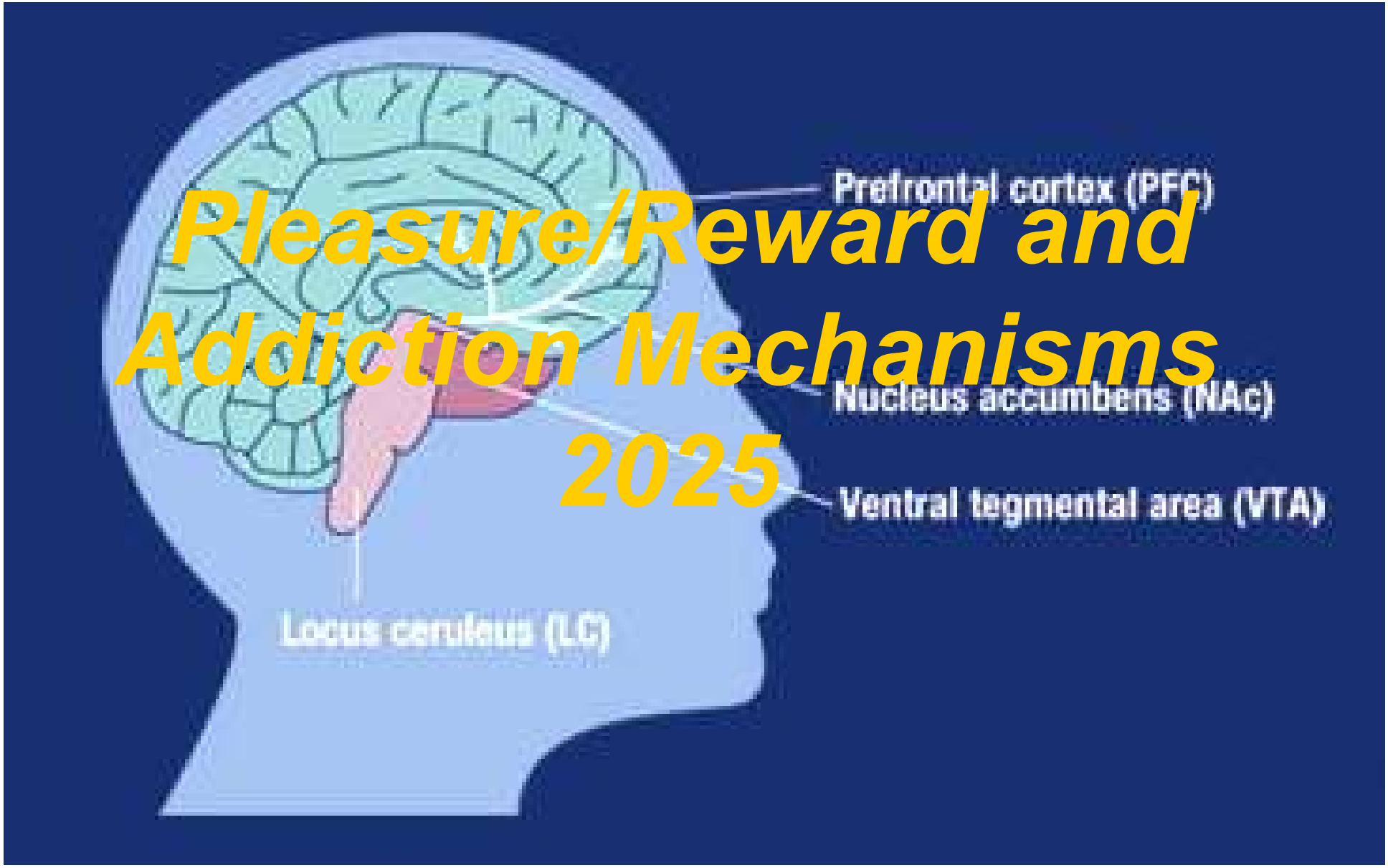
UCL School of Pharmacy



Pleasure/Reward and Addiction Mechanisms 2025

Pleasure/reward

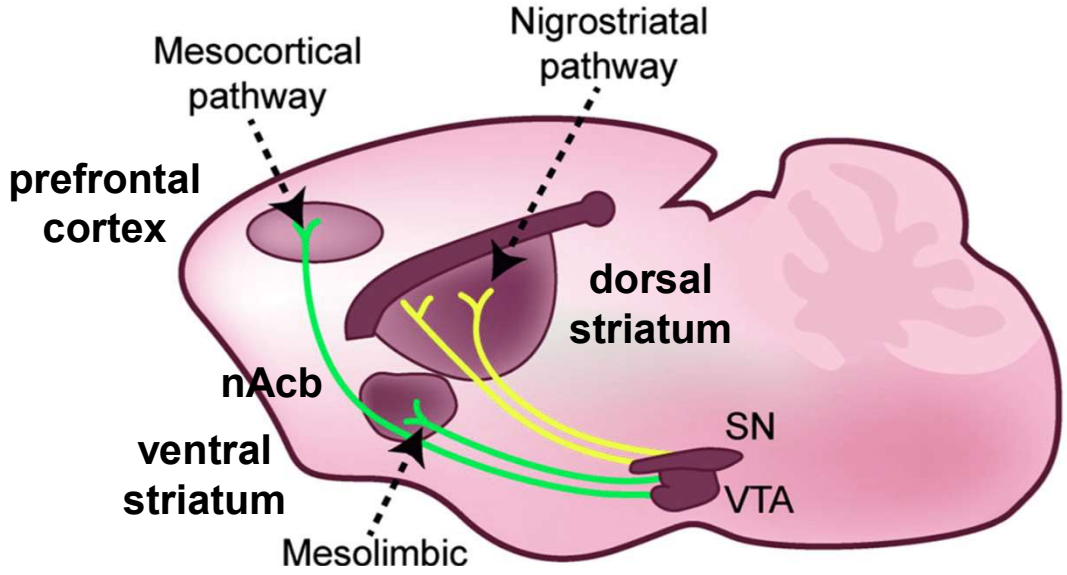
- **Pleasure** is a complex, subjective neurobiological phenomenon, described as **"a state or feeling of happiness and satisfaction resulting from an experience that one enjoys".**

