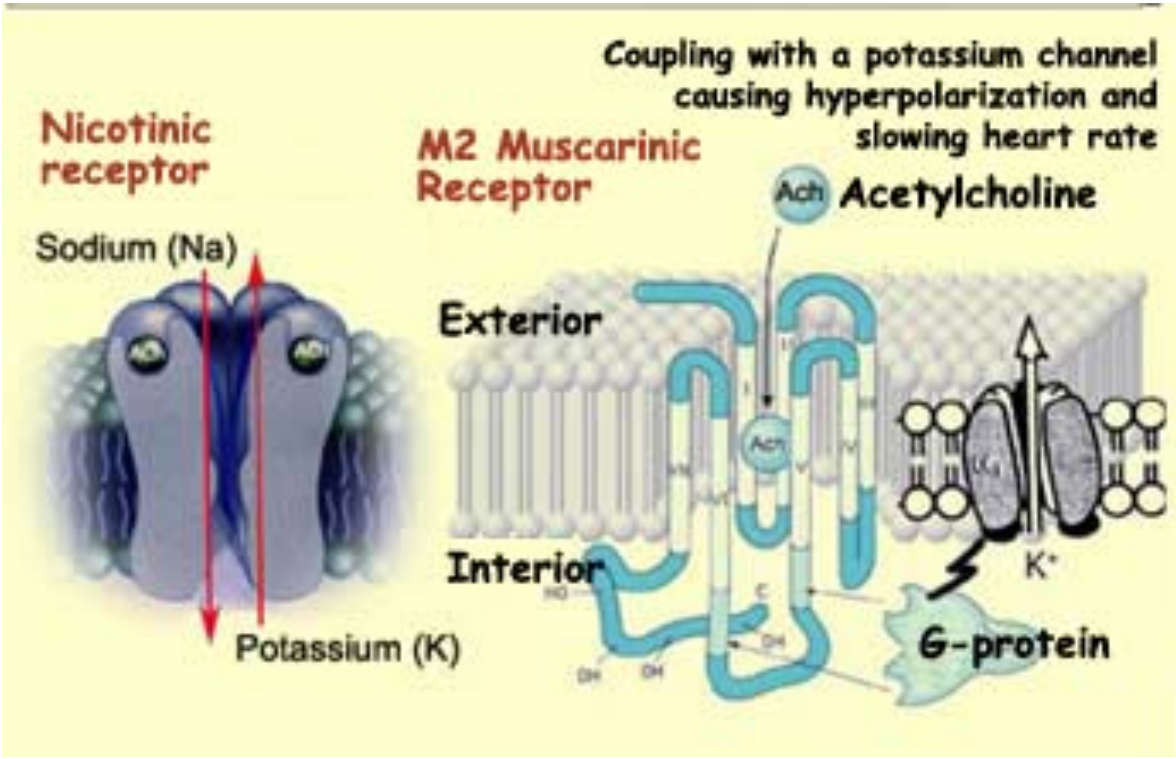
Source: Di Chiara and Imperato

Nicotine

Lots of cortical receptors for nicotine



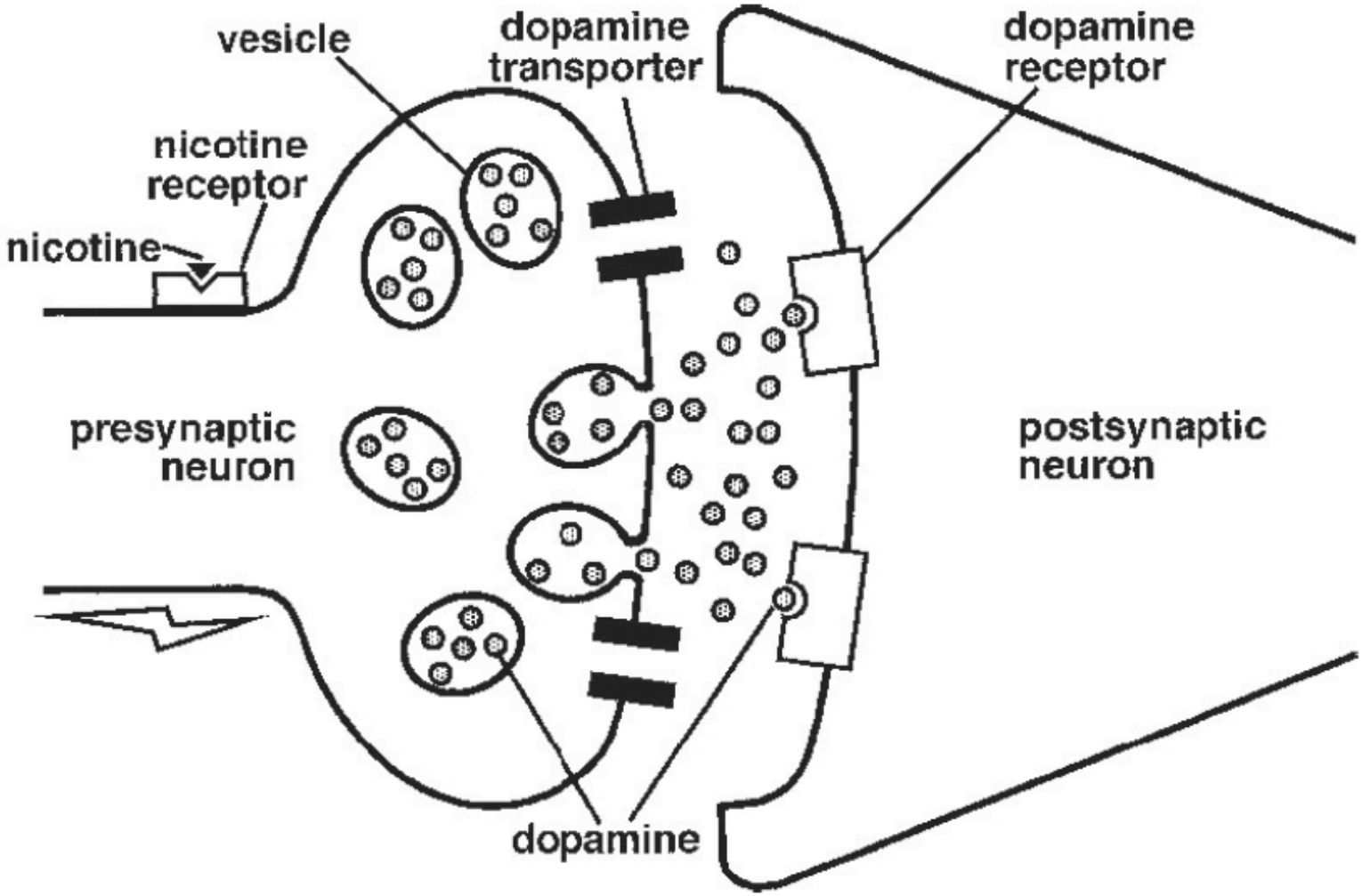
Two types of receptors for nicotine



Nicotinic: Ionotropic, cation selective

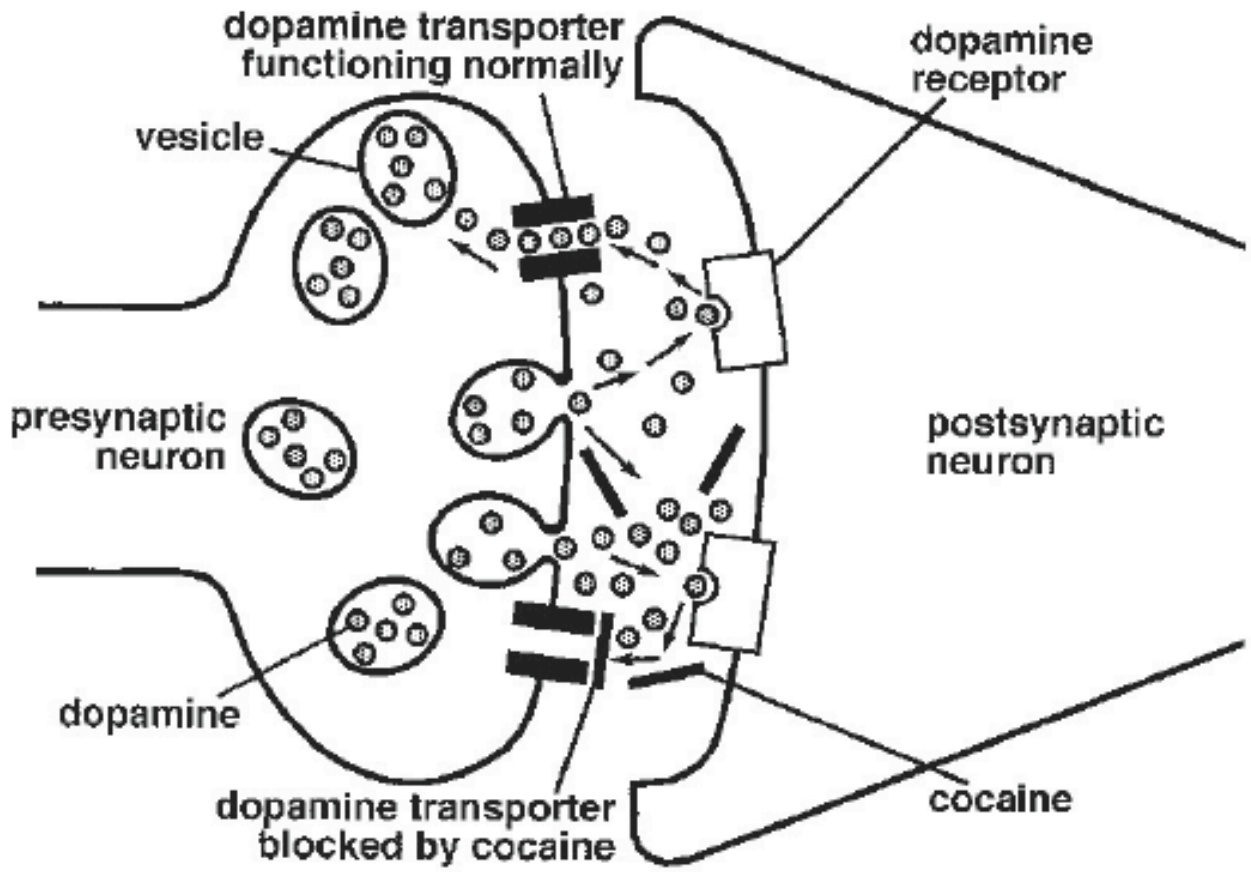
Muscarinic: Metabotropic (GPCR)

Nicotine

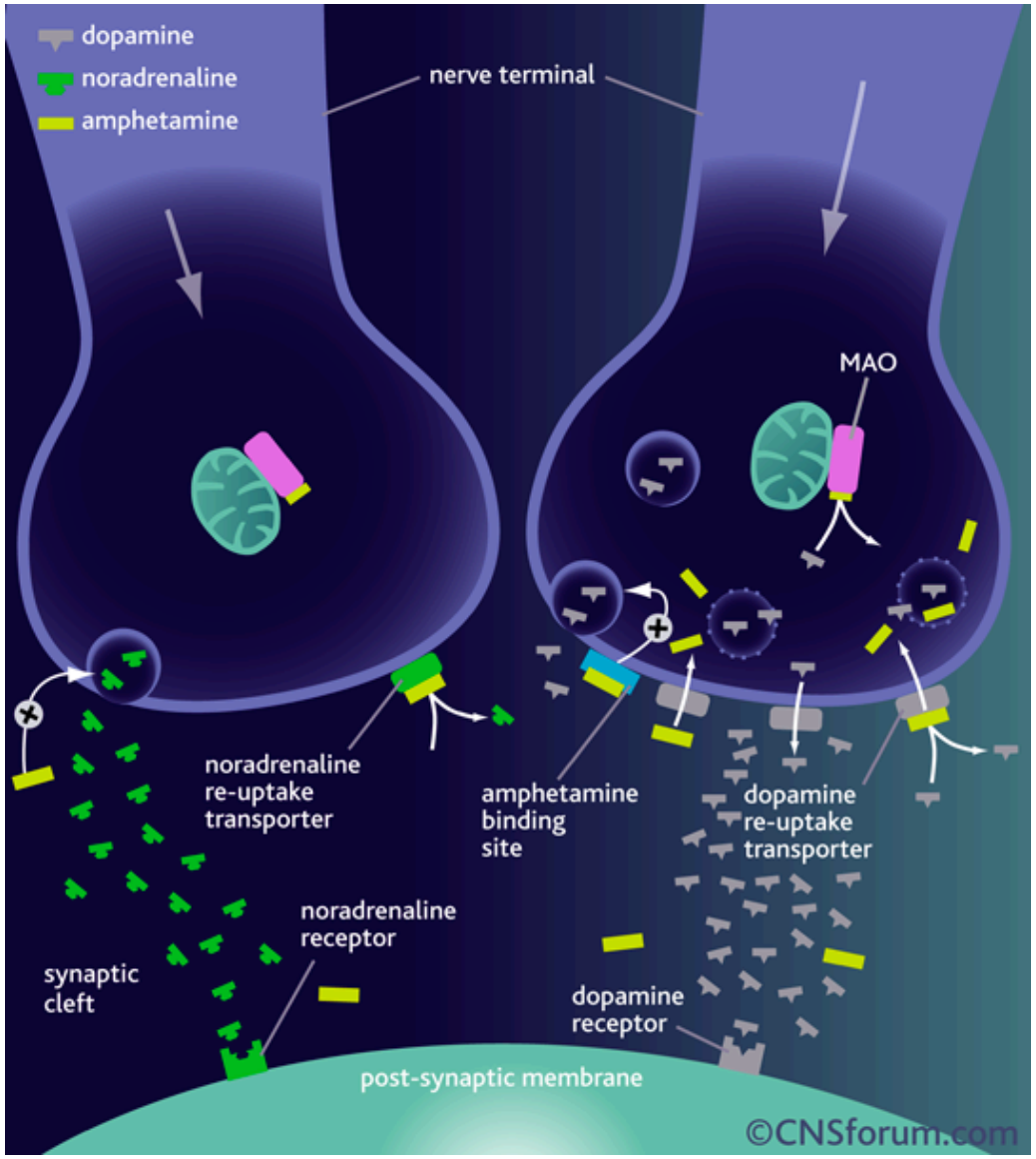


Nicotine video

Cocaine


dopamine transporter
functioning normally
dopamine
receptor
vesicle
presynaptic
neuron
postsynaptic
neuron
dopamine
dopamine transporter
blocked by cocaine
cocaine

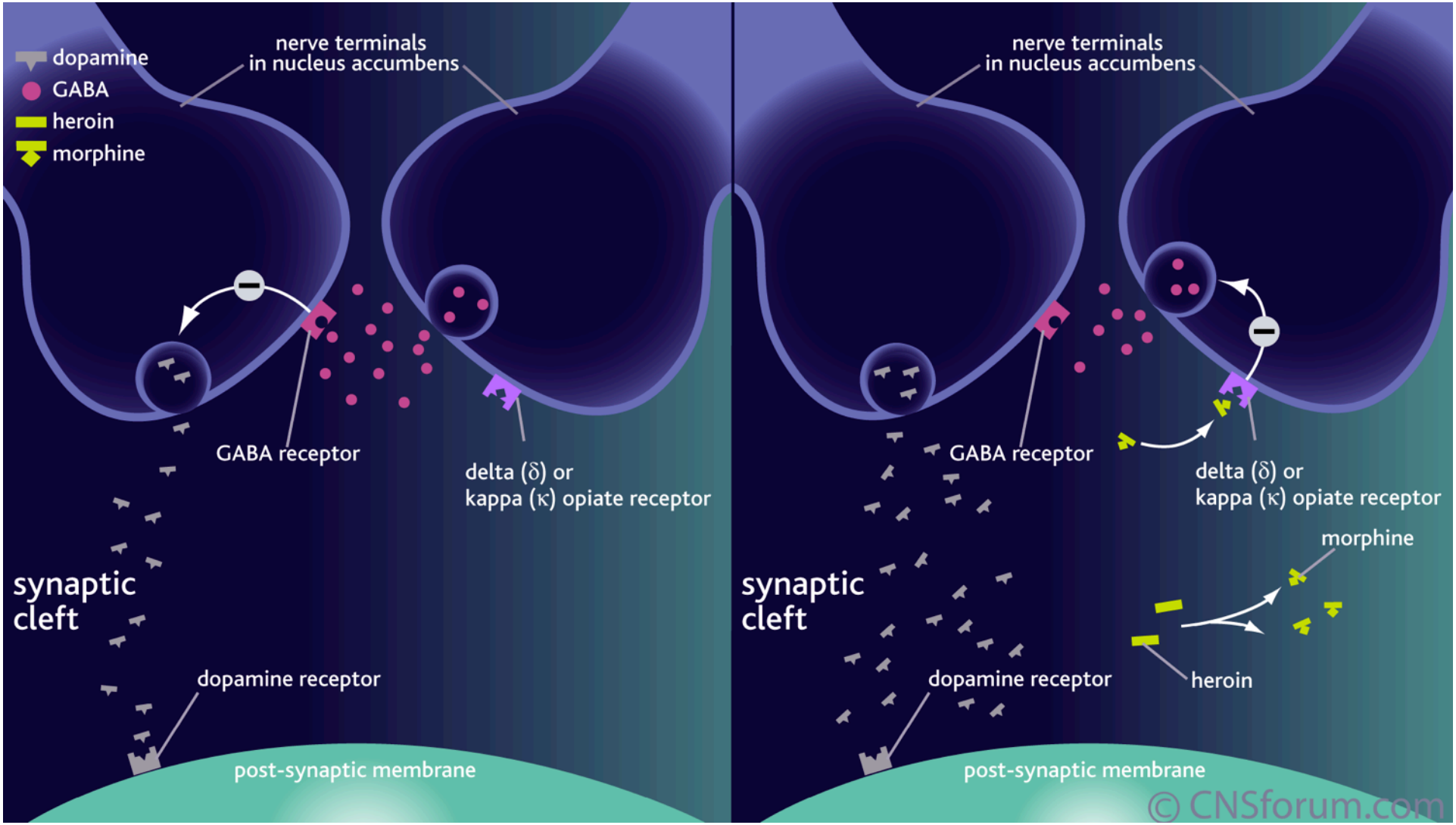
Amphetamines



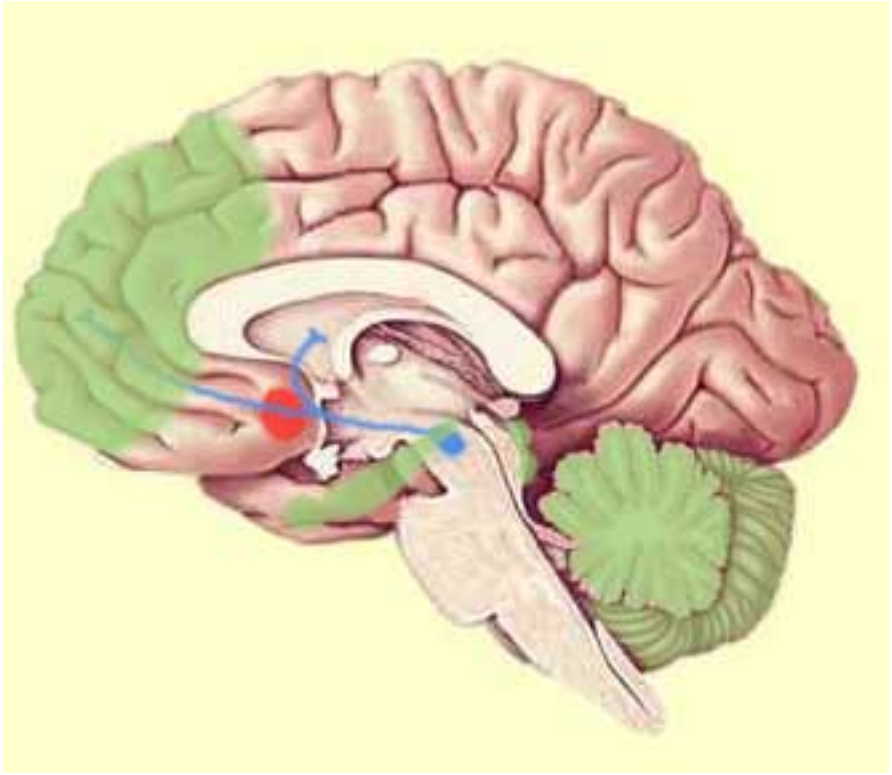
High does of amphetamines:

1) Bind pre-synaptically to cause the release of more dopamine vesicles
2) Binds to the dopamine re-uptake transporter
3) Binds to monoamine oxidase and prevents the breakdown of dopamine

Heroin

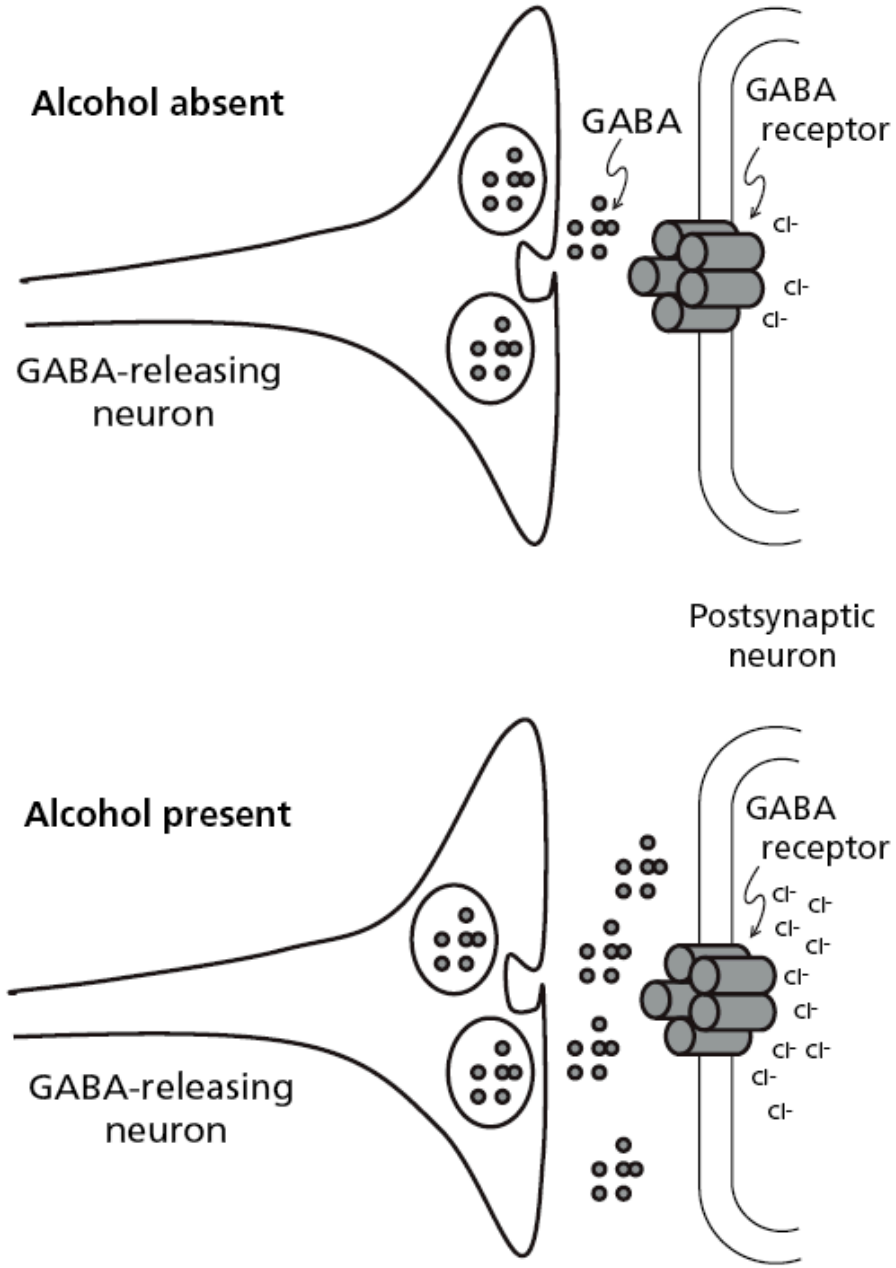

dopamine
GABA
heroin
morphine
nerve terminals
in nucleus accumbens
GABA receptor
delta (δ) or
kappa (κ) opiate receptor
synaptic
cleft
dopamine receptor
post-synaptic membrane
nerve terminals
in nucleus accumbens
GABA receptor
delta (δ) or
kappa (κ) opiate receptor
morphine
synaptic
cleft
dopamine receptor
heroin
post-synaptic membrane
© CNSforum.com

Depressants

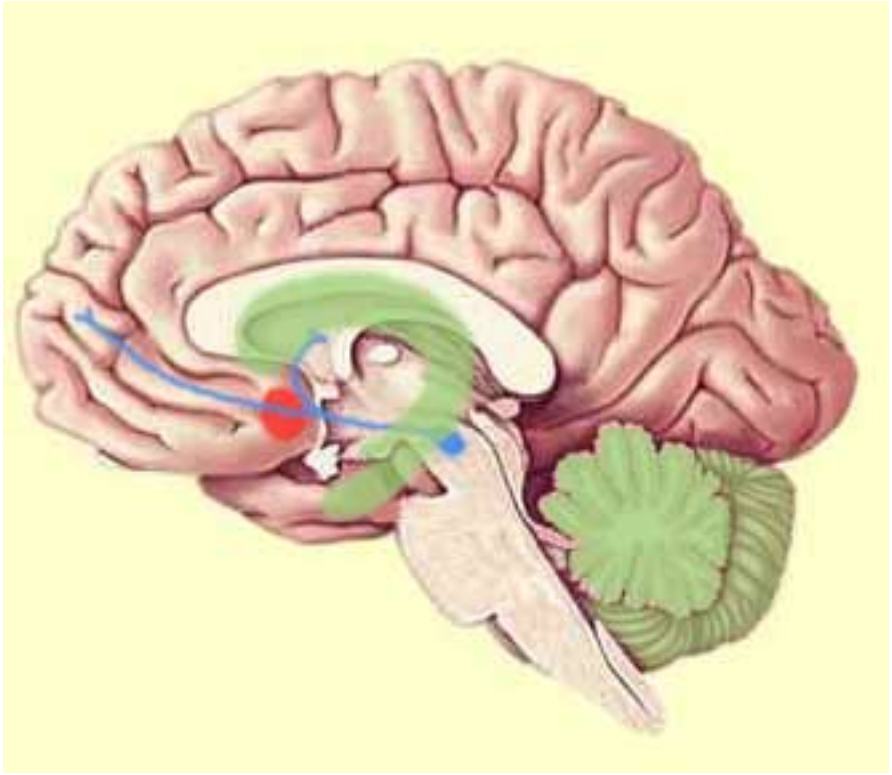


Alcohol

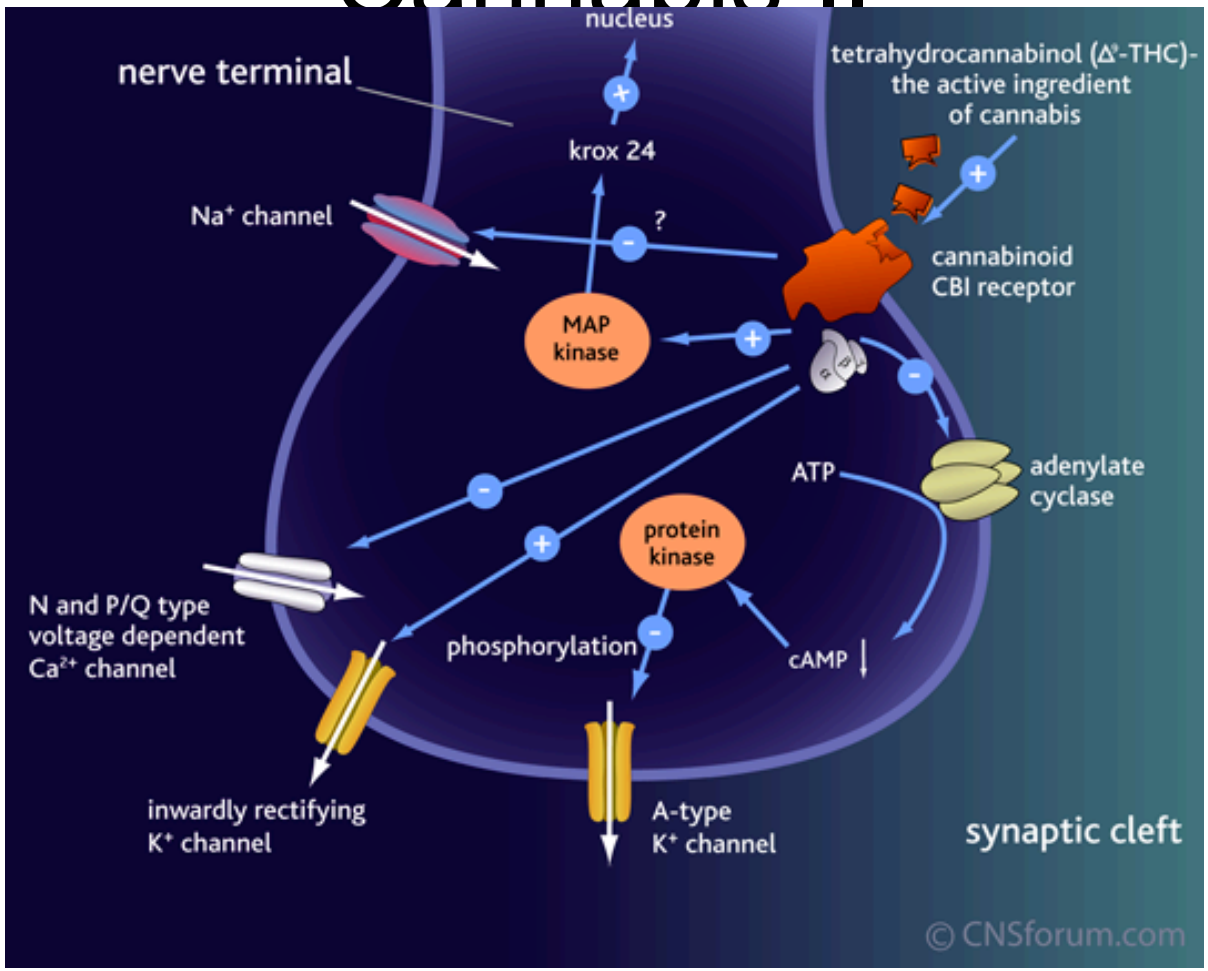
Alcohol


Alcohol absent
GABA
GABA receptor
Cl-
Cl-
Cl-
GABA-releasing neuron
Postsynaptic neuron
Alcohol present
GABA receptor
Cl-
Cl-
Cl-
Cl-
Cl-
Cl-
Cl-
Cl-
Cl-
Cl-
GABA-releasing neuron

Cannabis



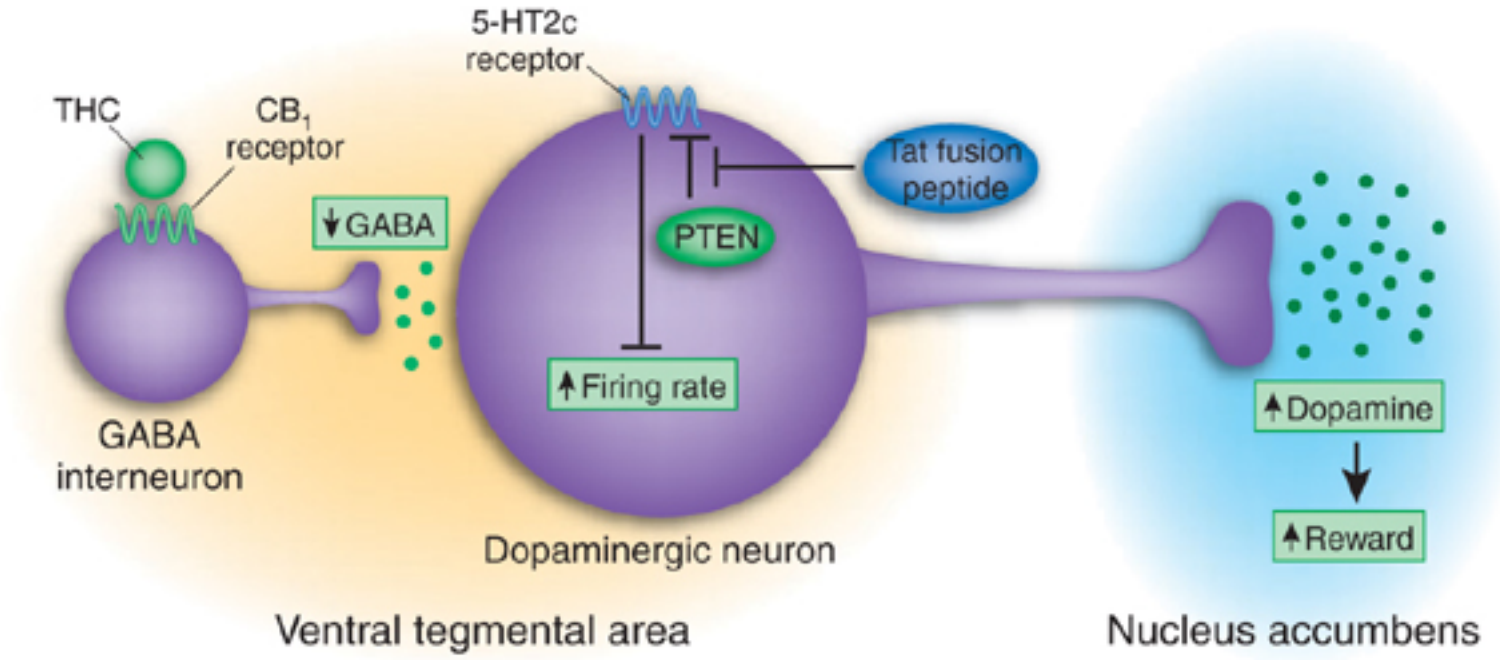
Cannabis II



Ok there's a lot going on here:

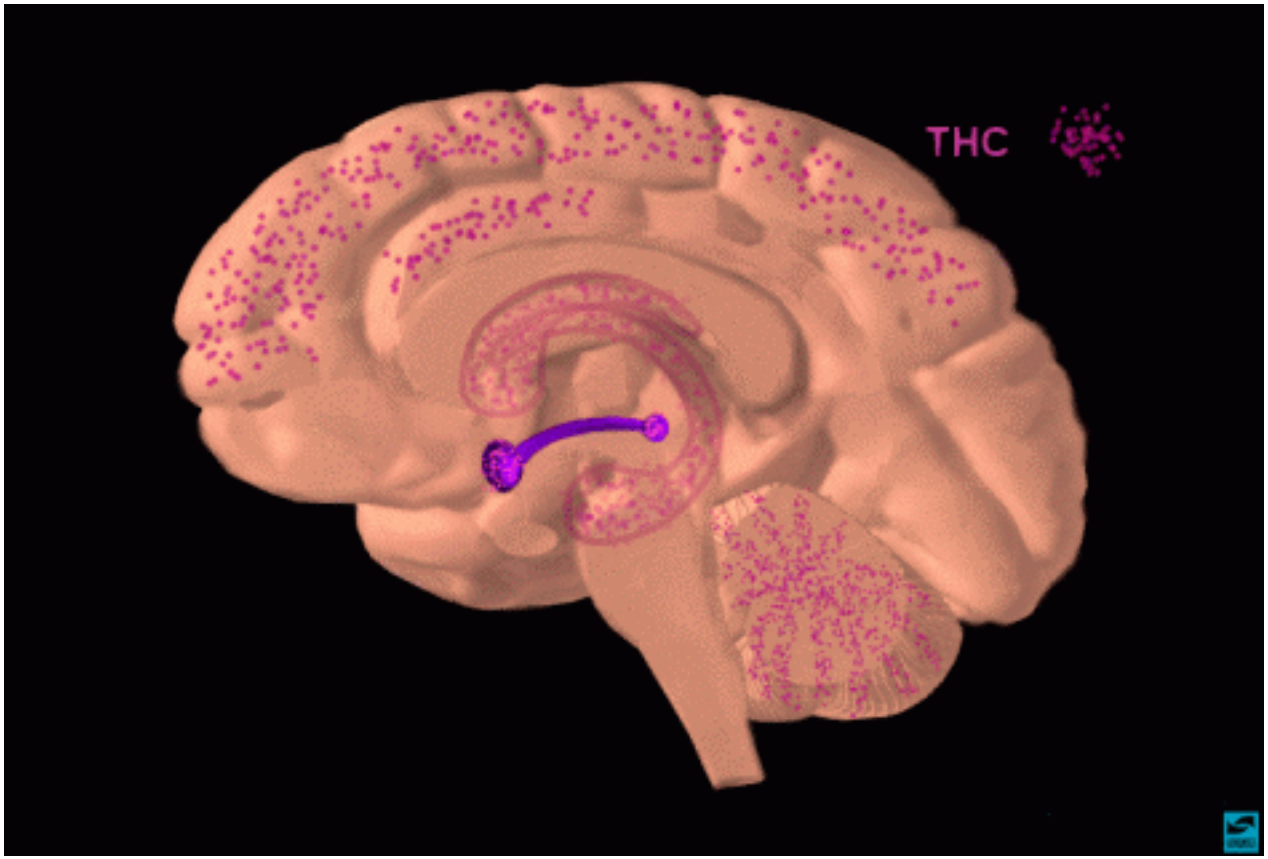
To emphasize: cannabis leads to less cAMP therefore less PKA therefor less NT relesease in many neurons- therefore reduced excitability

BUT…

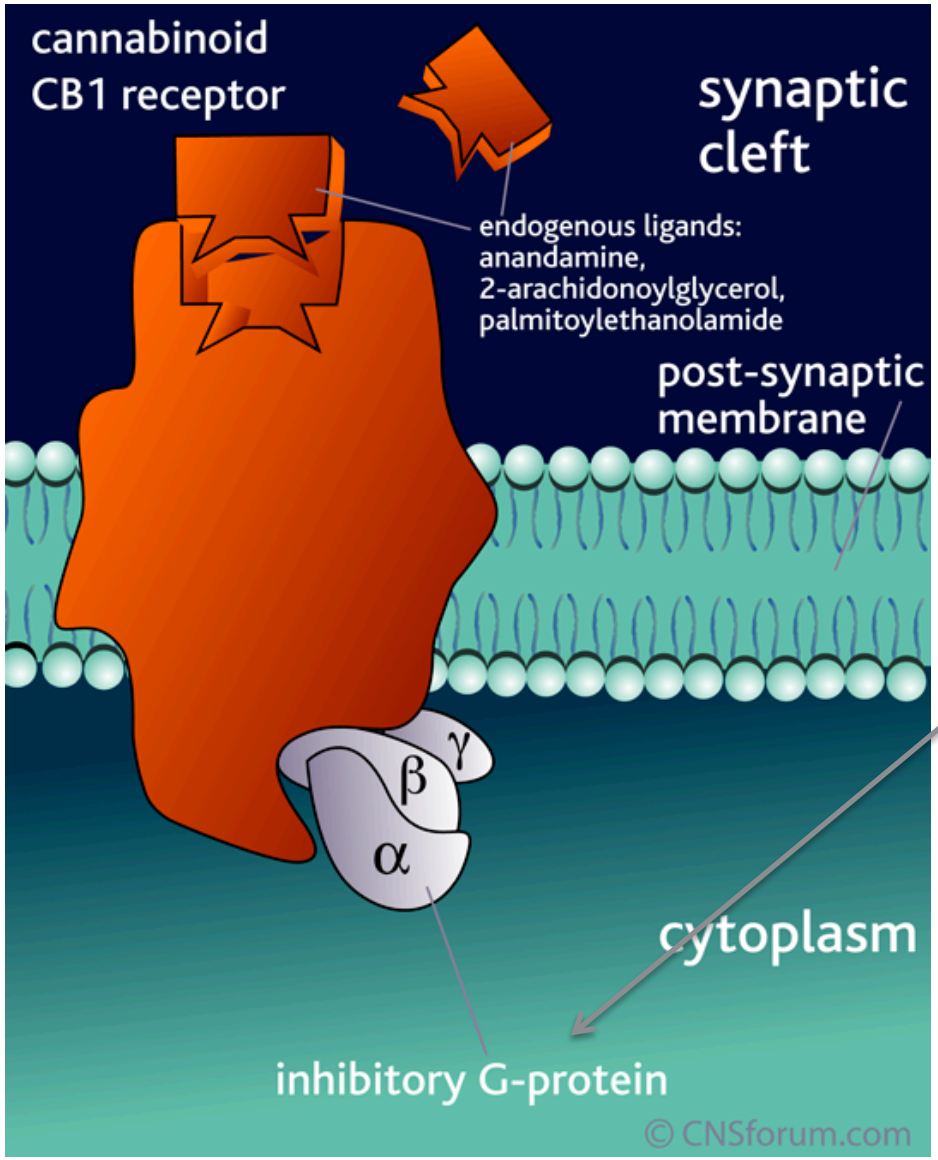


THC reduces firing of the inhibitory GABA neurons leading to INCREASED firing of the dopamine releasing VTA neurons