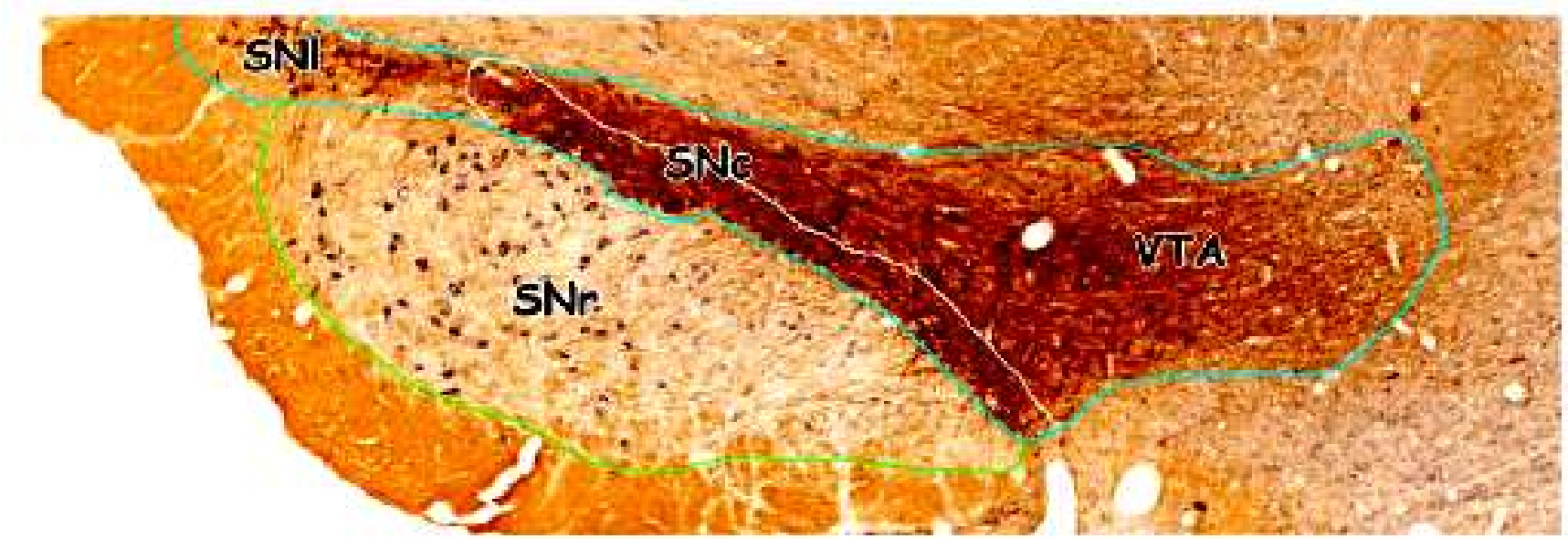
- During evolution, human survival has depended upon the development of pleasure/reward pathways in the brain, which on activation [by touch, sight, smell, hunger, thirst *etc*.] lead to strong emotional feelings of satisfaction and well-being.

Pleasure/reward circuit

- The central reward circuit consists of the **ventral tegmental area (VTA)** of the midbrain, and the **nucleus accumbens (NAcb)** – forming part of the **mesolimbic system.**
- The main neurotransmitter connection between these two areas involves dopamine-releasing neurones running in the **ascending mesolimbic dopamine pathway.** The dopaminergic neurones of the mesolimbic pathway project onto the GABAergic medium spiny neurones (MSNs) of the nucleus accumbens expressing either excitatory D1 or inhibitory D2-type dopamine receptors (or both).
- Dopaminergic axons also project from VTA to the amygdala and lateral hypothalamus.