THC also effects the cortex and the hippocampus

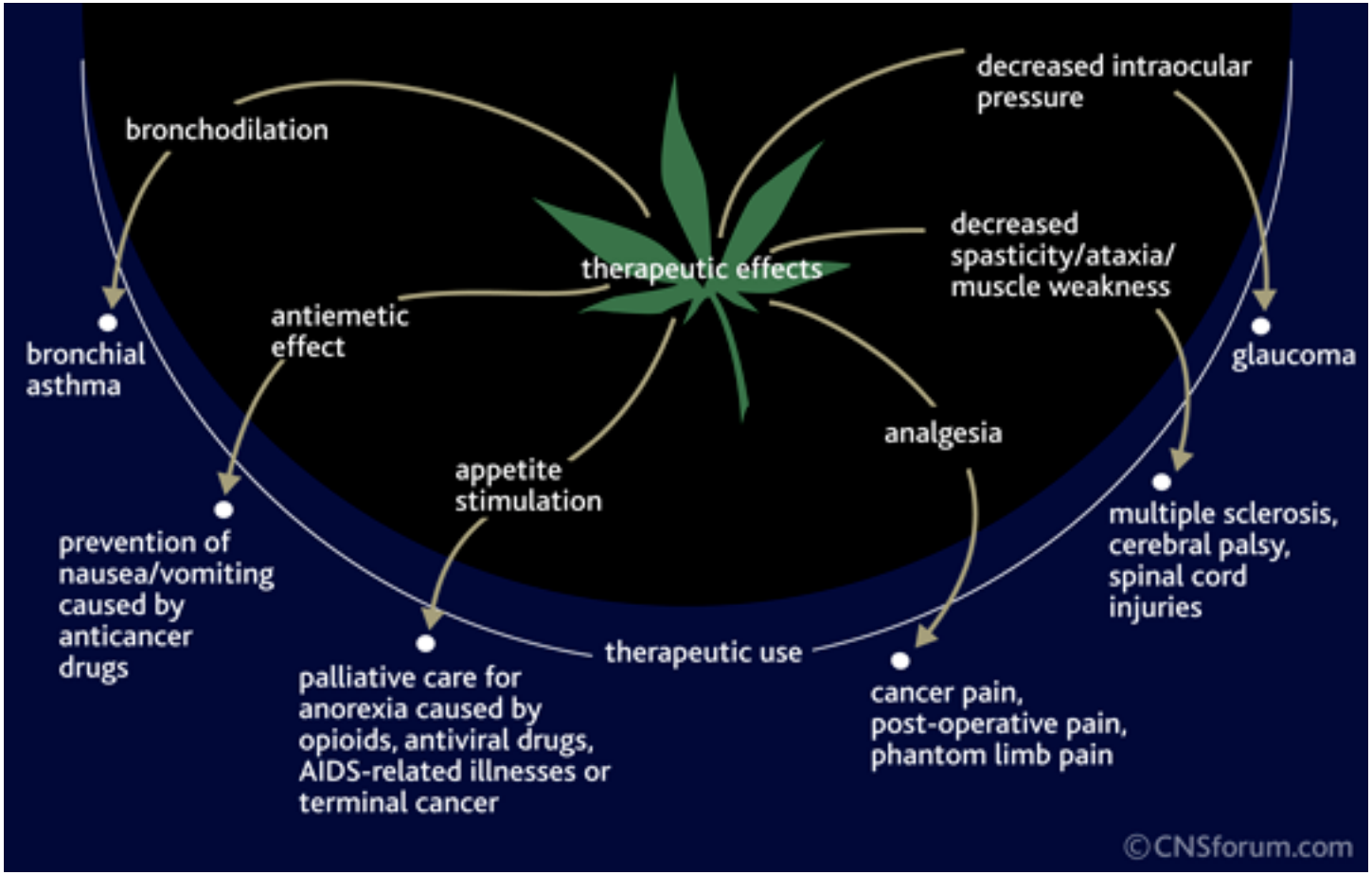


Cannabis I

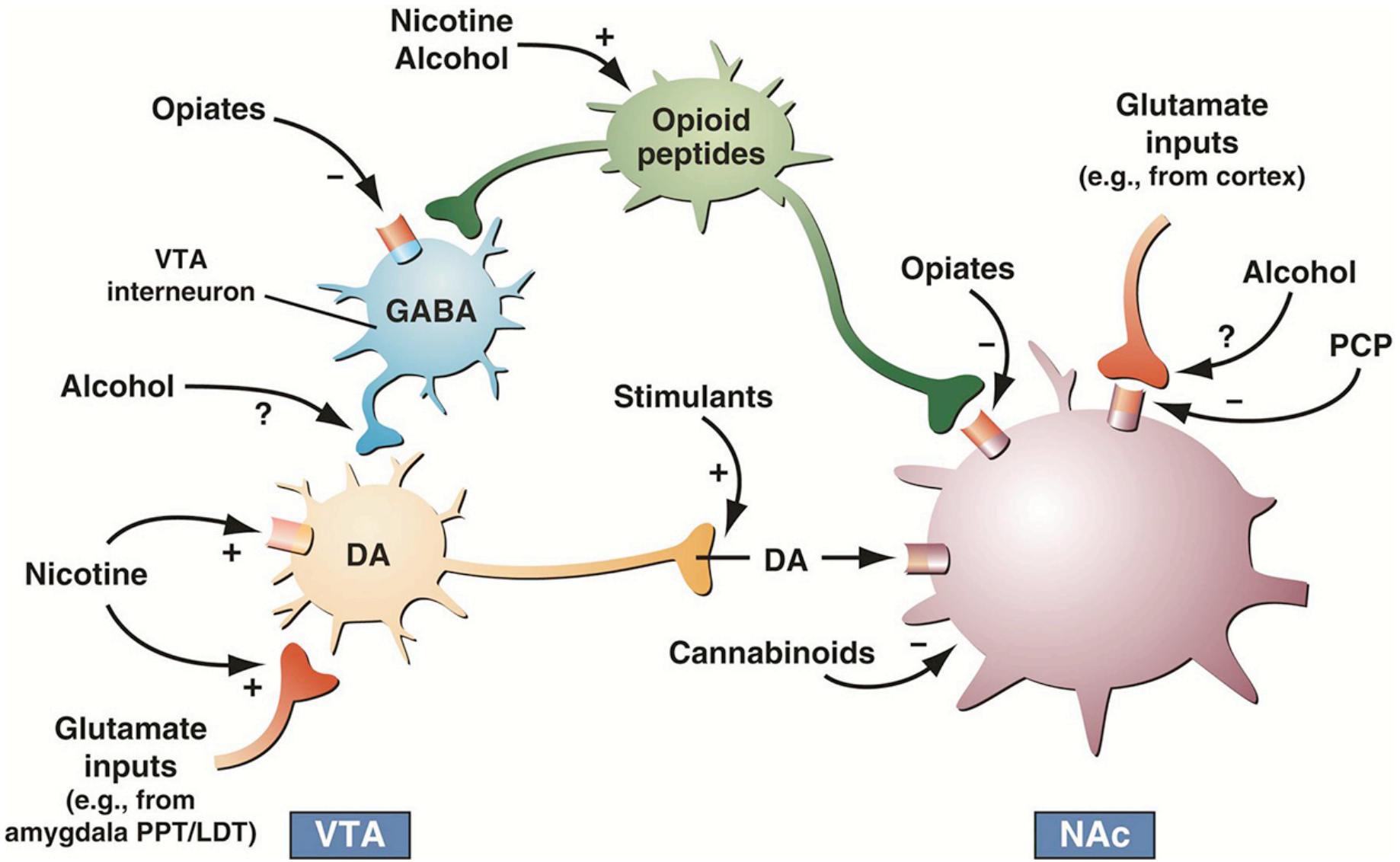


Inhibitory G protein results in inhibition of neurotransmission

Cannabis III



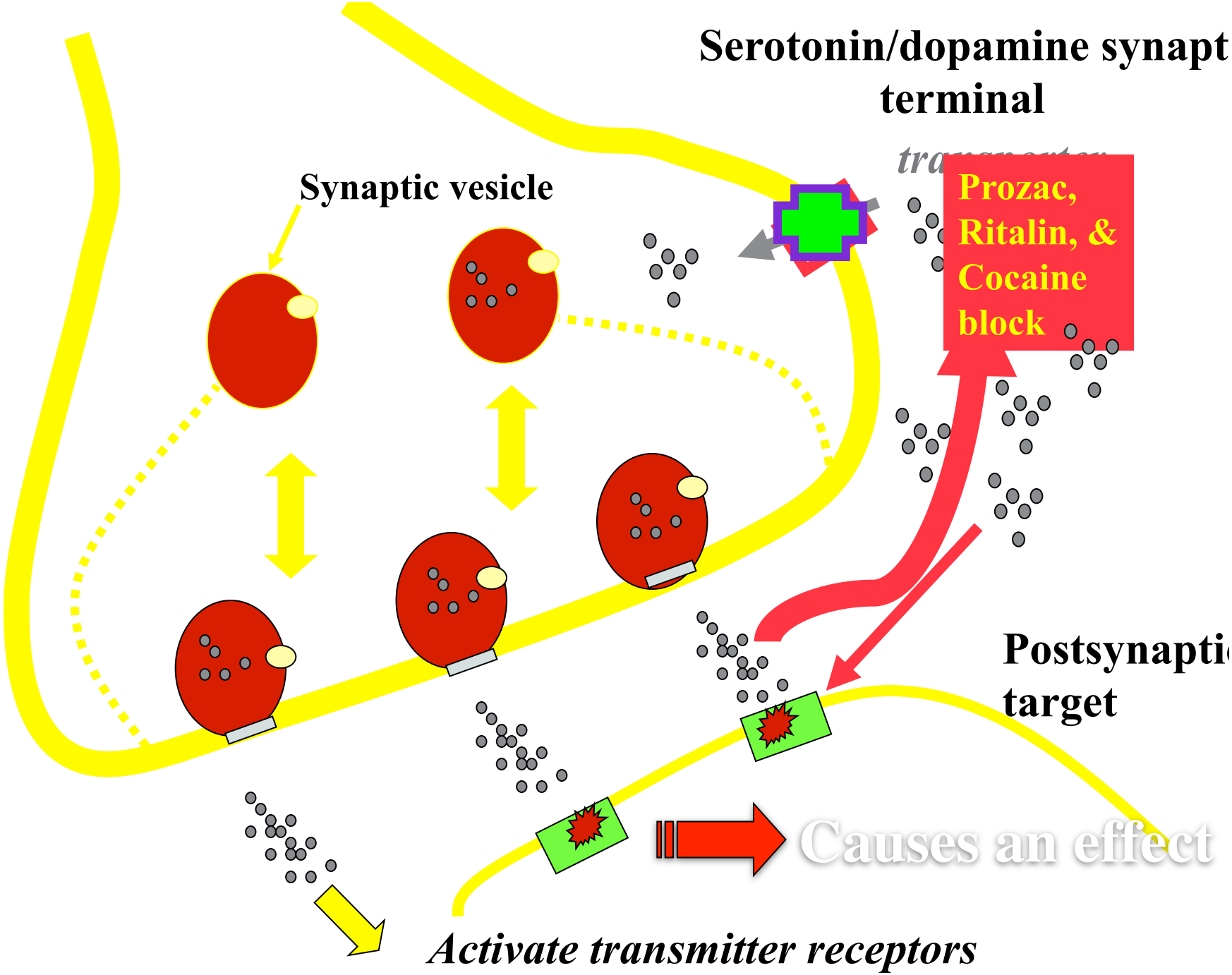
Diverse initial actions of various drugs



http://www.cbsnews.com/video/watch/?id=7406968n

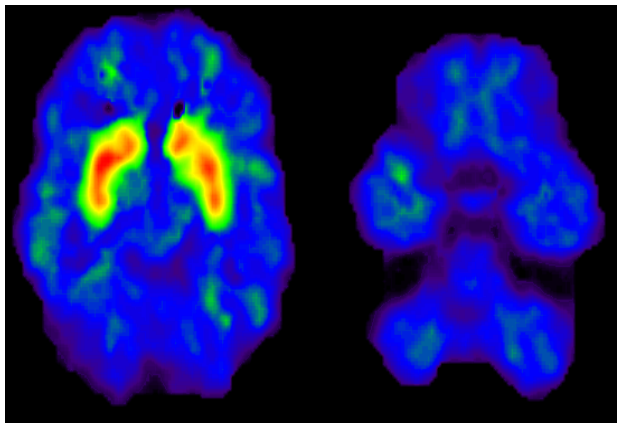
Some drugs of abuse have a mechanism of action similar to that of drugs used as psychotherapeutic agents

Significance: rationale for self-administration

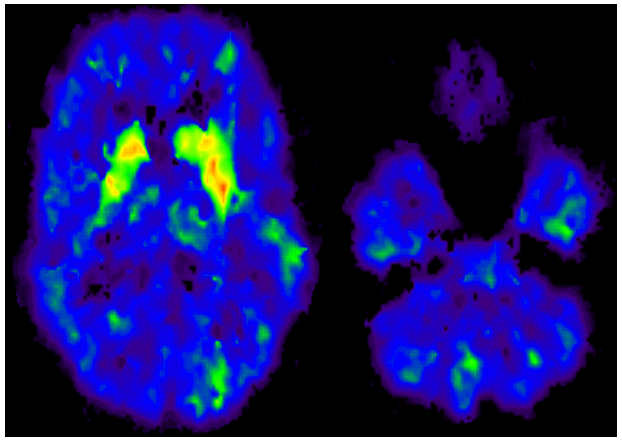

Serotonin/dopamine synapt
terminal
Synaptic vesicle
Prozac,
Ritalin, &
Cocaine
block
Postsynapti
target
Causes an effect
Activate transmitter receptors

Prolonged Drug Use Changes The Brain In Fundamental and Long-Lasting Ways

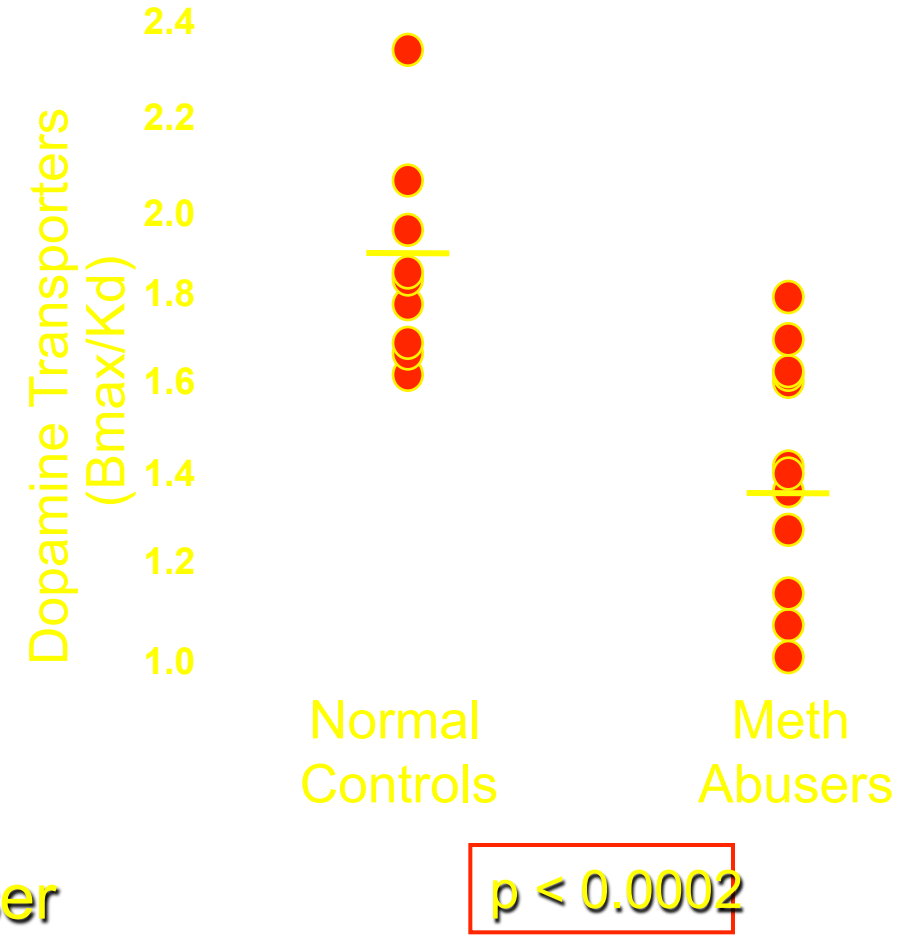
Dopamine Transporters in Methamphetamine Abusers