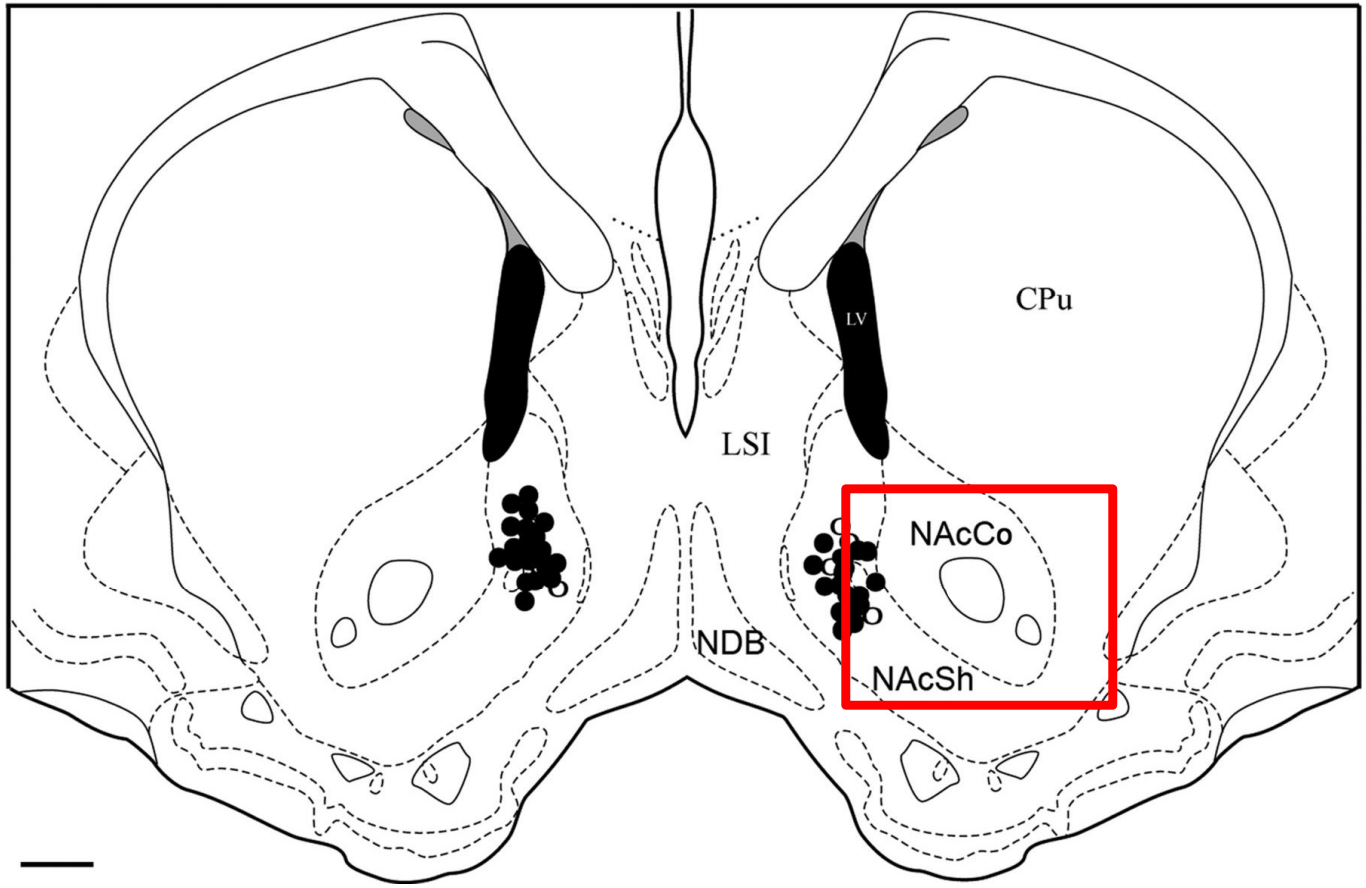
Pleasure/reward circuit





Coronal section of ventral midbrain of the rat showing VTA and SN

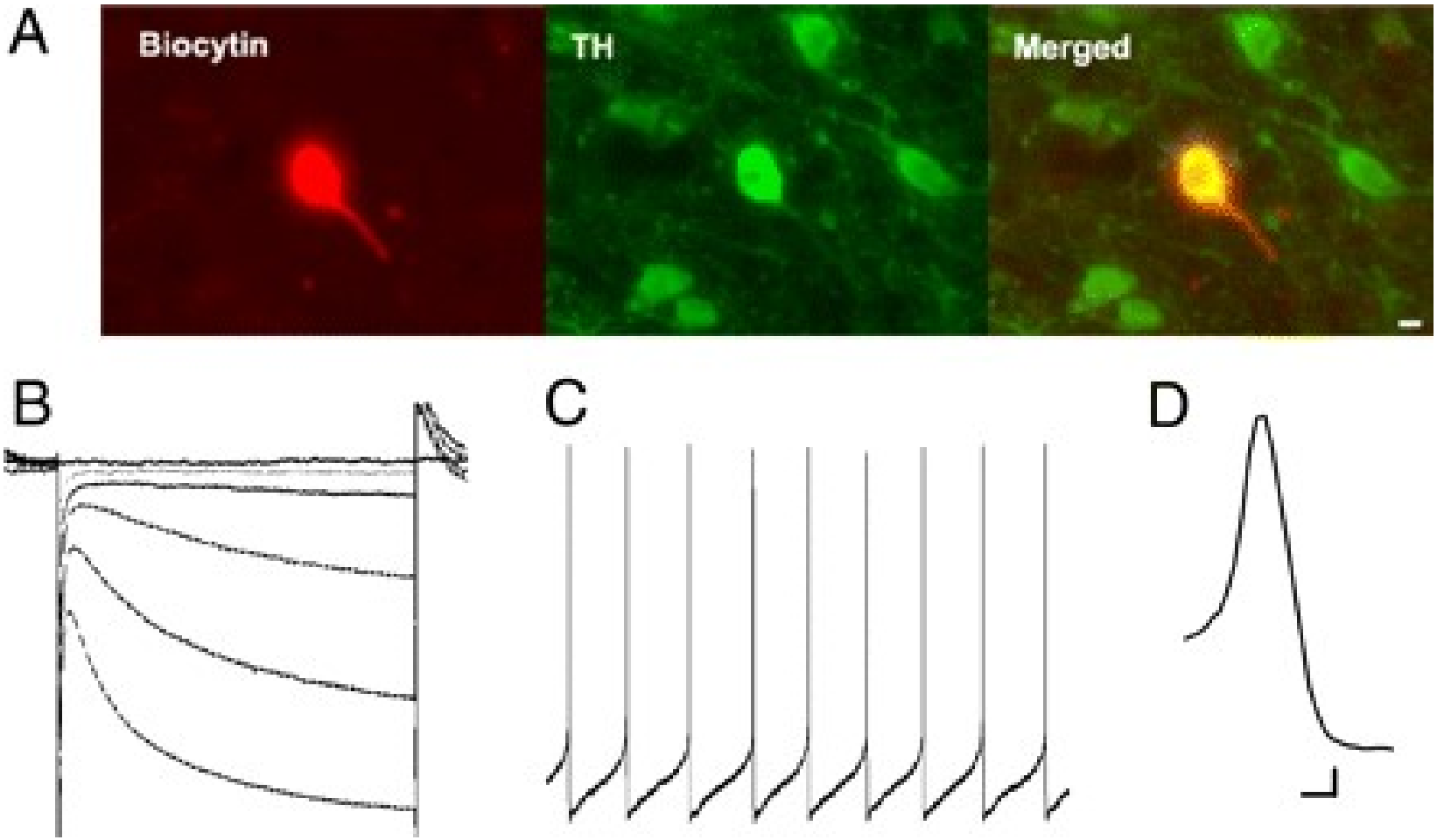
Pleasure/reward circuit



Coronal section of rat brain showing the position of the nucleus accumbens core (NAcCo) and nucleus accumbens shell (NAcSh).

CPu=Caudate putamen; LSI=Lateral septal nucleus pars intermedia; NDB=Diagonal band nucleus

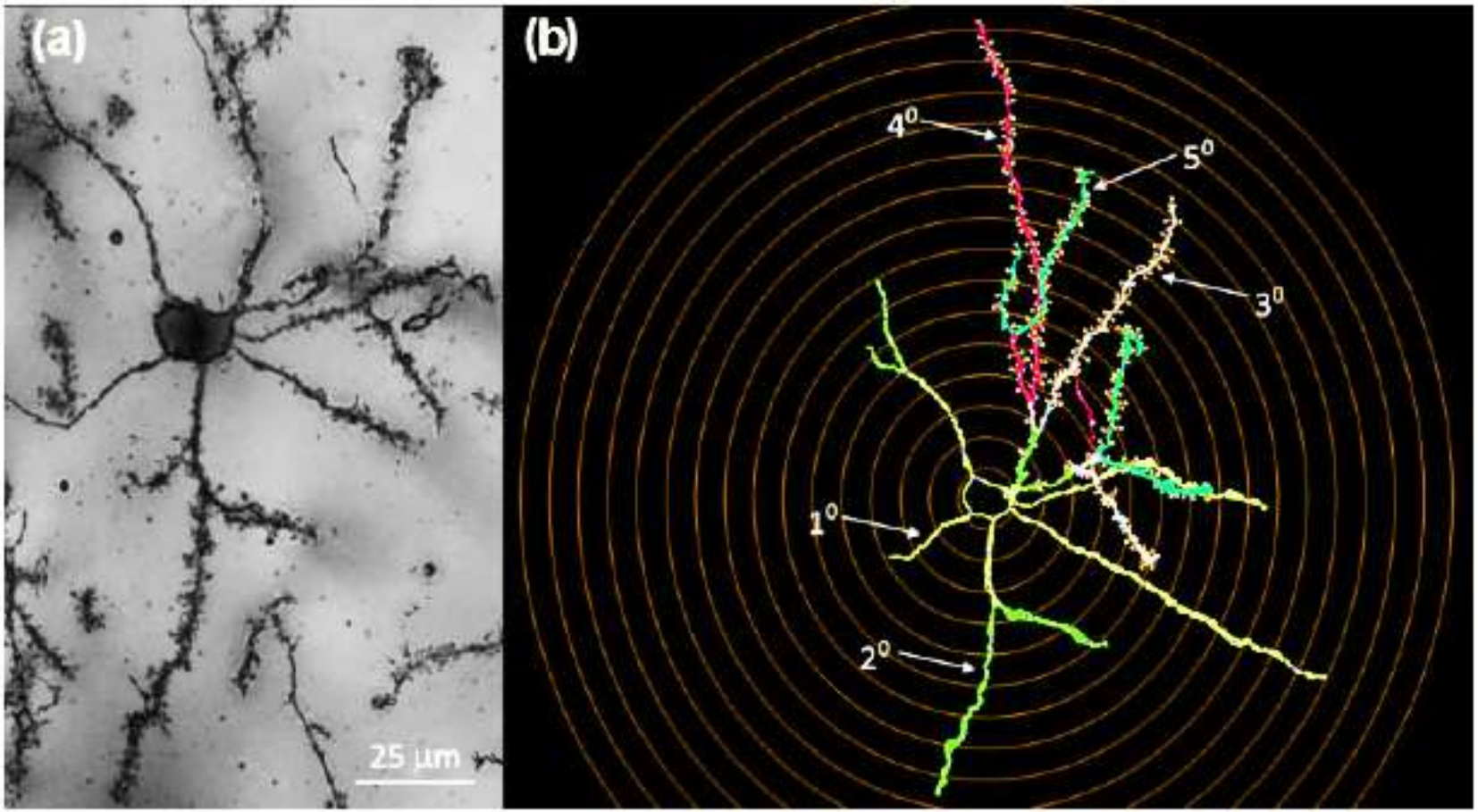
Pleasure/reward circuit



Dopamine VTA neurone ***A***, Immunohistochemistry: Left, Biocytin staining; middle, TH staining; right, co-labeling of biocytin and TH ***B***, I_h currents induced by 10 mV hyperpolarizing steps from -40 mV, in a VTA neurone. ***C***, Whole-cell recording of regular spontaneous firing in a VTA neurone. ***D***, Single action potential from a VTA neuron. Scale bar: ***A***, 10 μm. Calibration: ***B***, 80 ms, 80 pA; ***C***, 350 ms, 6.25 mV; ***D***, 1.0 ms, 10 mV.

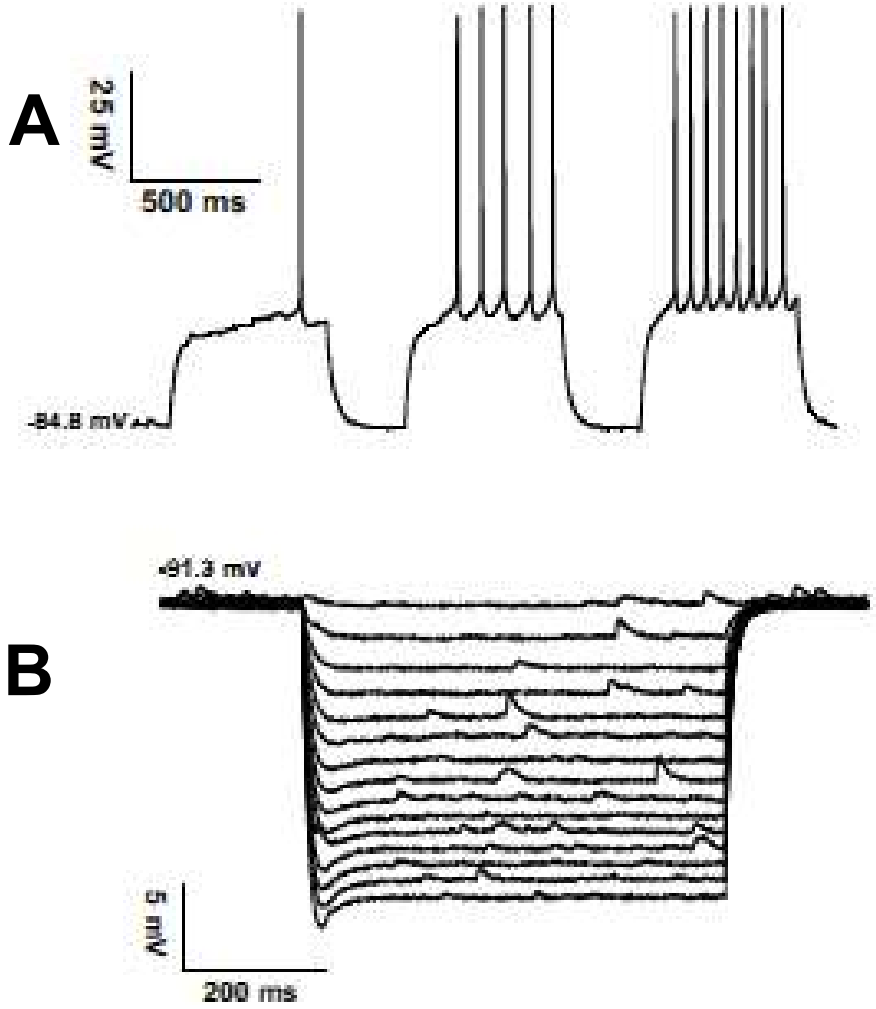
Danyan et al., (2011). J. Neurosci., 31 (18) 6710-6720

Pleasure/reward circuit



Nucleus accumbens medium spiny neurone (MSN) and its digital tracing. (a) A 60× photomicrograph of a MSN in the mouse nucleus accumbens (NAc) stained with the Golgi-Cox method. (b) Digital tracing of the same NAc MSN. A grid of concentric circles of increasing radii is superimposed on the neurone's digital tracing for Sholl analysis. The number of dendritic intersections is defined as the number of times each circle is contacted by a dendritic branch. ***Kobrin et al., (2016). Addict Biol. 21(6):1086-1096.***

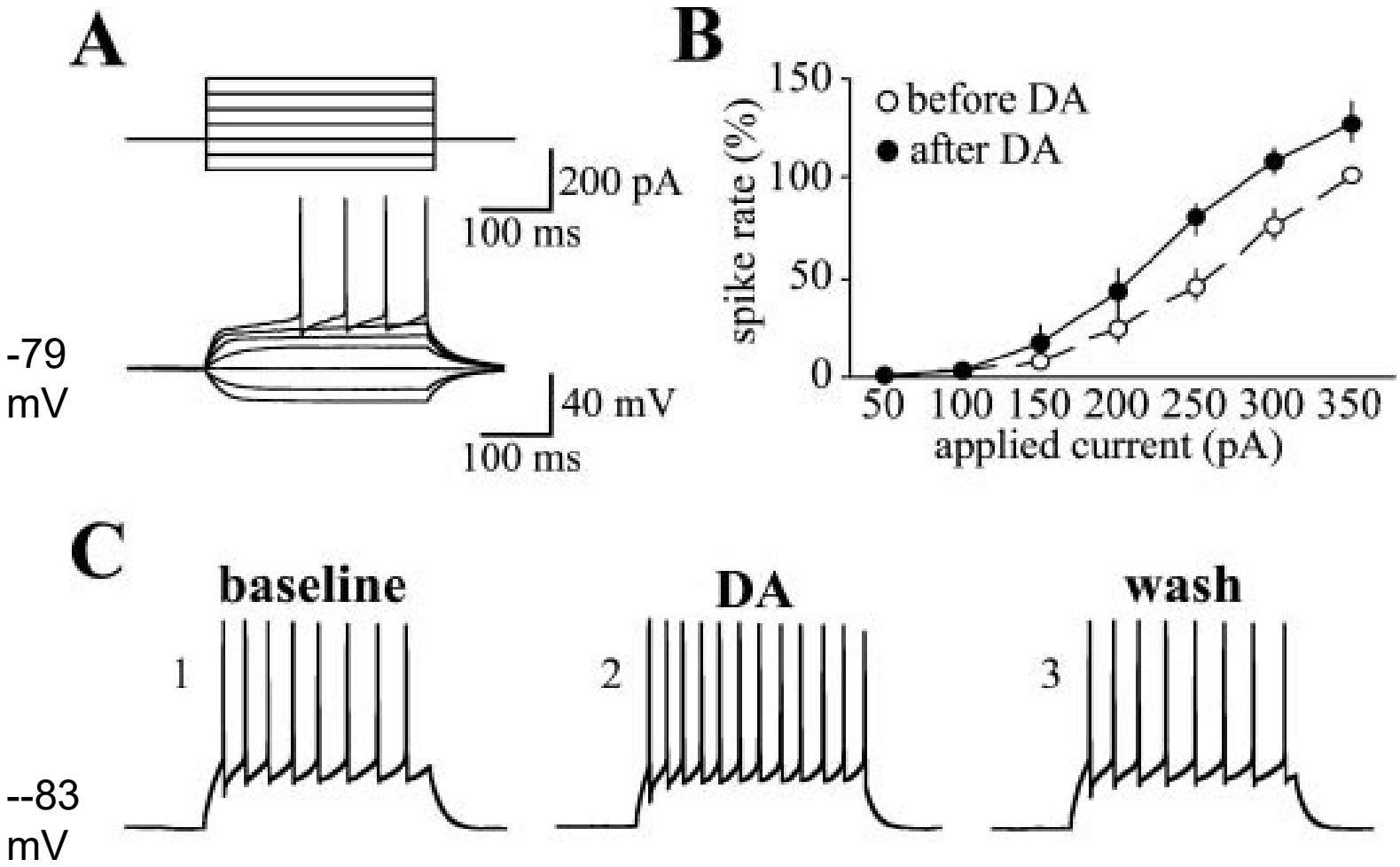
Pleasure/reward circuit



Medium spiny neurone (MSN) action potential properties. A, Voltage response of a **rat nucleus accumbens MSN** to a series of depolarizing current injections. B, Voltage response of a MSN to a series of hyperpolarizing current injections showing fast-type inward rectification at very negative potentials. Spontaneous mEPSPS (recorded in TTX/PTX) are shown superimposed.