Normal Control



Methamphetamine Abuser

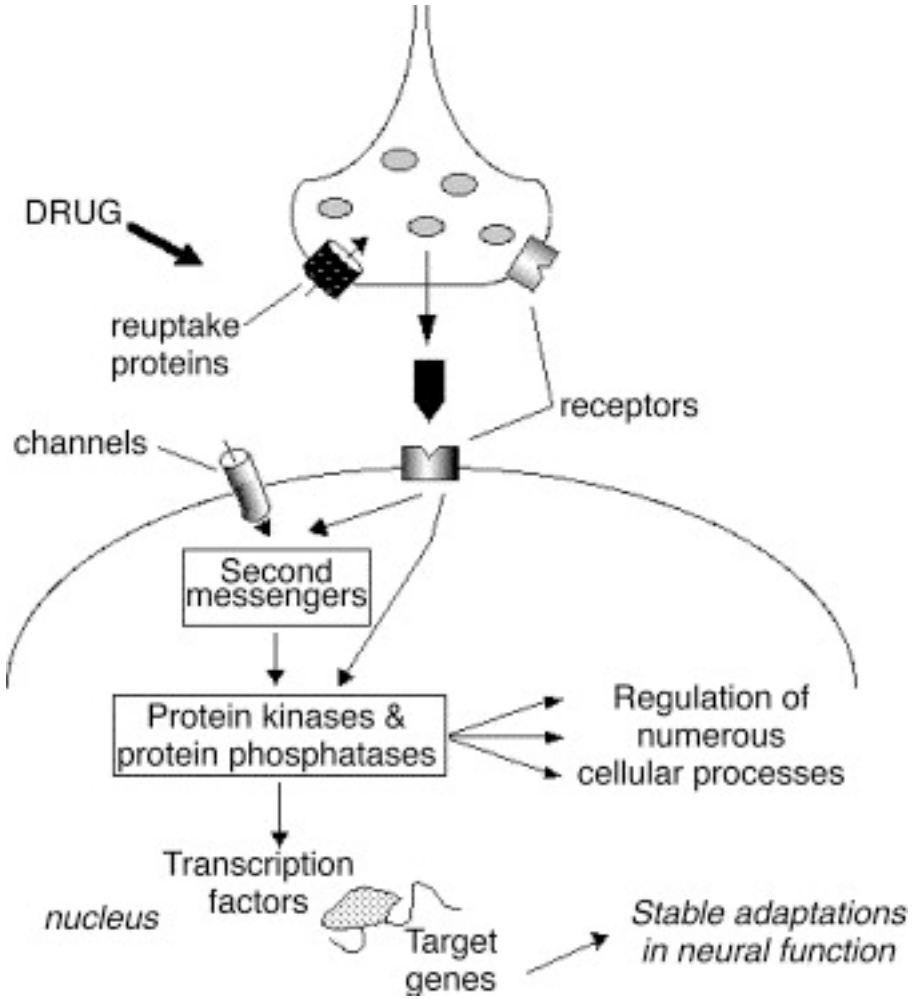


BNL - UCLA - SUNY
NIDA - ONDCP - DOE

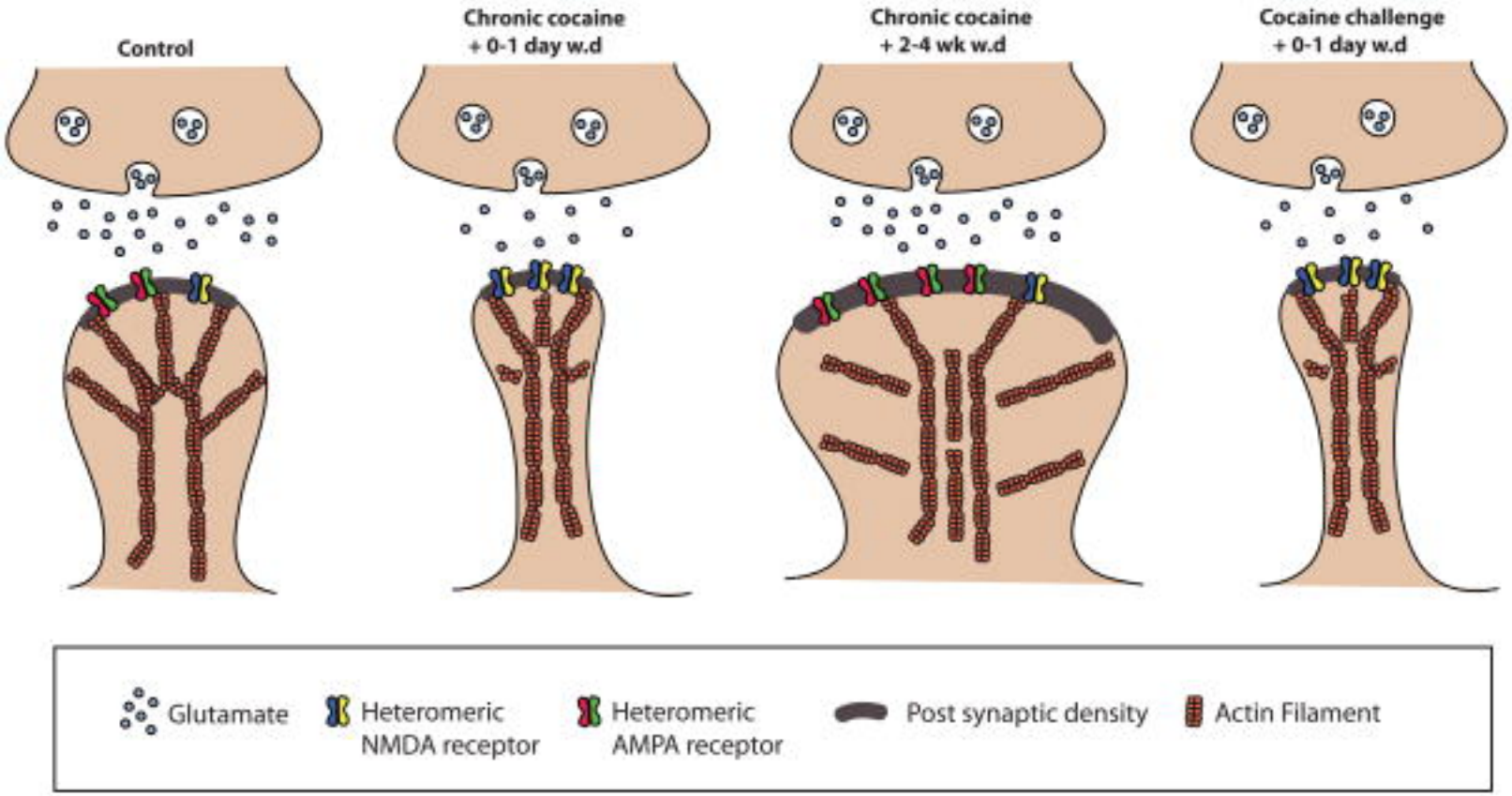
Implications – Down Regulation

- Immediate effect of drug use is an increase in dopamine or NT's
- *Continued use of drugs reduces the brain's dopamine (or NT) production*
- Because dopamine is part of the reward system, the brain is "fooled" that the drug has survival value for the organism
- The reward system responds with "drug seeking behaviors"

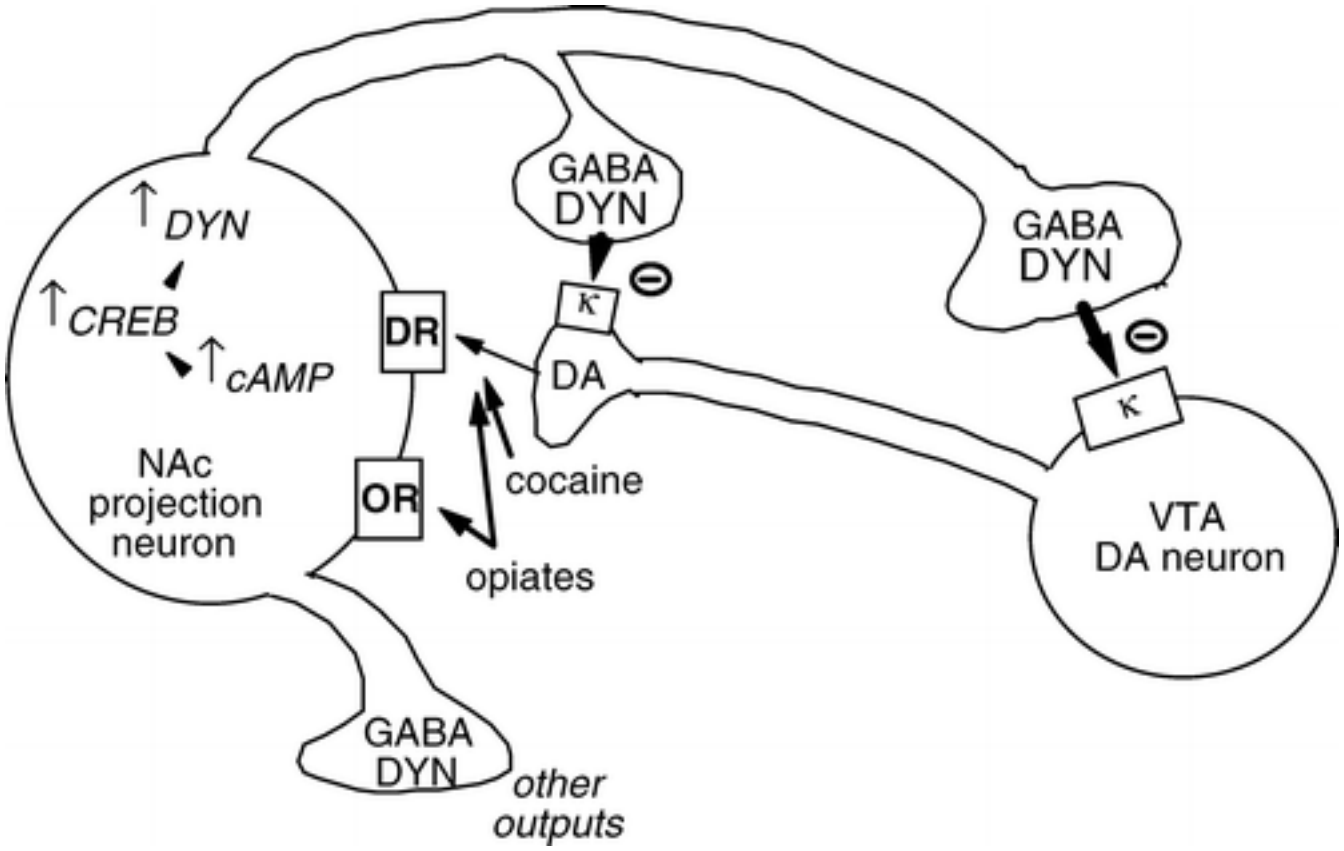
Long-term changes

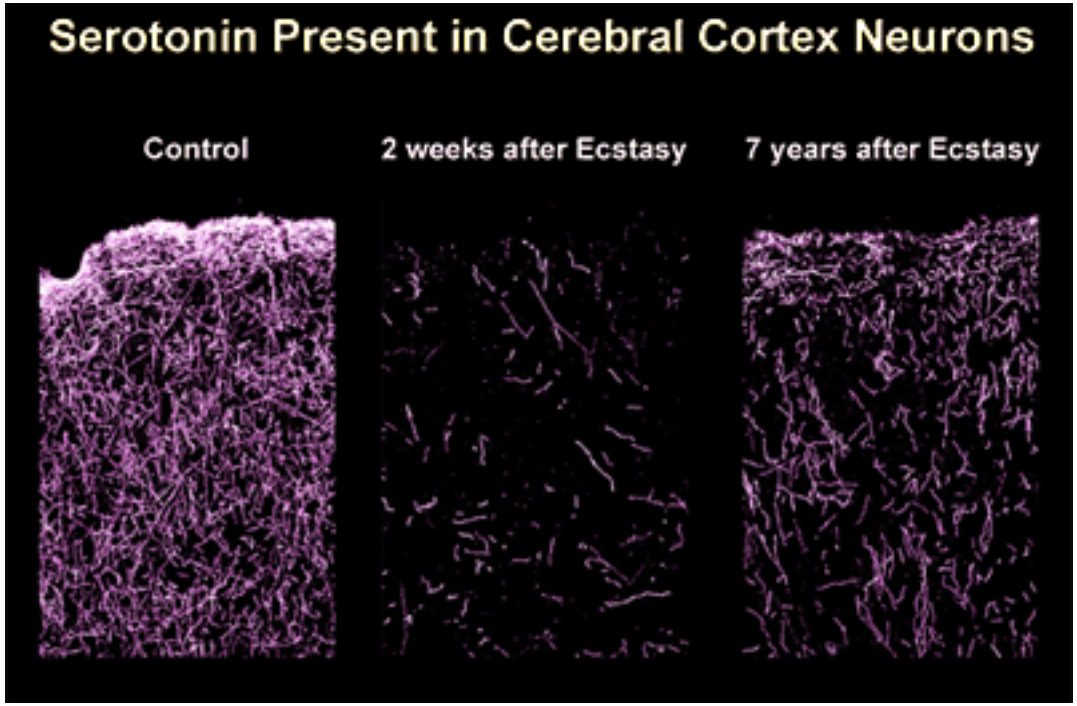


Synaptic changes following chronic cocaine exposure



Drug induced adaptations




Serotonin Present in Cerebral Cortex Neurons
Control
2 weeks after Ecstasy
7 years after Ecstasy

Neuromodulation

Neurotransmitters

Excitatory

Glutamate

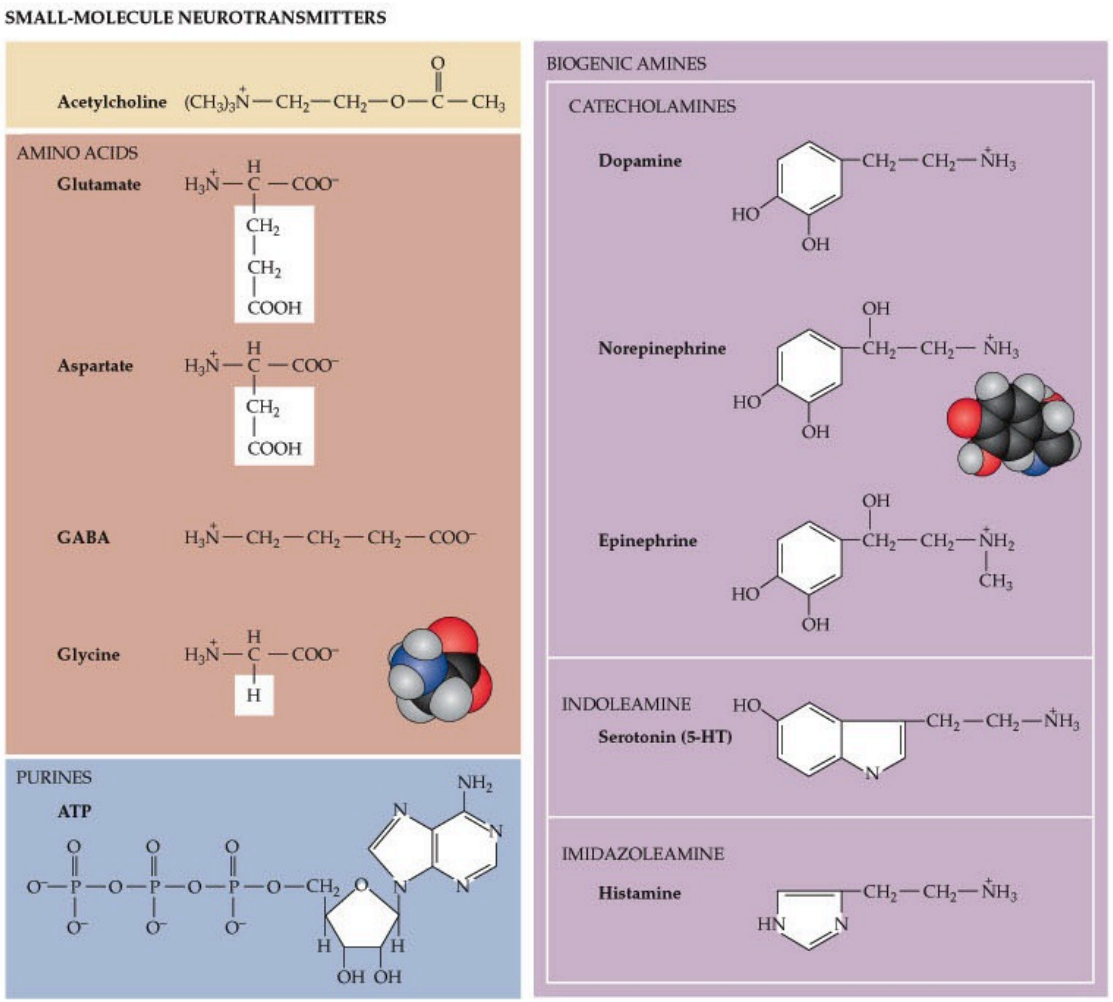
Inhibitory

GABA
glycine

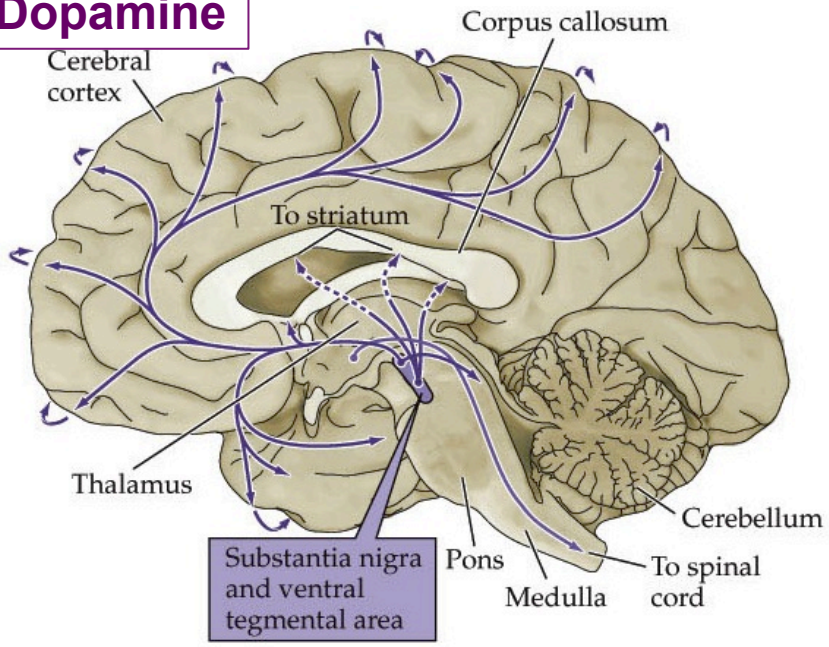
Modulatory

Dopamine
Norepinephrine
Serotonin
Acetylcholine

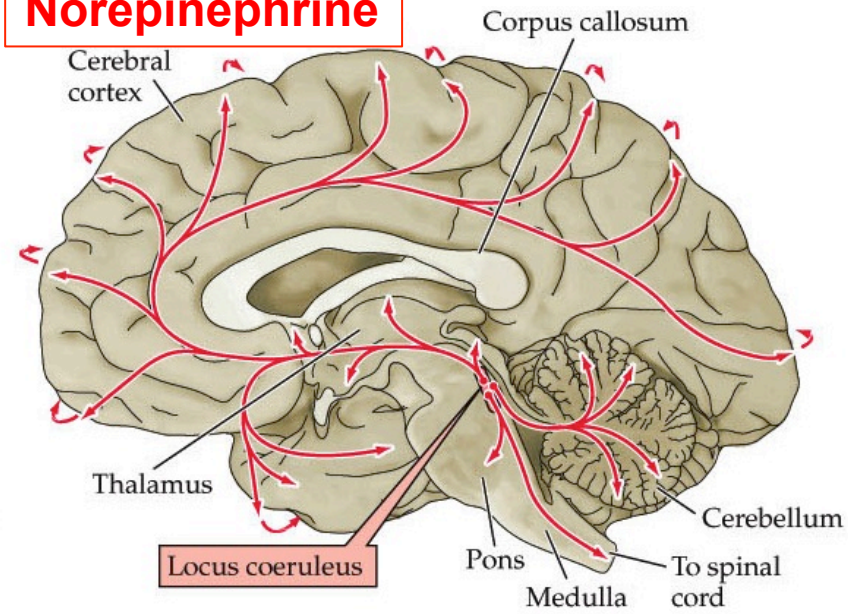
Neuropeptides



Dopamine



Norepinephrine

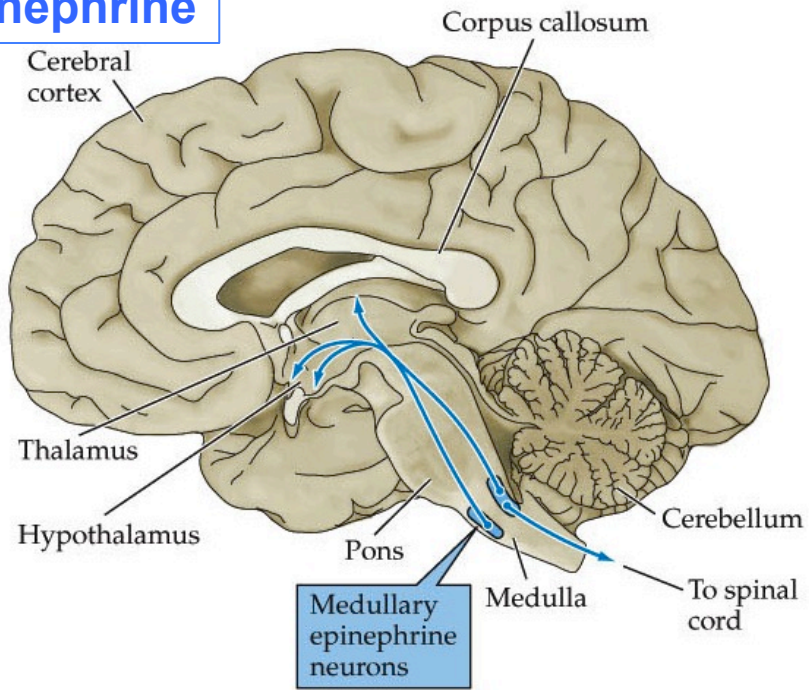


Neuromodulators have global effects!

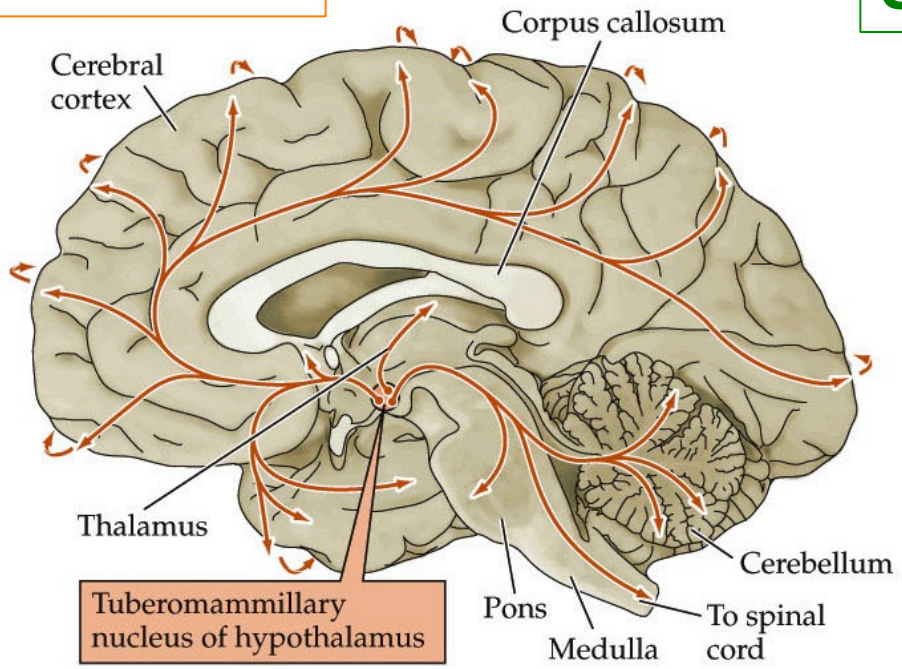
made by small clusters of cells (nuclei) in brain stem or midbrain

project axons to many areas of brain

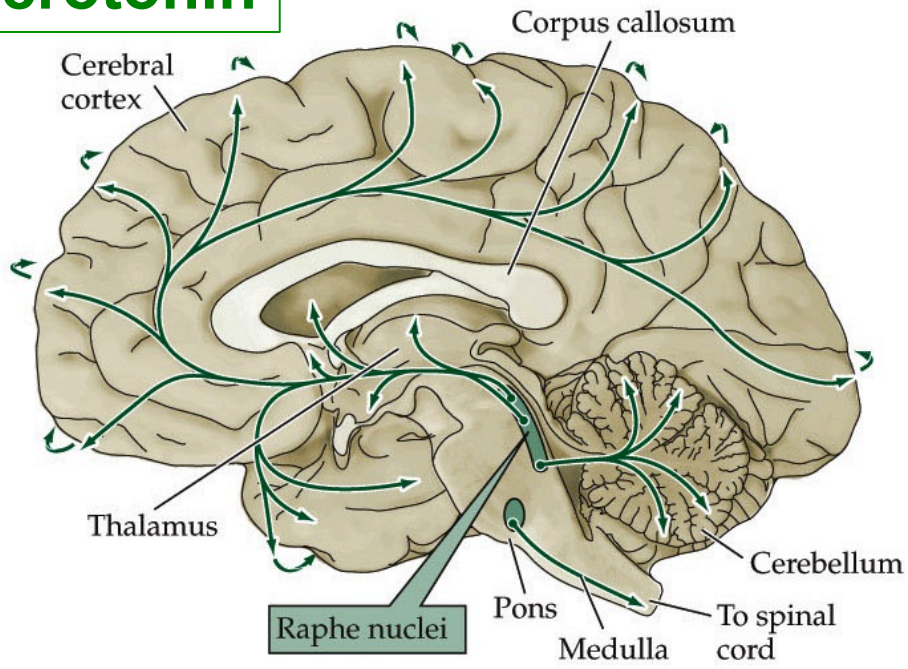
Epinephrine



Histamine



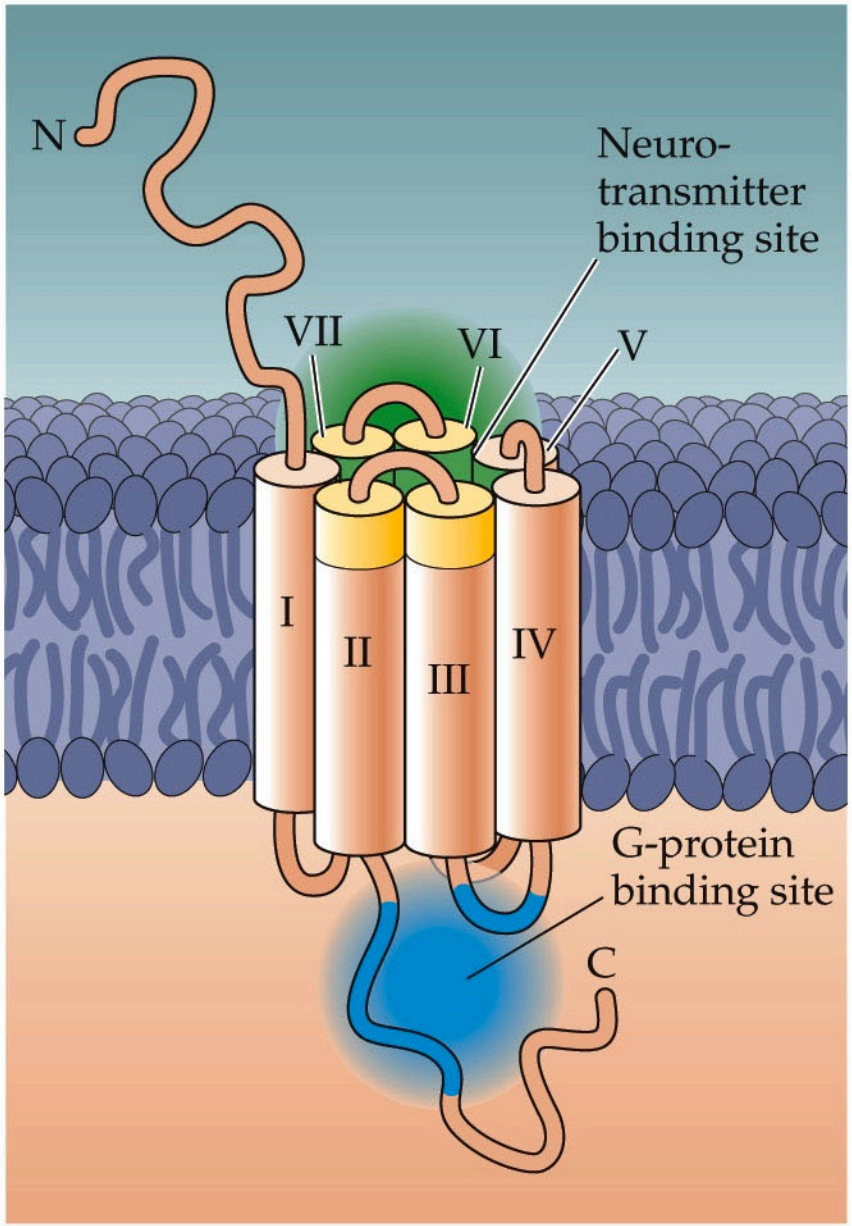
Serotonin



Neuromodulators have global effects!

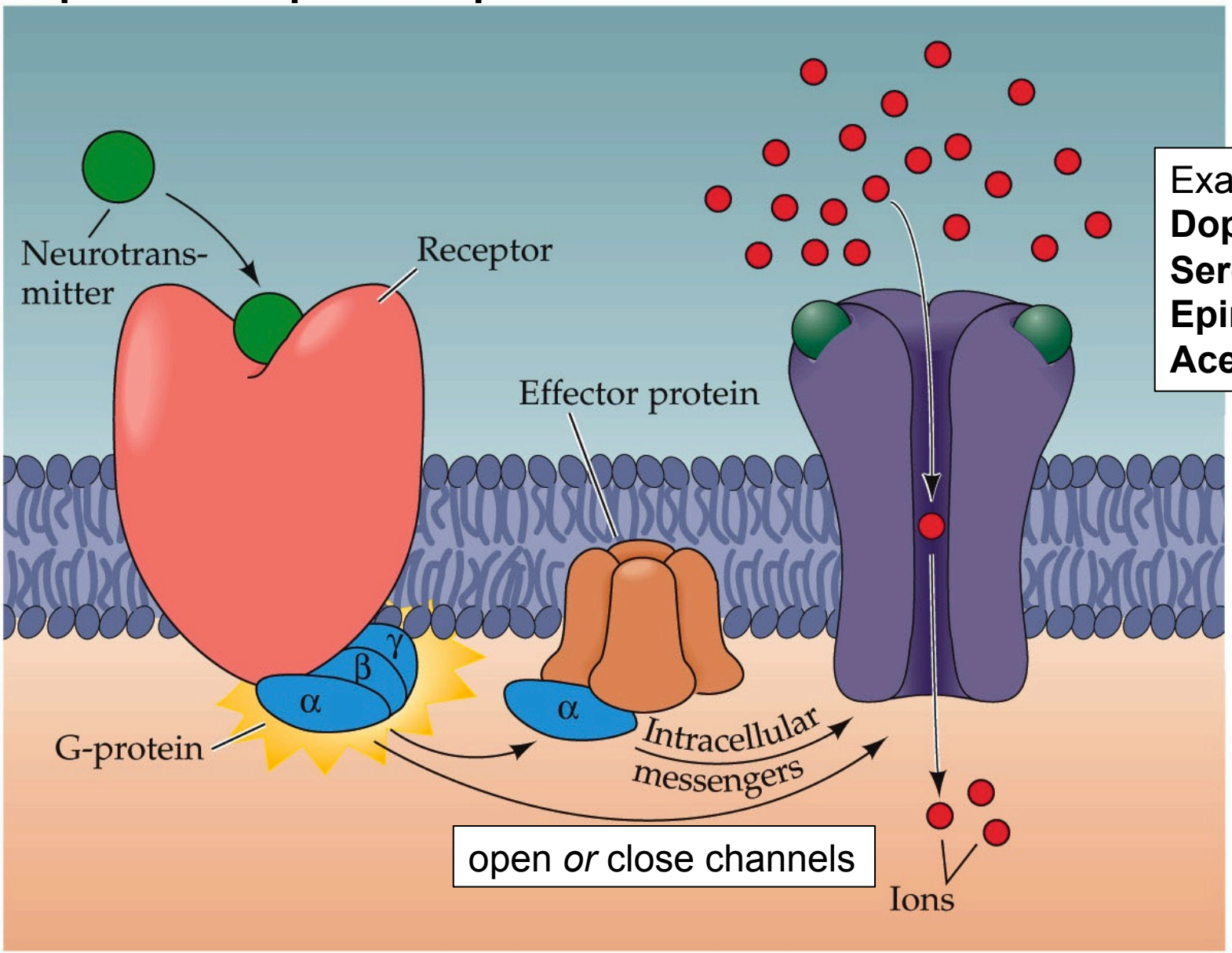
made by small clusters of cells (nuclei)
in brain stem or midbrain

project axons to many areas of brain

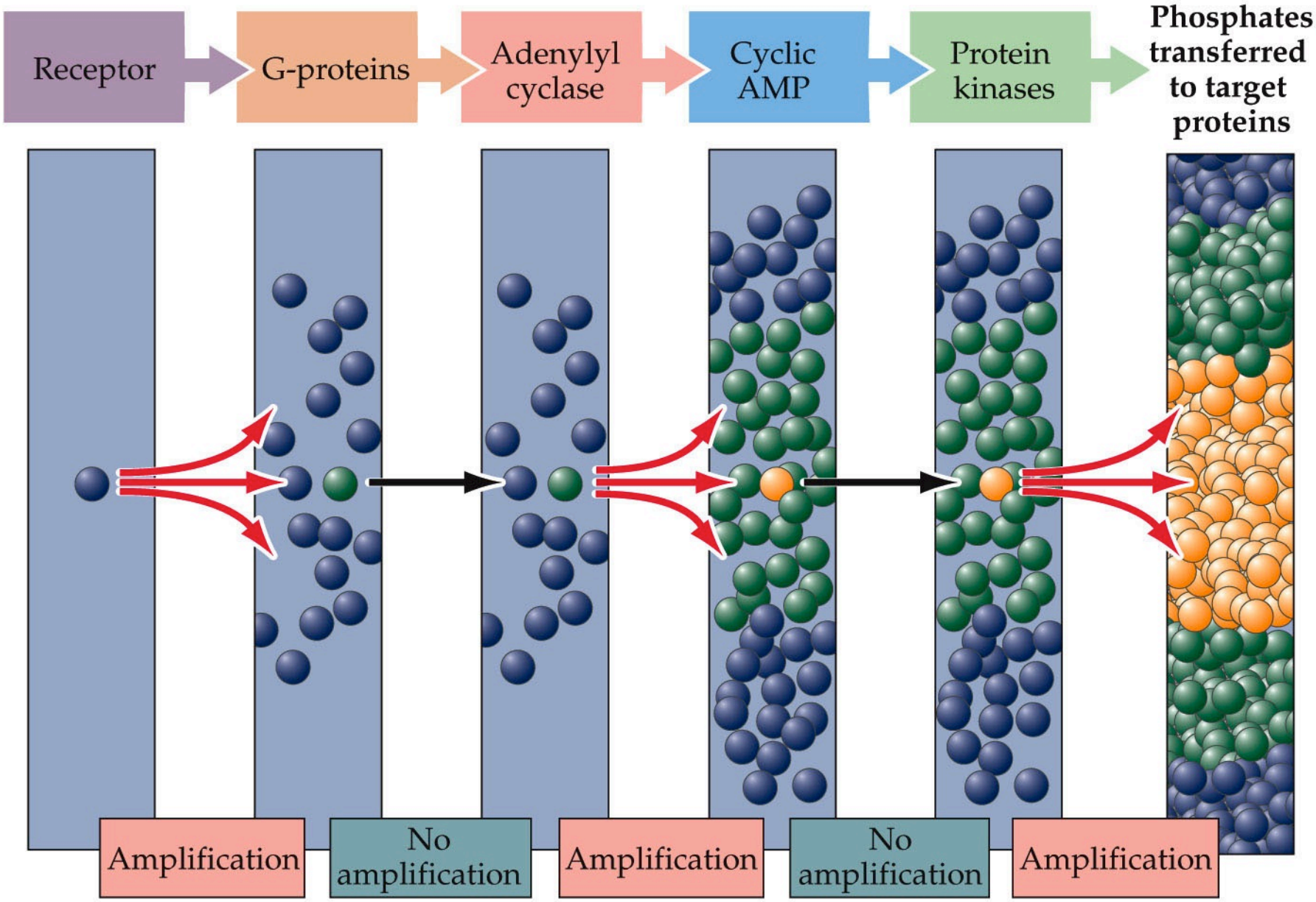


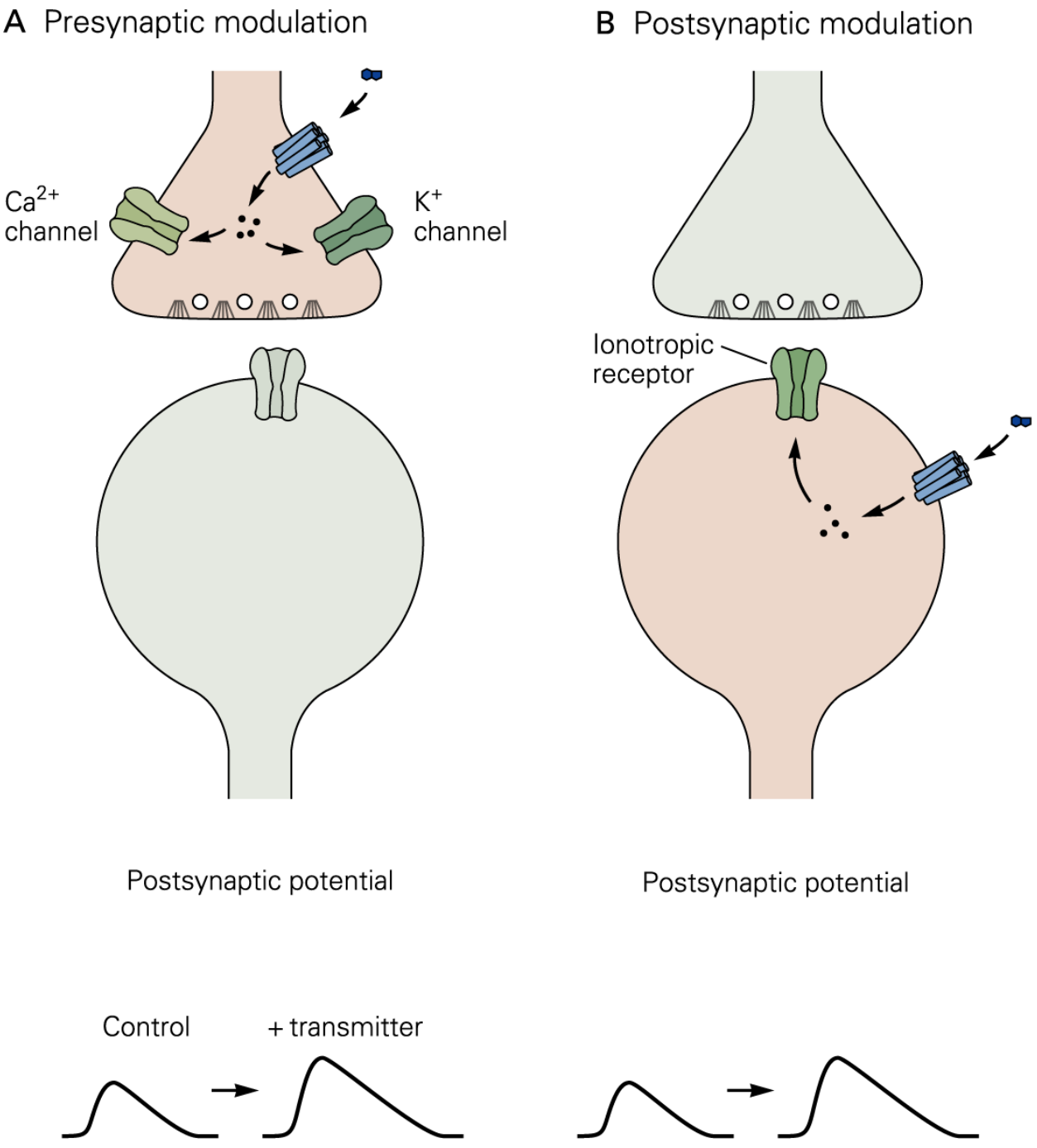
Examples:
Dopamine
Serotonin
Epinephrine
Acetylcholine