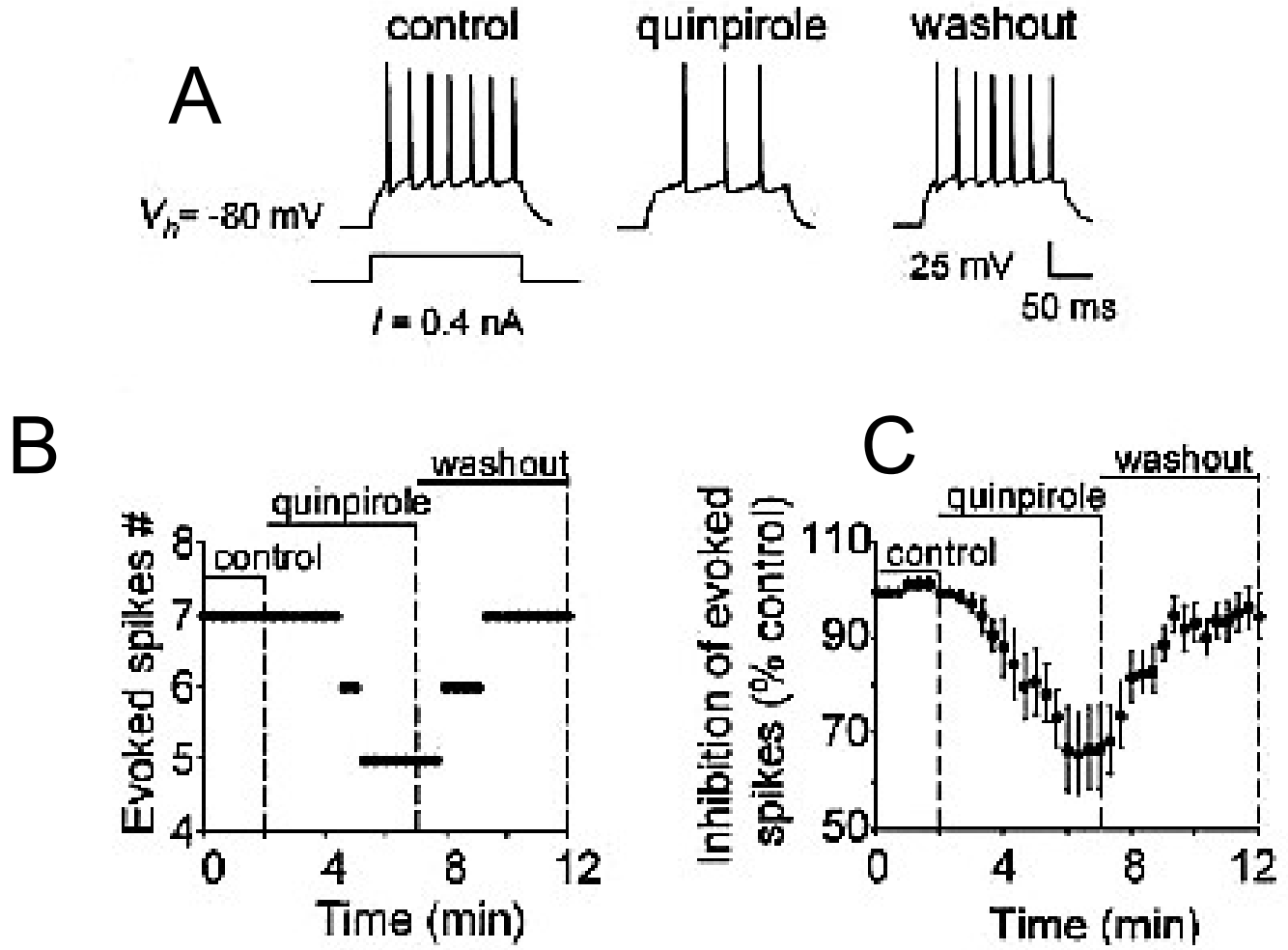
Willett et al., (2016). eNeuro.;3(1):ENEURO.0147-15.2016.

Pleasure/reward circuit



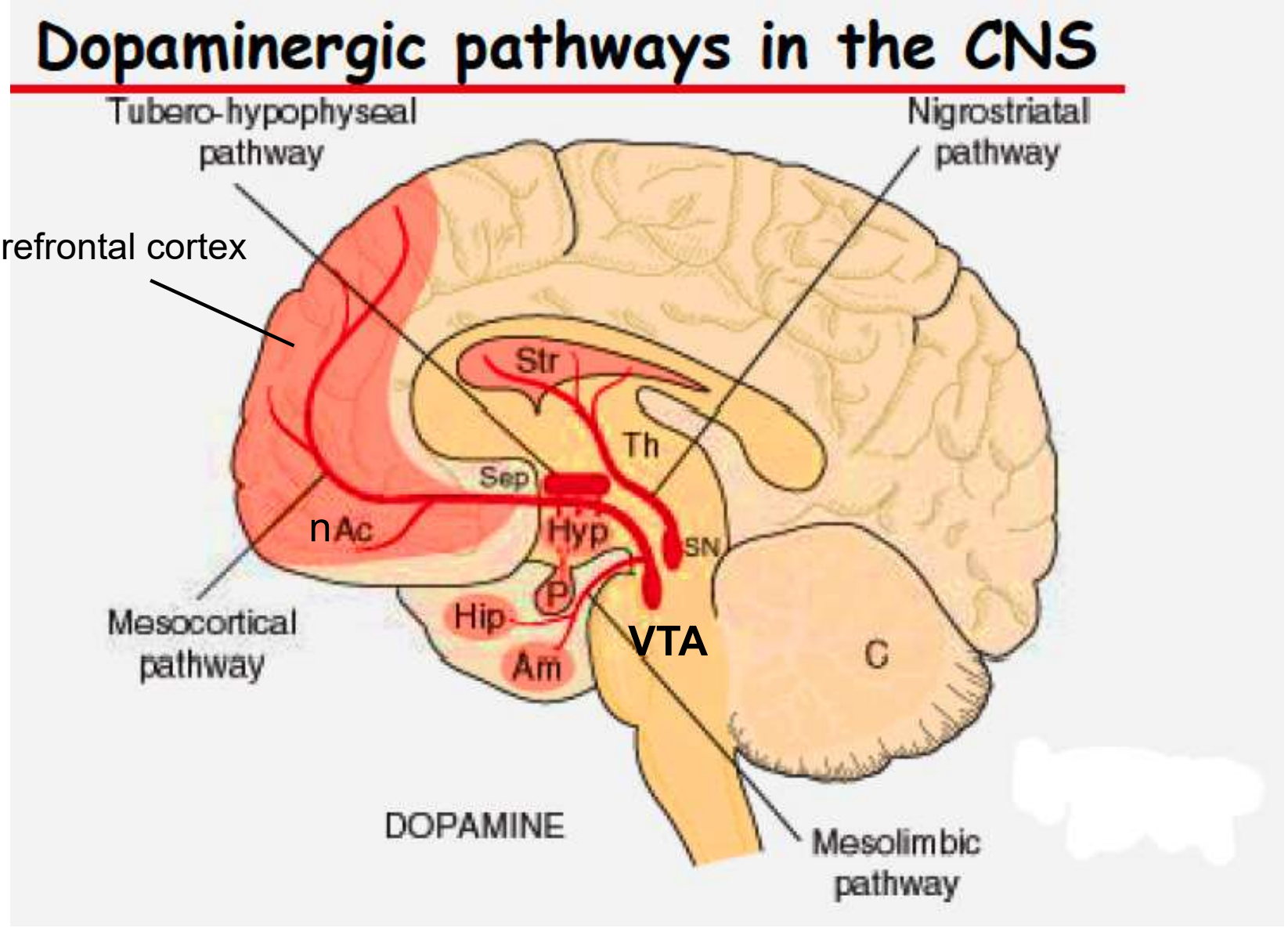
Dopamine (75 μM) increased spike firing in MSNs (medium spiny neurones) from the NAcb shell. A, Example of applied current pulses and voltage responses. The traces represent subthreshold current pulses and the first pulse able to elicit spikes. **B**, Input–output relationship showing significant enhancement of spike firing by DA for all current pulses. **C**, Example traces showing reversible increase in spike firing in the presence of DA (250 pA current pulse). ***Hopf et al., (2003). The Journal of Neuroscience, 23(12):5079–5087***

Pleasure/reward circuit



A. D2-type dopamine class receptor (D2R) stimulation with quinpirole (10 μM) reversibly decreased action potentials evoked in a nucleus accumbens (NAc) core MSN (medium spiny neurone). B and C: time–response curves indicate that the D2R-mediated inhibition in evoked Na^+ spikes achieved its maximal levels about 5 min after bath application of quinpirole, and returned to control levels after 3–5 min of washout (B: single cell; C: *n*=12 cells, with post-hoc test, *P*<0.05). ***Perez et al., (2006). J Neurosci.. 23(12):5079–5087***

Mesolimbic and other dopamine pathways

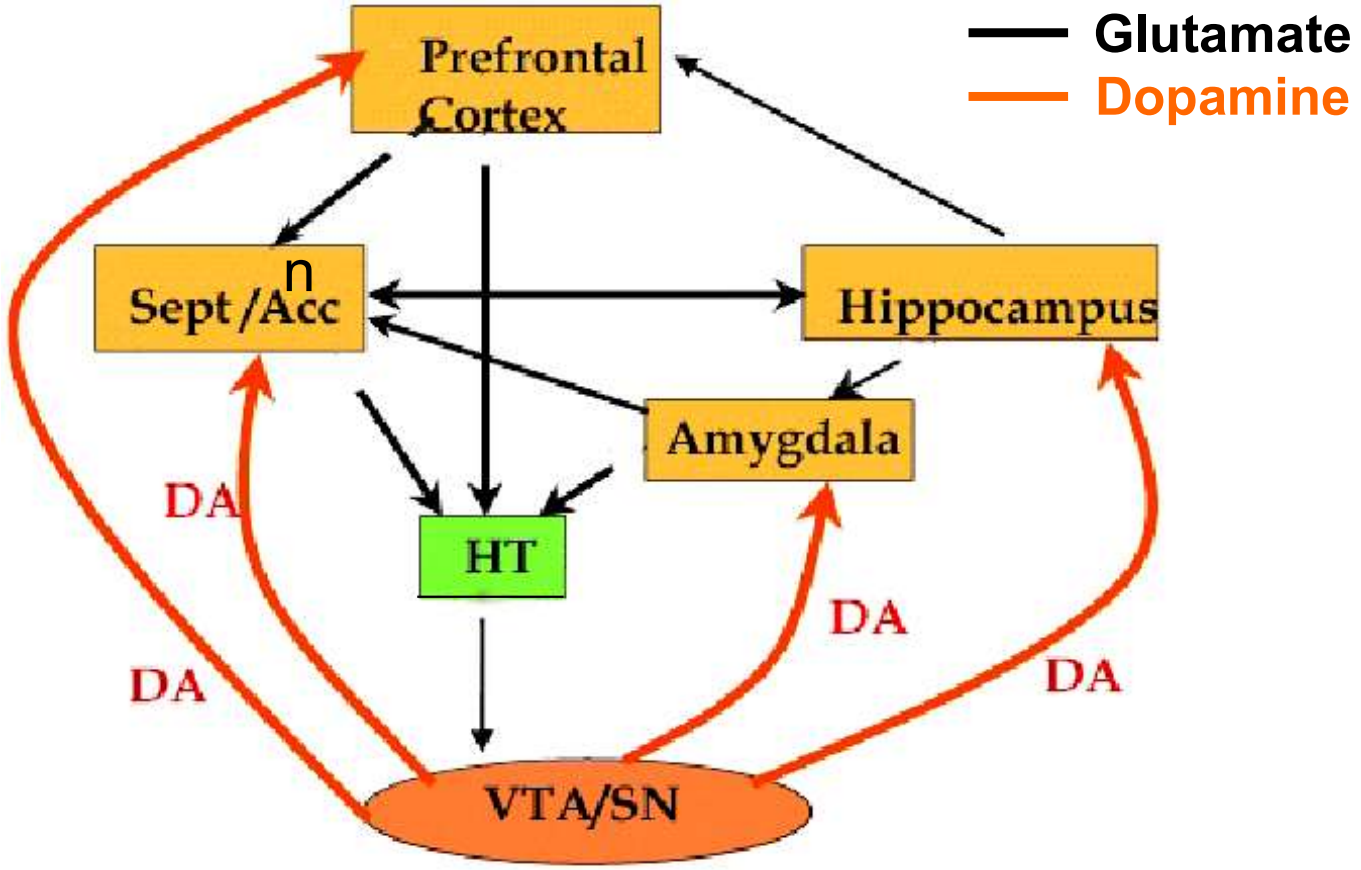


Other dopaminergic pathways

- **The mesocortical pathway** projects from the VTA to sensory *(e.g.* visual), motor, limbic and prefrontal association cortices – involved in motivation and emotional response; dysfunction of this pathway can cause hallucinations and **schizophrenia**.
- **Nigrostriatal pathway** arising in the complex part of the substantia nigra to the striatum - important for motor control; dysfunction causes **Parkinson's disease.**
- **Tuberoinfundibular pathway** (hypothalamus to anterior pituitary gland), involved in hormonal regulation of milk production (prolactin), maternal behaviour and pregnancy.