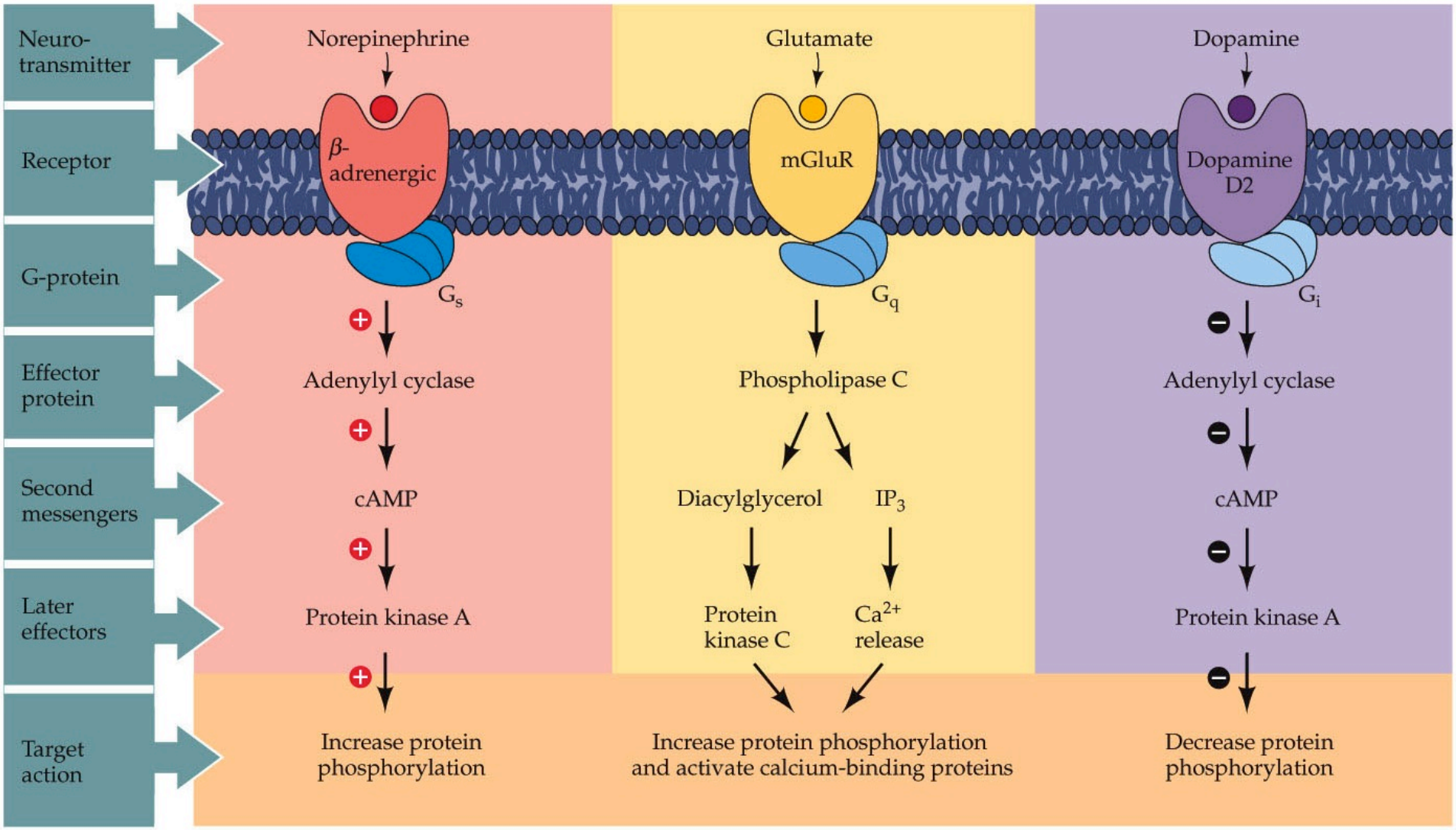
G-protein-coupled receptors



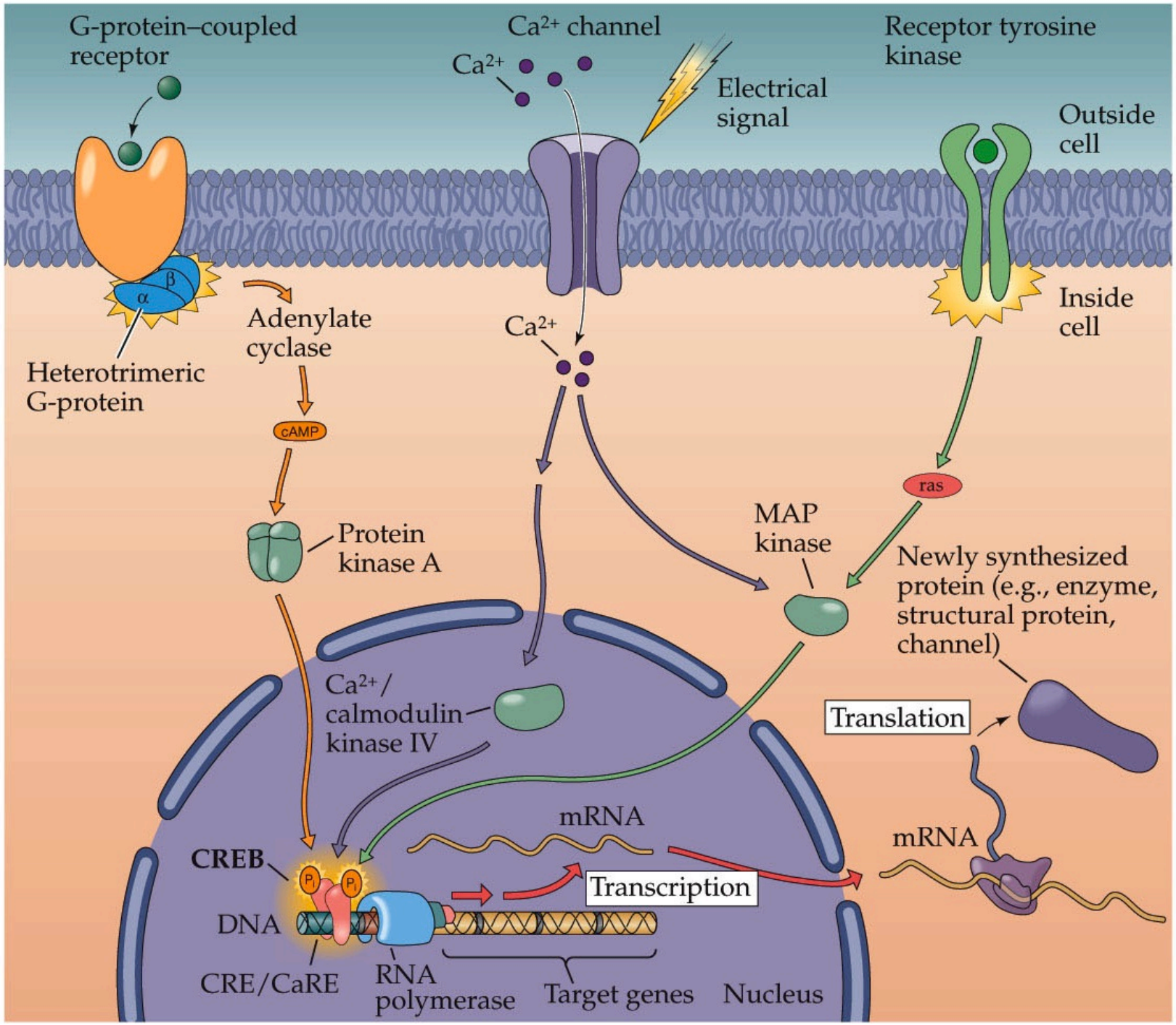
Examples:
Dopamine
Serotonin
Epinephrine
Acetylcholine

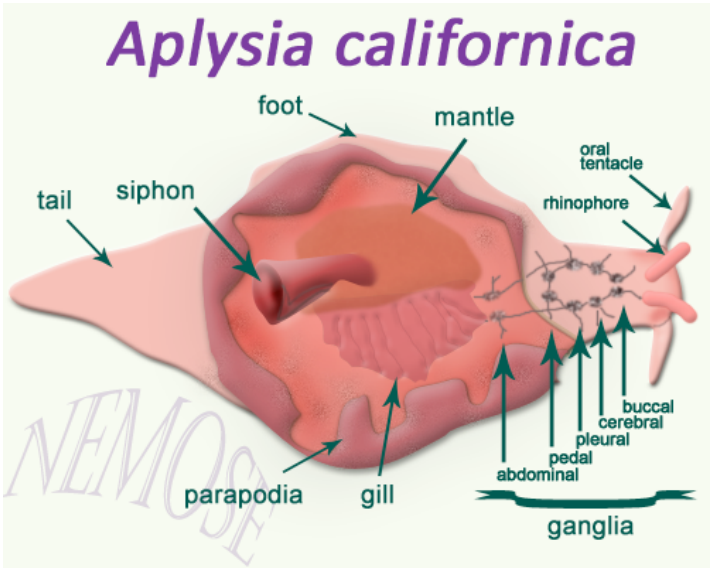

Receptor
G-proteins
Adenylyl cyclase
Cyclic AMP
Protein kinases
Phosphates transferred to target proteins
Amplification
No amplification
Amplification
No amplification
Amplification

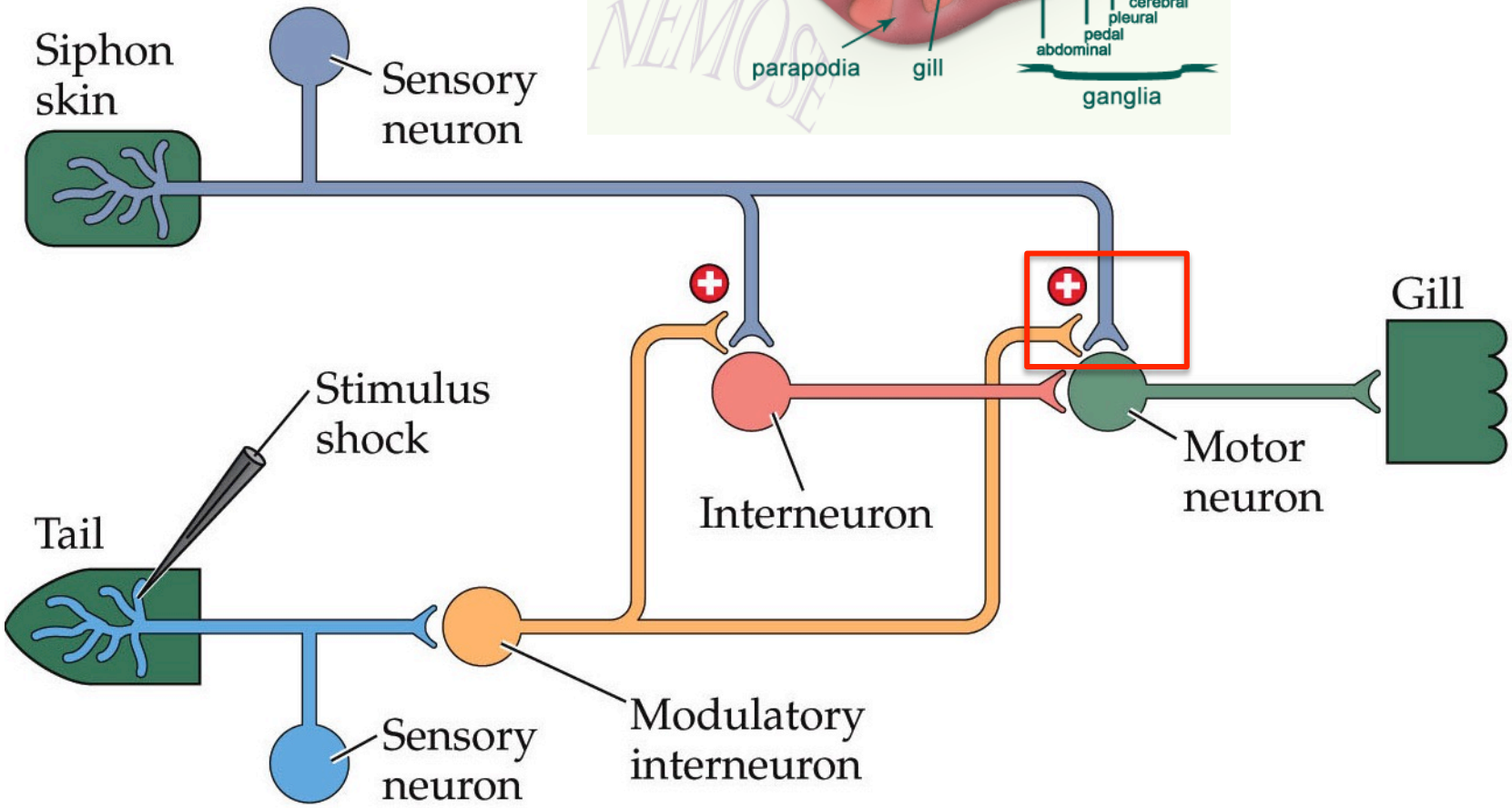

A Presynaptic modulation
Ca2+ channel
K+ channel
Postsynaptic potential
Control
+ transmitter
B Postsynaptic modulation
Ionotropic receptor
Postsynaptic potential

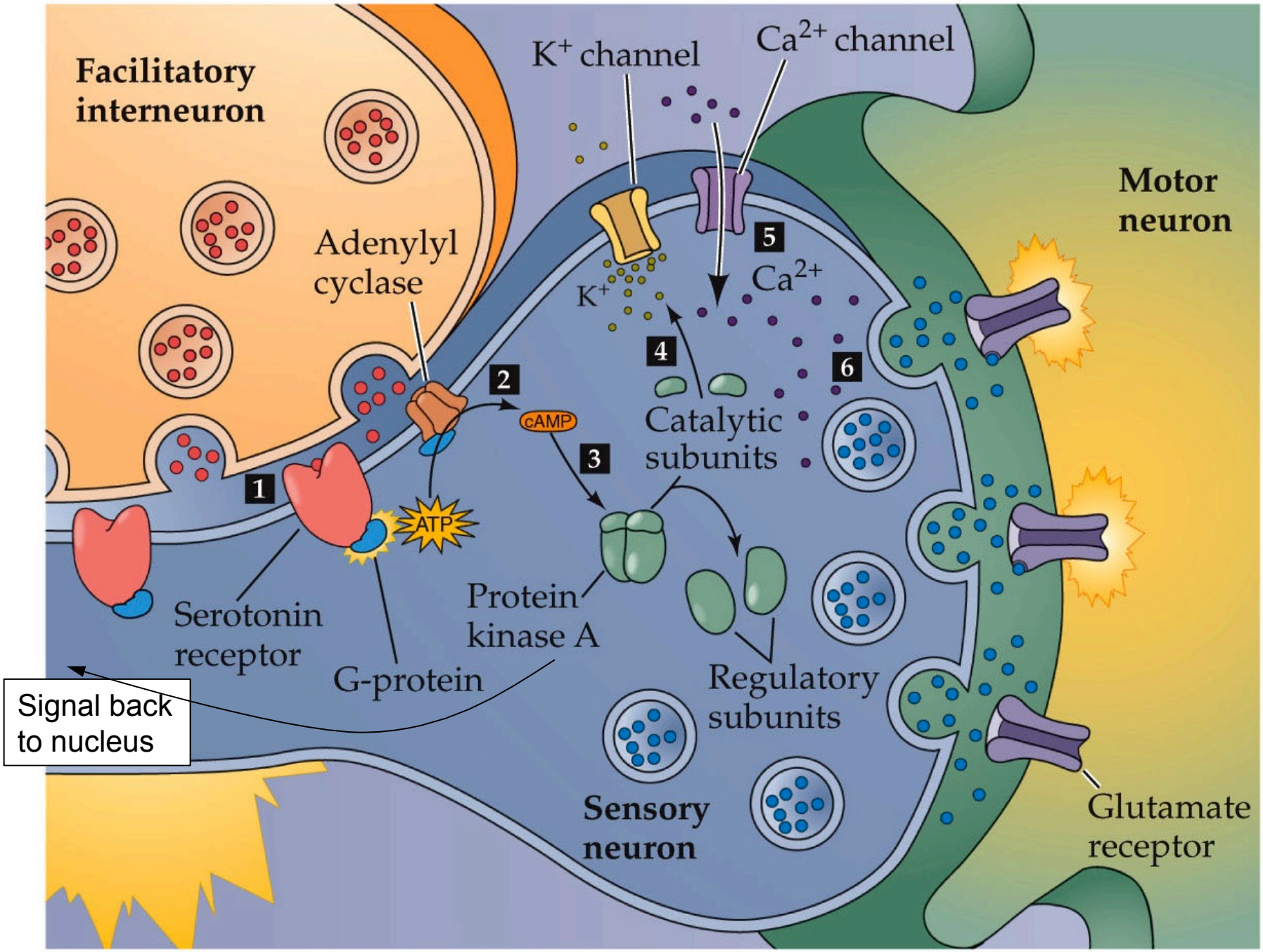


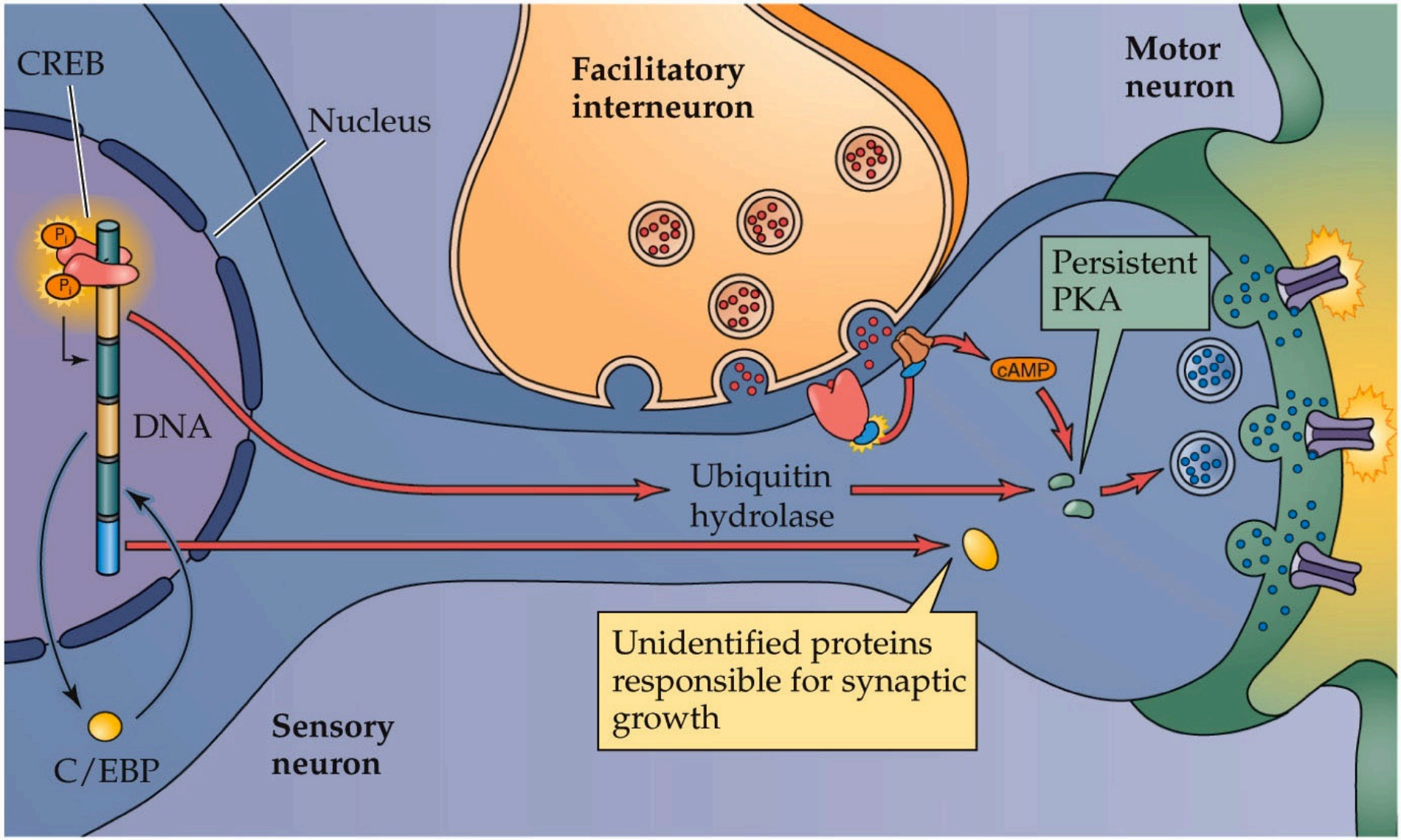
open/close ion channels
change gene expression
…