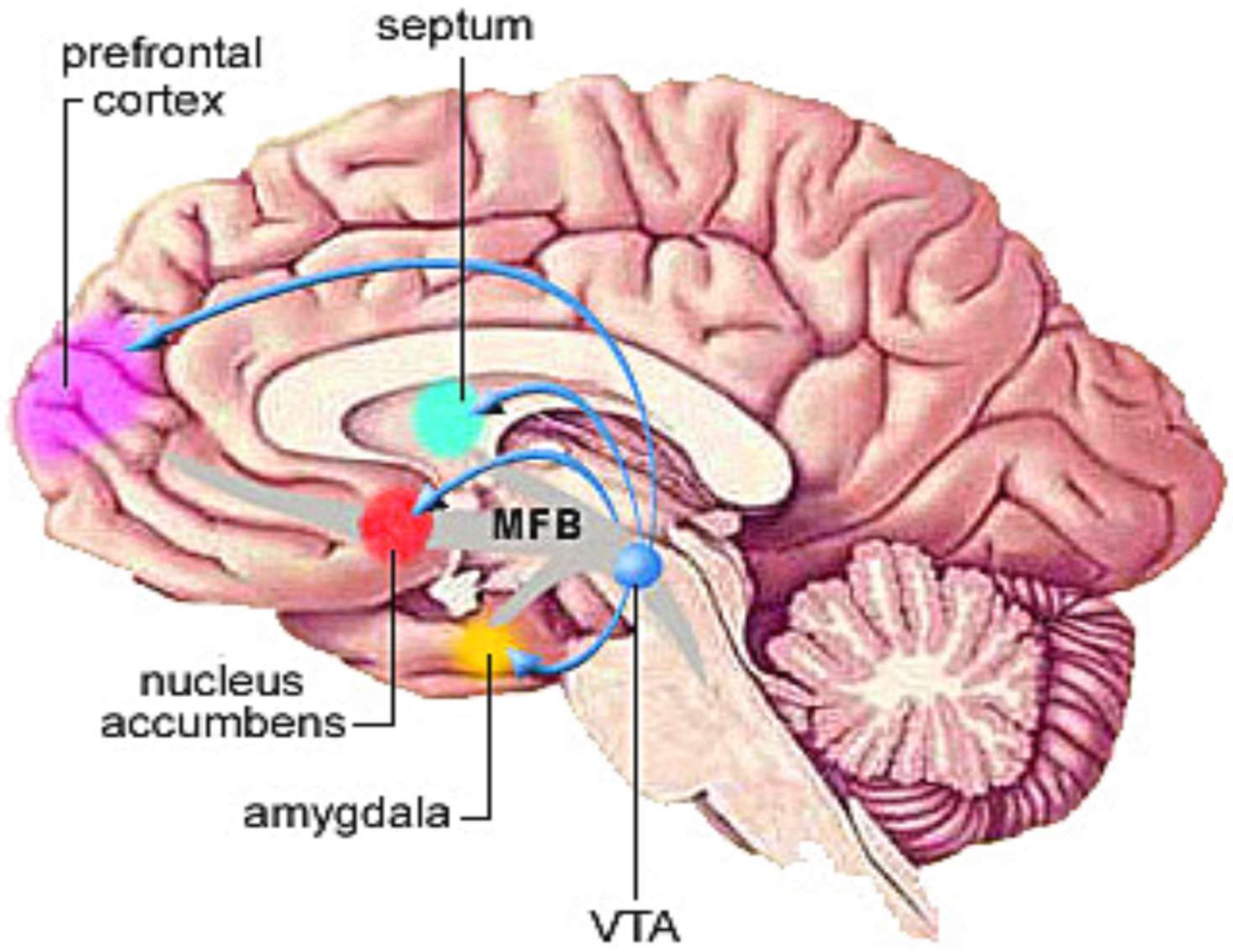
Glutamatergic inputs from Prefrontal Cortex

The VTA and NAcb also receive strong glutamatergic inputs from the prefrontal cortex, amygdala and hippocampus.



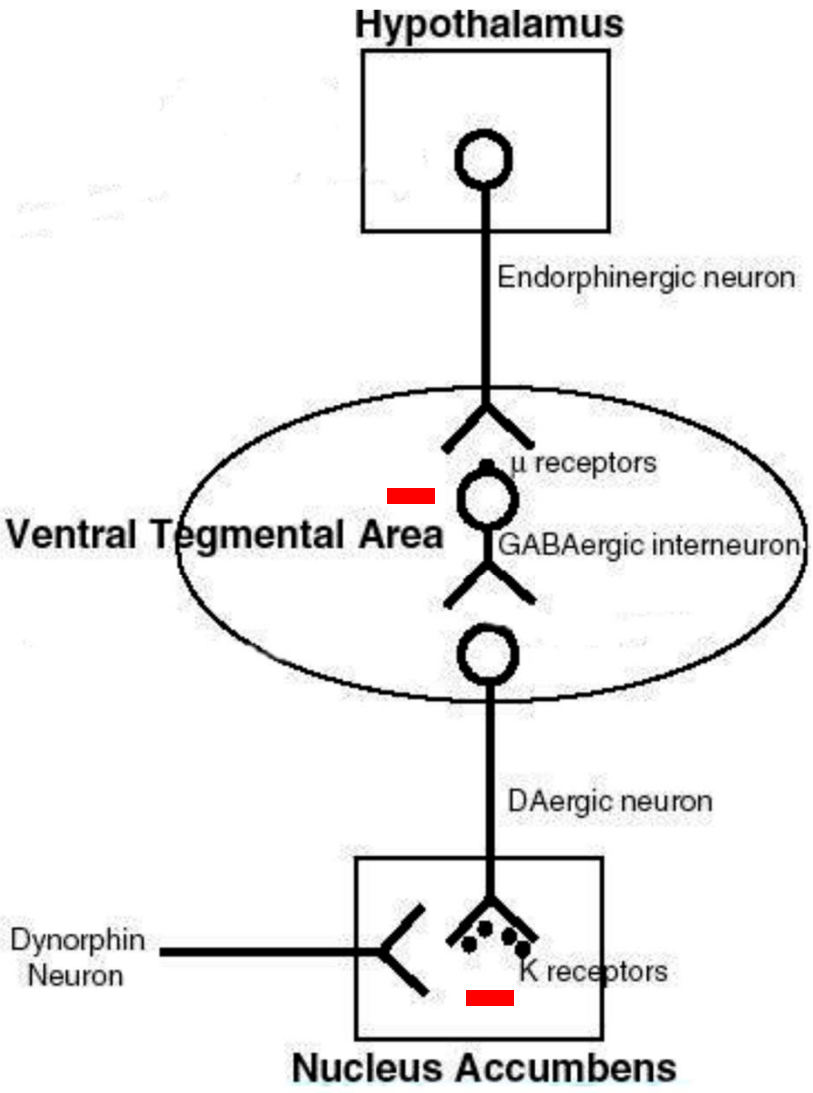
HT, hypothalamus; nAcc, nucleus accumbens; SN, substantia nigra; Sept, Septum; VTA, ventral tegmental area; DA, dopamine