G-protein–coupled receptor
Ca2+ channel
Ca2+
Electrical signal
Receptor tyrosine kinase
Outside cell
Inside cell
β
α
Heterotrimeric G-protein
Adenylate cyclase
cAMP
Ca2+
ras
MAP kinase
Protein kinase A
Newly synthesized protein (e.g., enzyme, structural protein, channel)
Ca2+/ calmodulin kinase IV
Translation
mRNA
mRNA
CREB
Pi
Pi
Transcription
DNA
CRE/CaRE
RNA polymerase
Target genes
Nucleus


Aplysia californica
foot
mantle
oral tentacle
tail
siphon
rhinophore
buccal
cerebral
pleural
pedal
abdominal
parapodia
gill
ganglia
NEMOSE

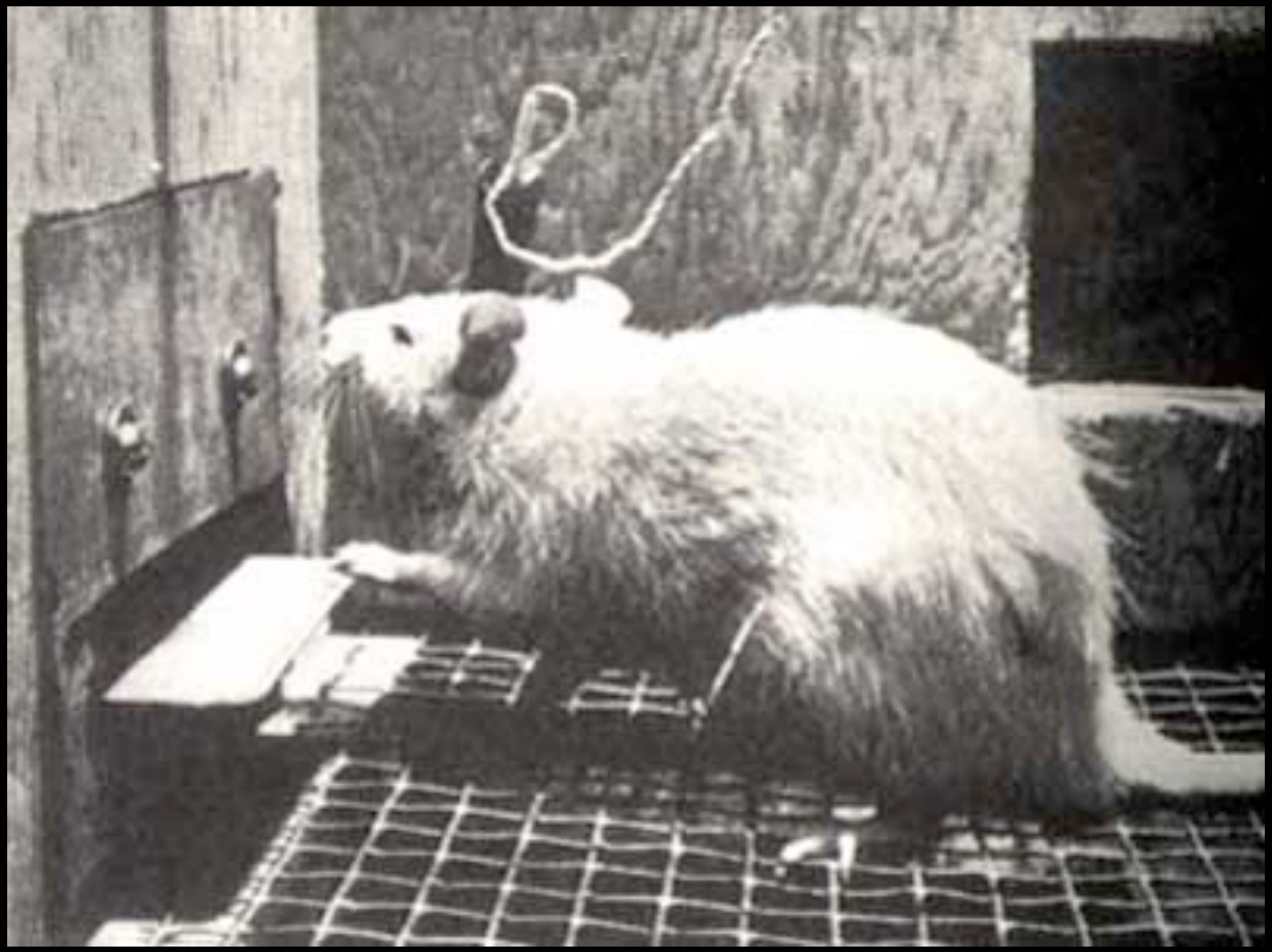

Siphon skin
Sensory neuron
Stimulus shock
Tail
Interneuron
Motor neuron
Gill
Sensory neuron
Modulatory interneuron


Facilitatory interneuron
K+ channel
Ca2+ channel
Motor neuron
Adenylyl cyclase
5
Ca2+
K+
4
6
2
cAMP
Catalytic subunits
3
1
ATP
Serotonin receptor
G-protein
Protein kinase A
Regulatory subunits
Signal back to nucleus
Sensory neuron
Glutamate receptor

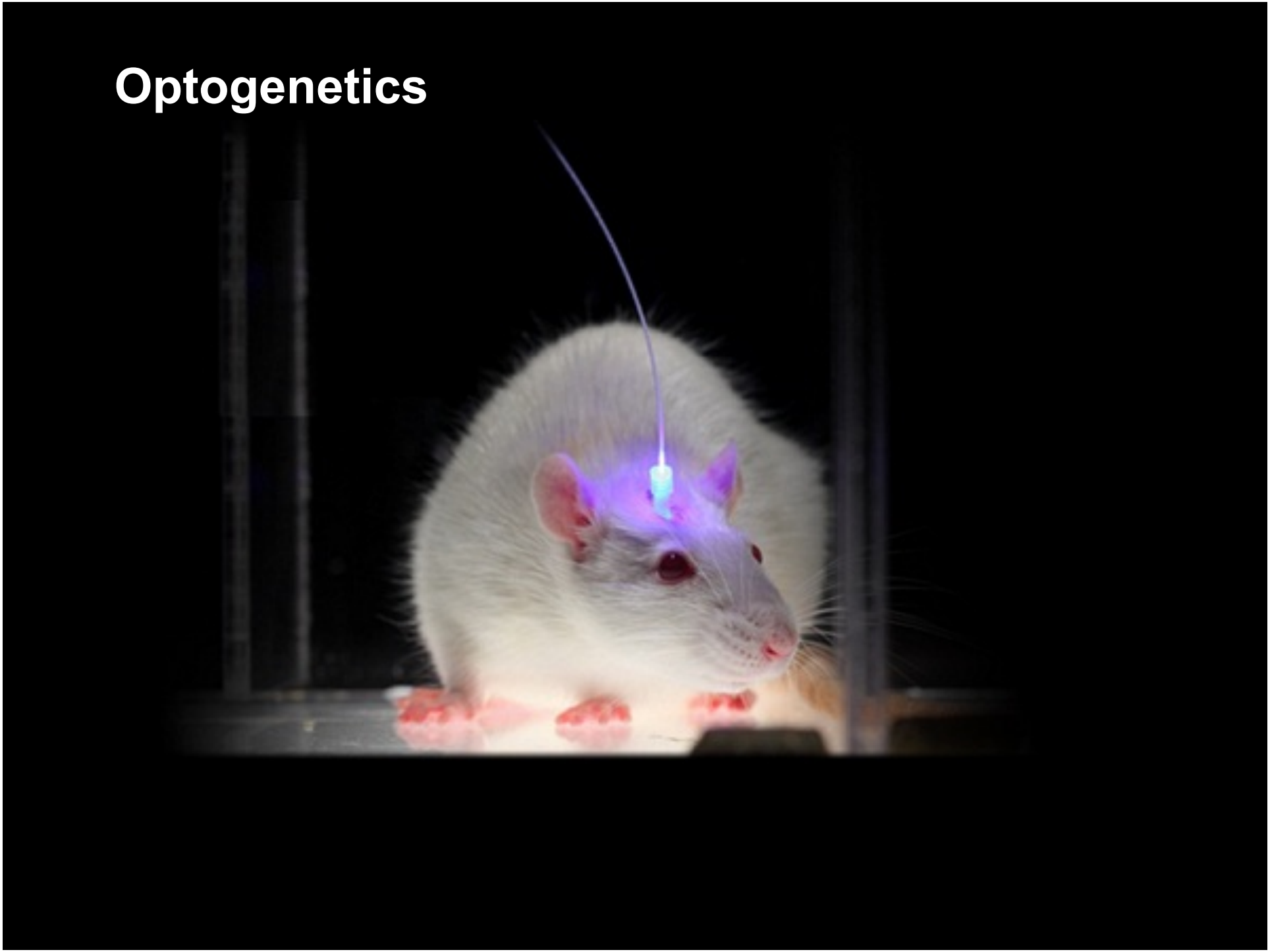

CREB
Nucleus
Facilitatory interneuron
Motor neuron
Persistent PKA
cAMP
DNA
Ubiquitin hydrolase
Unidentified proteins responsible for synaptic growth
C/EBP
Sensory neuron

Brain stimulation reward

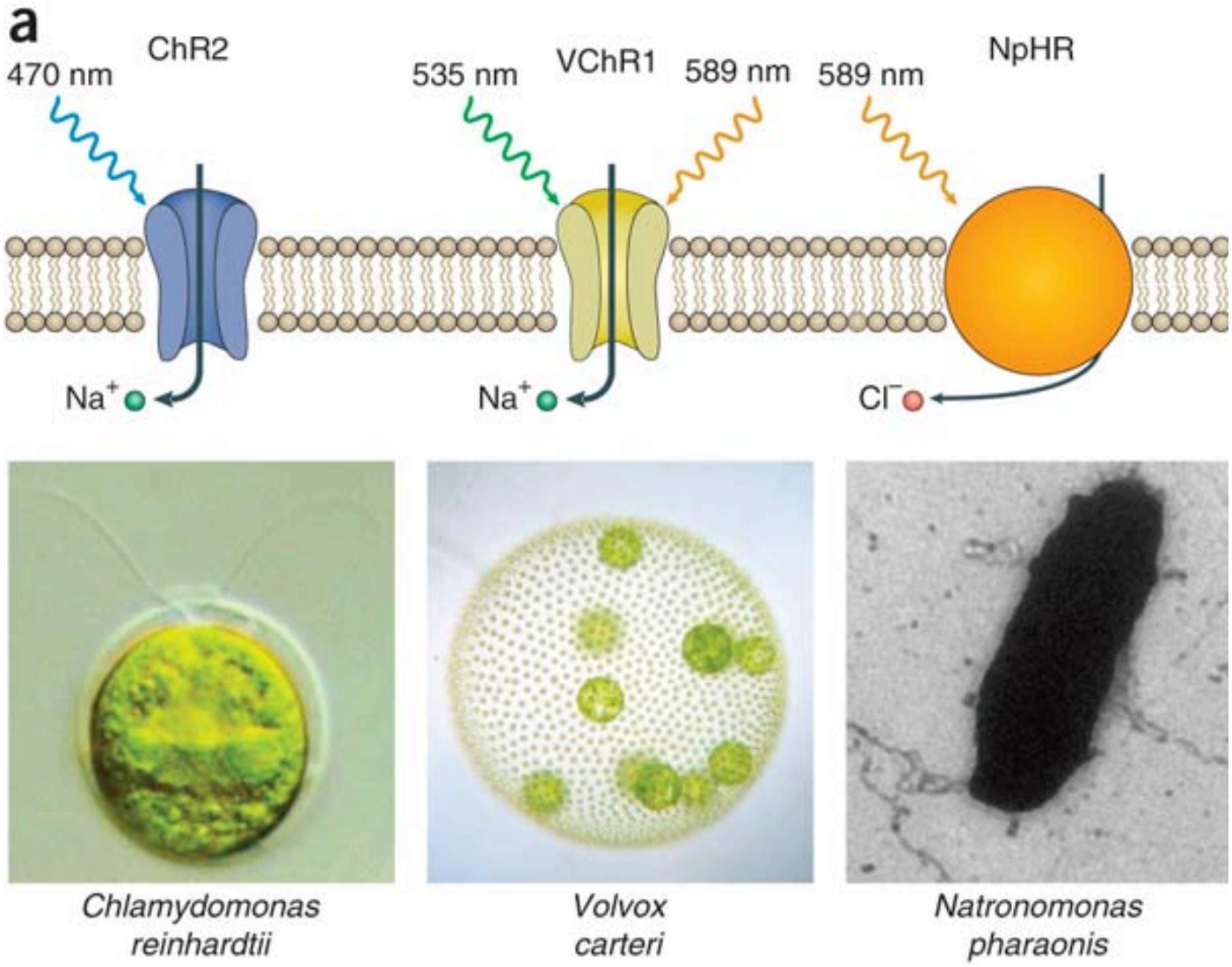
Olds and Milner 1953



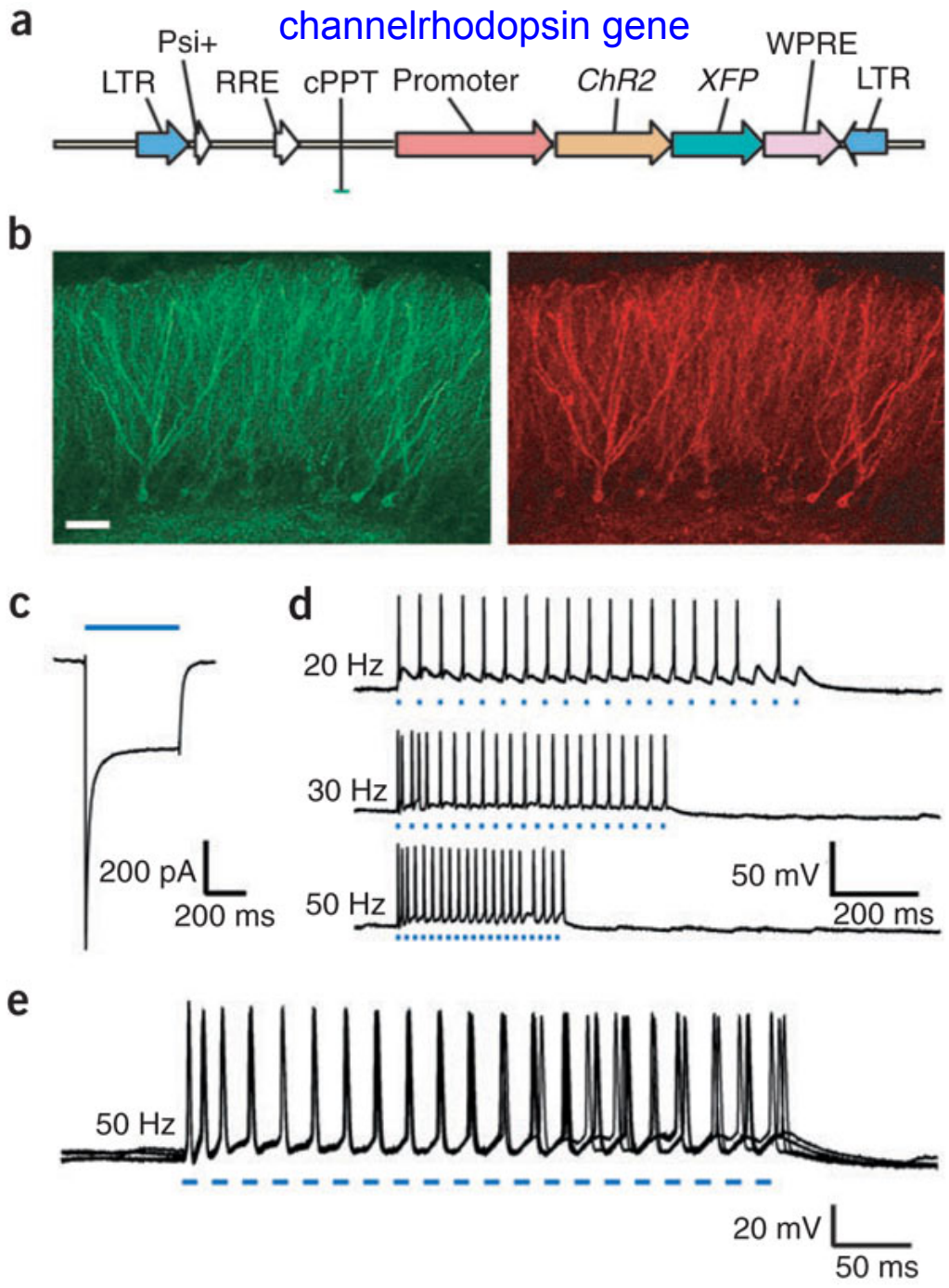
Optogenetics



Optogenetics activating neurons with light



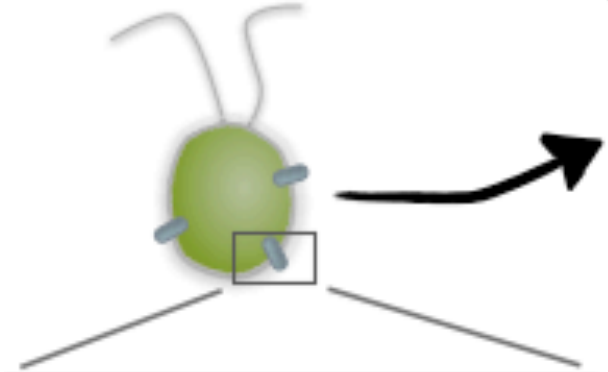
Zhang *et al.* 2010



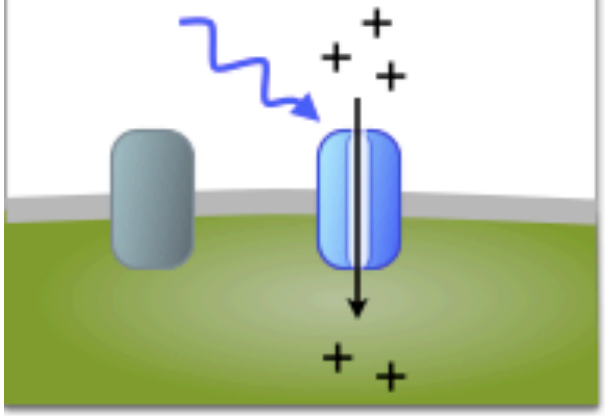
Zhang *et al.* 2006

How optogenetics works

A light-sensitive protein from algae

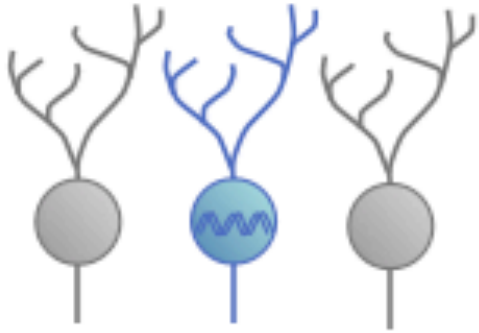


This protein is an ion channel that opens in response to **blue light**



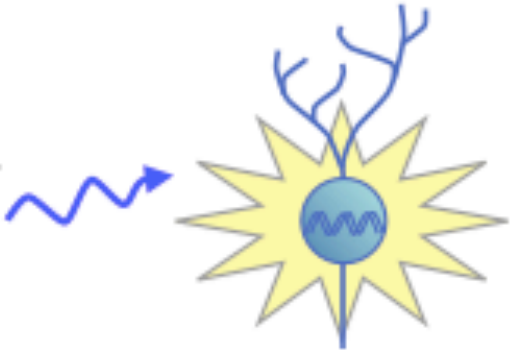
Take the gene for this protein...

... and insert the DNA into specific neurons in the brain

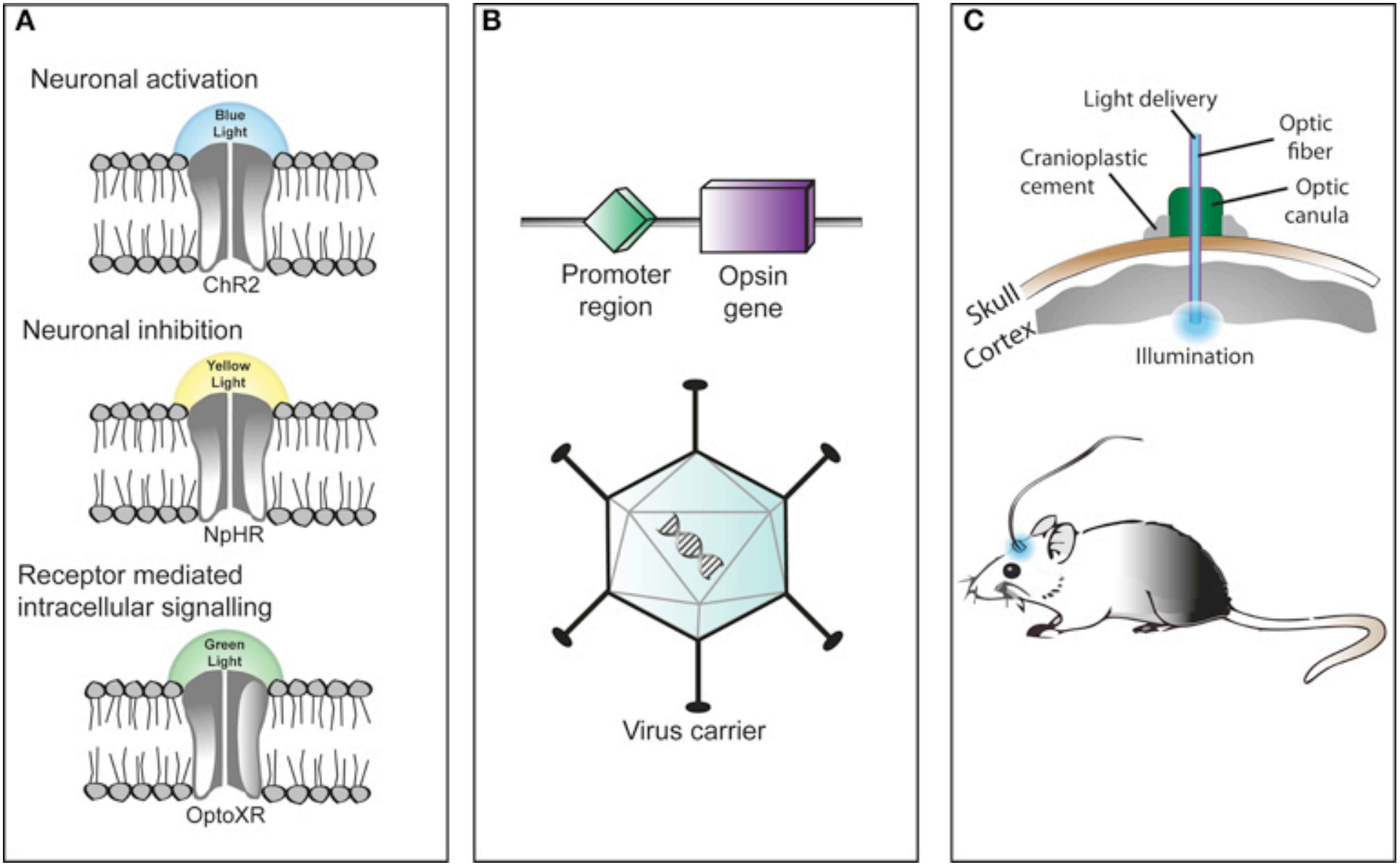


Neurons communicate by "**firing**." This is an electrical signal created by opening & closing ion channels.

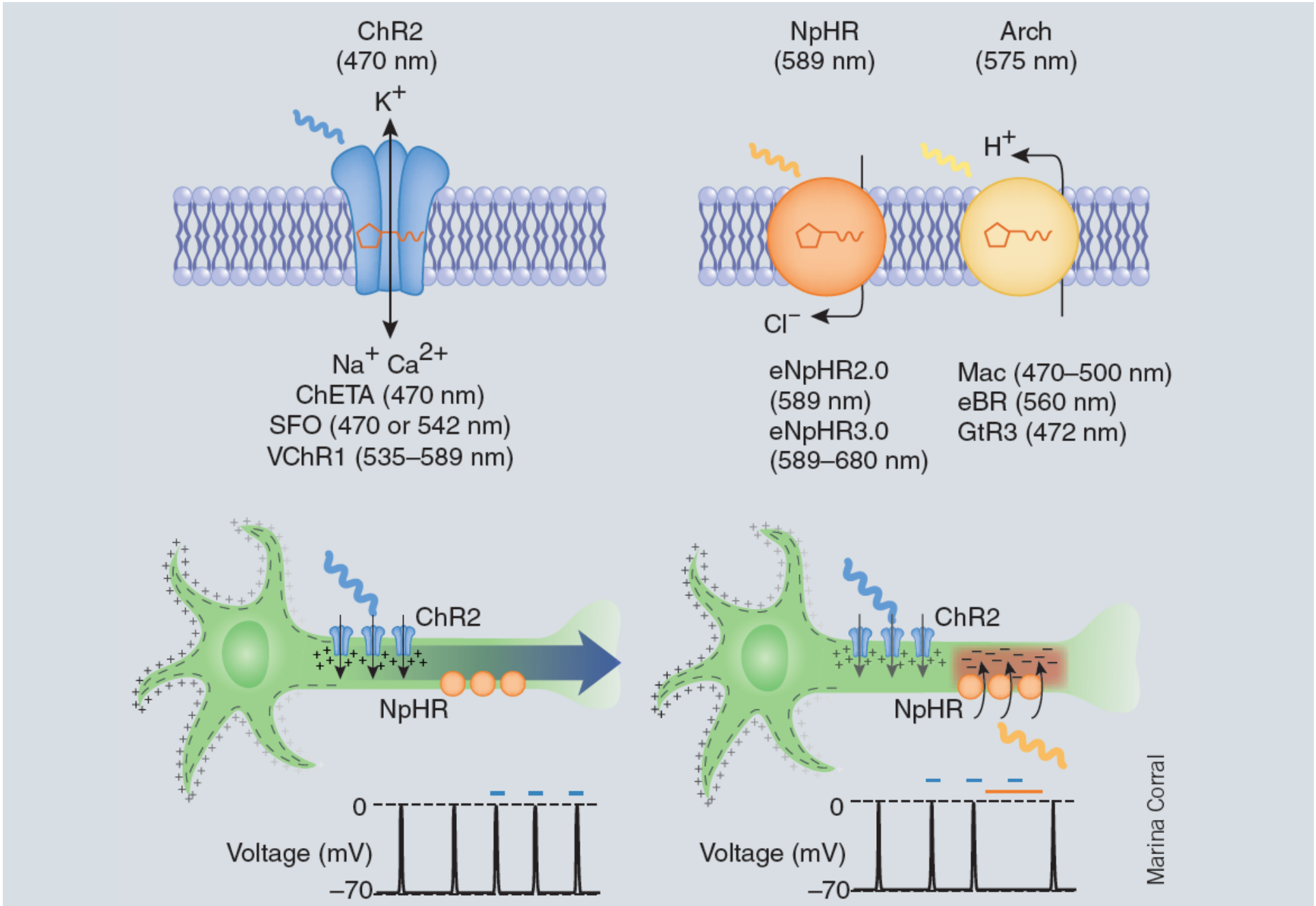
So now you can cause neurons to fire just by flashing **blue light!**



With the right combination of neurons, you can activate an entire brain circuit to control specific behaviors (like movement)



Pama *et al.* 2013



Optogenetic tools for modulating membrane volage potential.

Journal Club

LETTER

doi:10.1038/nature10194

Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking

Garret D. Stuber[1,2], Dennis R. Sparta[1,2], Alice M. Stamatakis[1], Wieke A. van Leeuwen[2], Juanita E. Hardjoprajitno[2], Saemi Cho[2], Kay M. Tye[2,3], Kimberly A. Kempadoo[2], Feng Zhang[3], Karl Deisseroth[3] & Antonello Bonci[2,4]

Acronym soup:

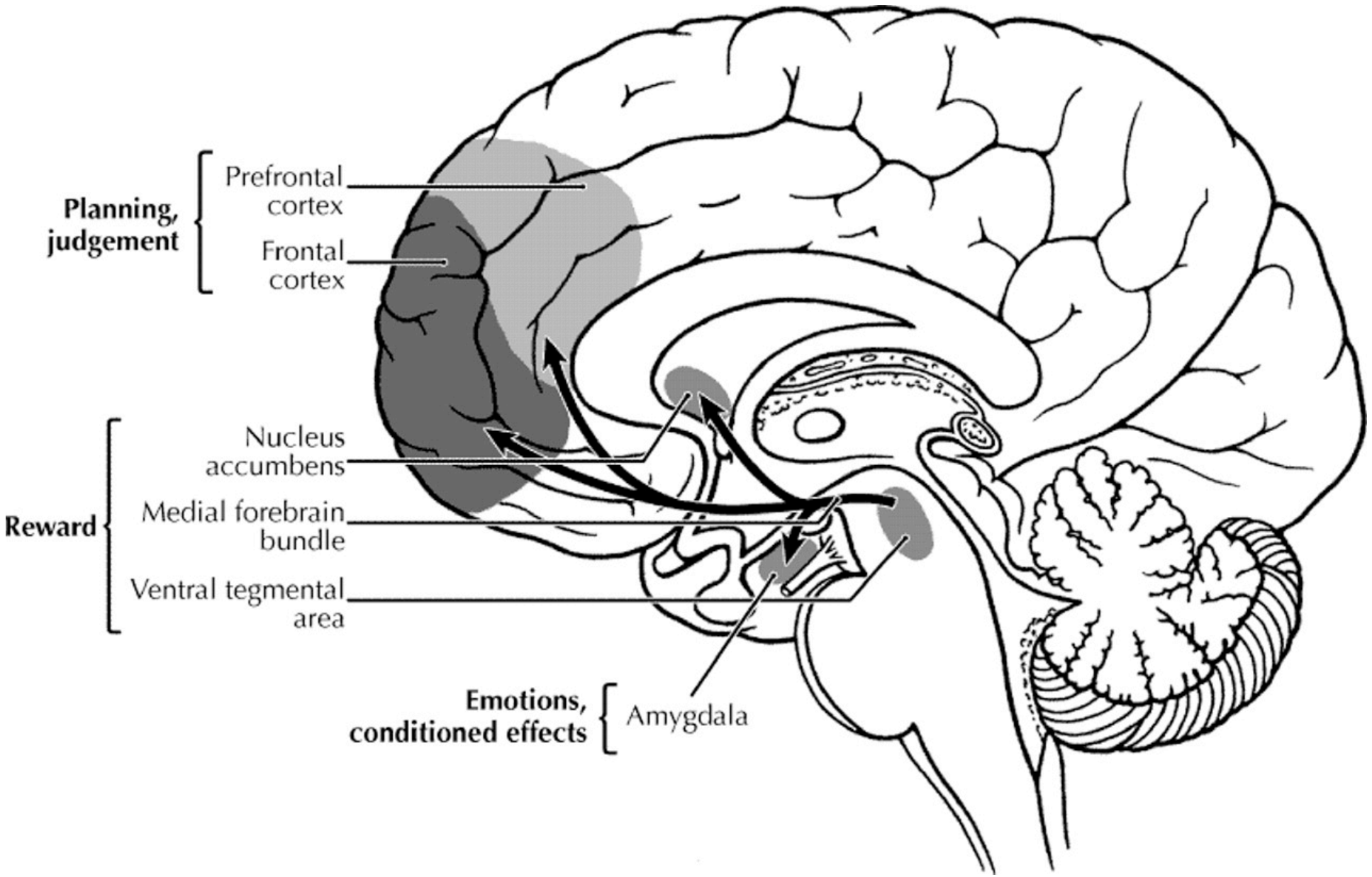
BLA = basolateral amygdala

NAc = nucleus accumbens

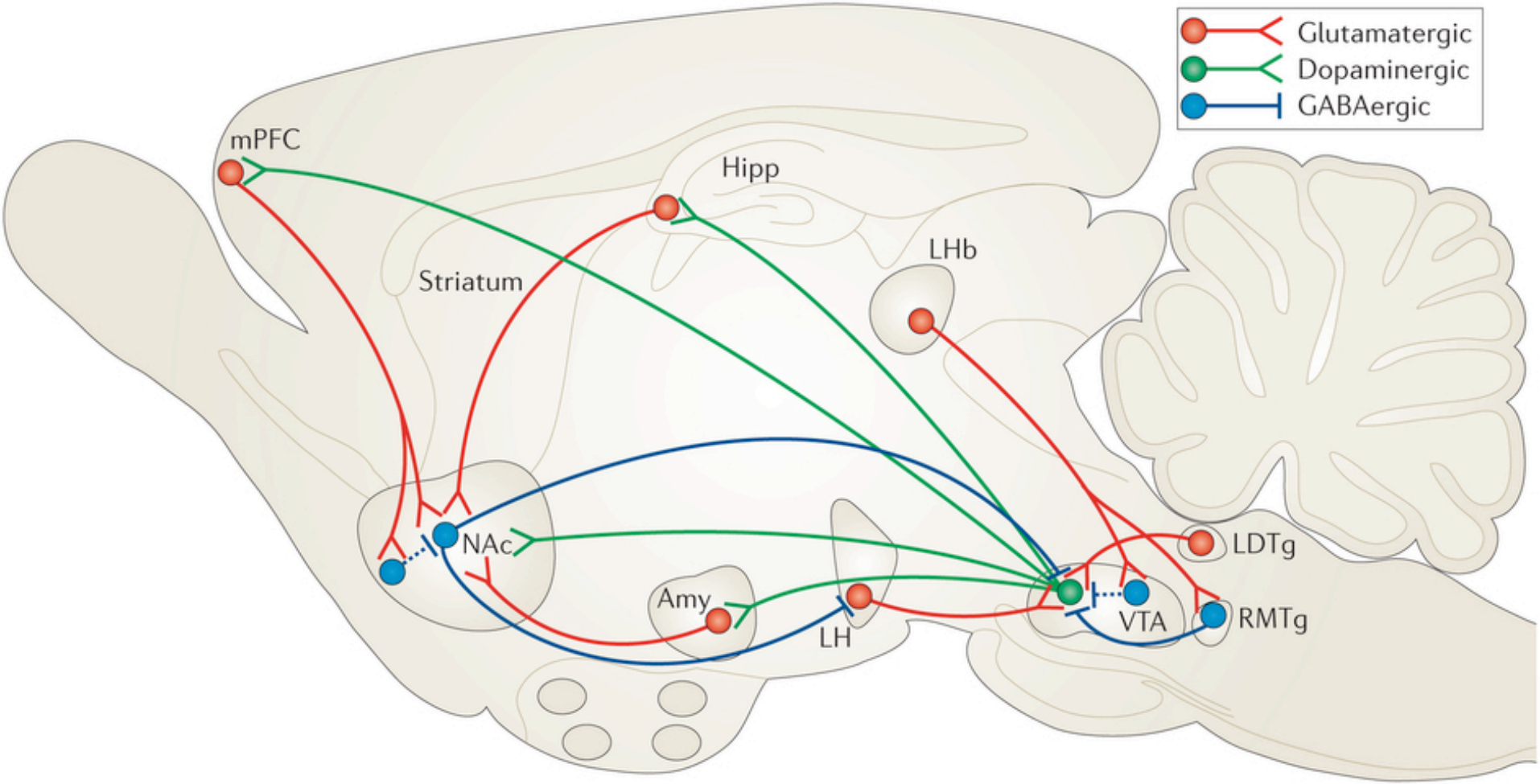
ChR2 = channelrhodopsin-2

EYFP = enhanced yellow fluorescent protein

Mesolimbic reward system



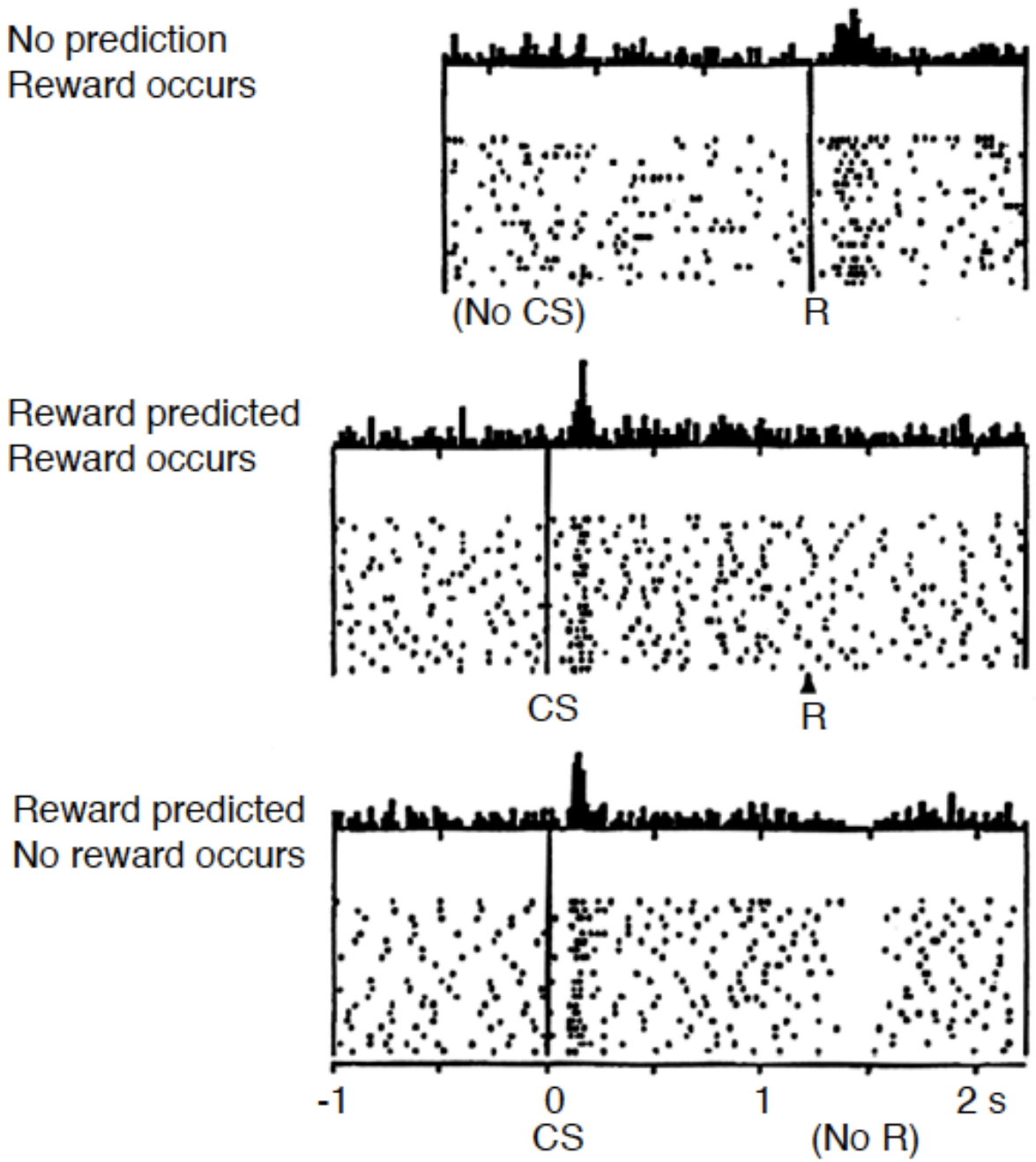
Mesolimbic reward system



Nature Reviews | Neuroscience

SJ Russo and EJ Nestler 2013

Do dopamine neurons report an error in the prediction of reward?



Schultz *et al.* 1997

Figure 1: **Expression of ChR2–EYFP in BLA neurons and fibres projecting to the NAc.**