Medial forebrain bundle

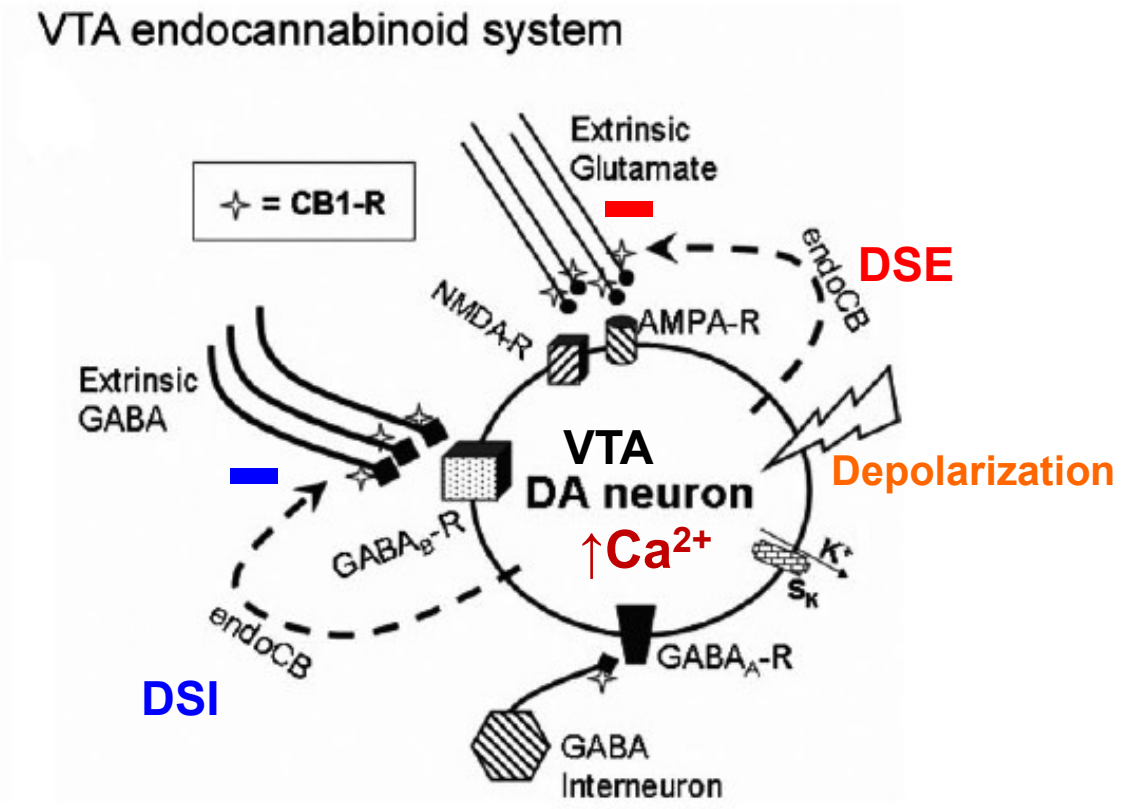


The medial forebrain bundle (MFB) of nerve fibres connects the NAcb to the VTA. It contains both ascending and descending fibres.

Pleasure/reward circuit



DSE = Depolarization-induced suppression of excitation



DSI = Depolarization-induced suppression of inhibition

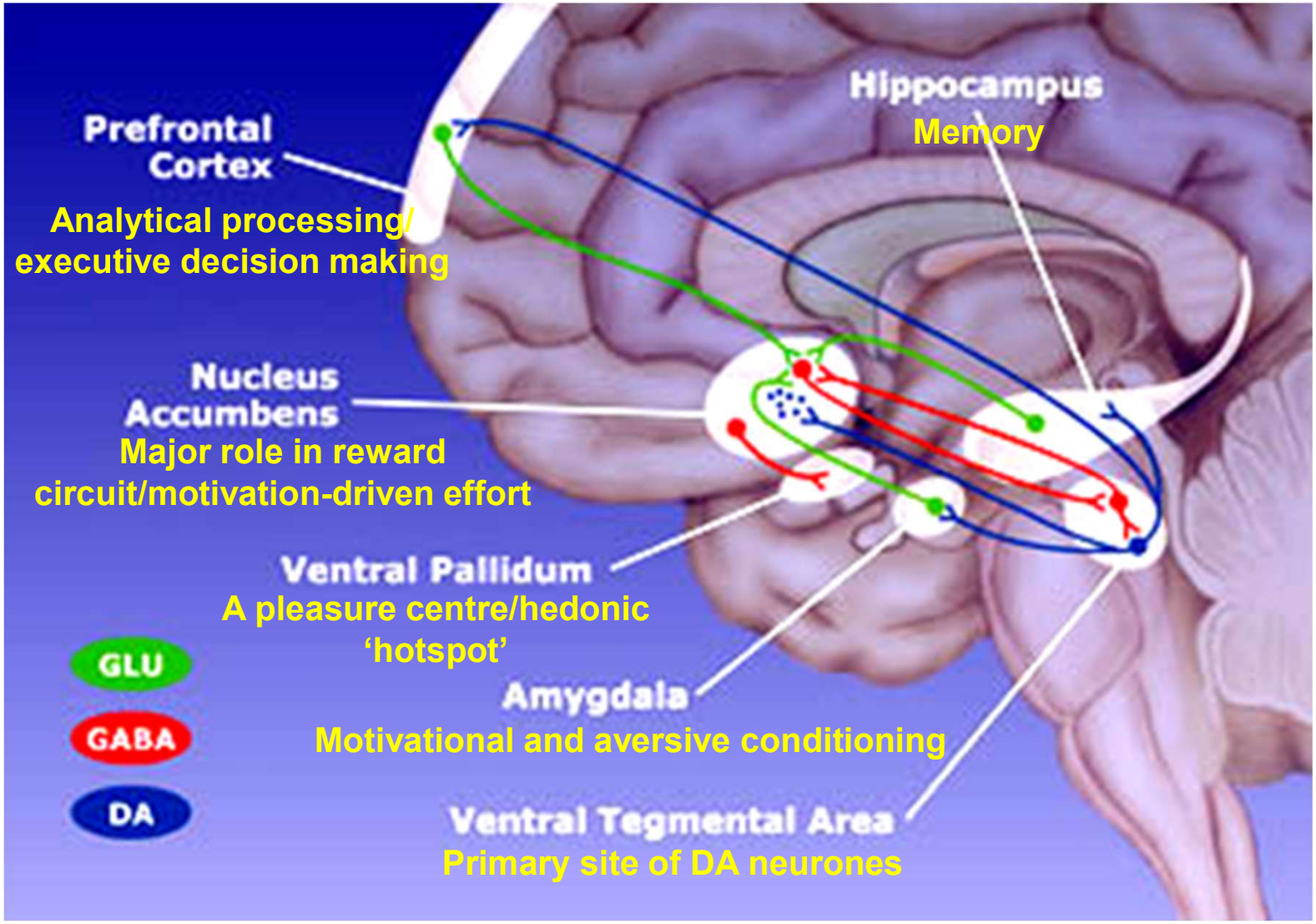
Endogenous endorphins, dynorphin and endocannabinoids also influence the VTA dopamine neurones.

Pleasure/reward circuit

- **The reward pathway also connects with several other important brain areas,** to allow the gathering of sensory information from surroundings, and to reinforce the brain circuits that control desirable/beneficial behaviour.

- **Connection is also made with brain regions involved in memory storage,** (*e.g.* the **hippocampus**) so that memory of a pleasurable stimulus is retained for future reference. This increases the likelihood that the pleasurable stimulus will be repeated.

Connections to other brain areas



Pleasure/reward circuit

- **Psychoactive drugs (opiates, cocaine, amphetamines, nicotine, alcohol, cannabis, ecstasy)** produce pleasurable effects by (over)stimulating pleasure/reward circuits directly - **↑dopamine levels in NAcb** →long-lasting positive reinforcement→ motivation to repeat the pleasurable experience → persistent drug-seeking behaviour and dependency.

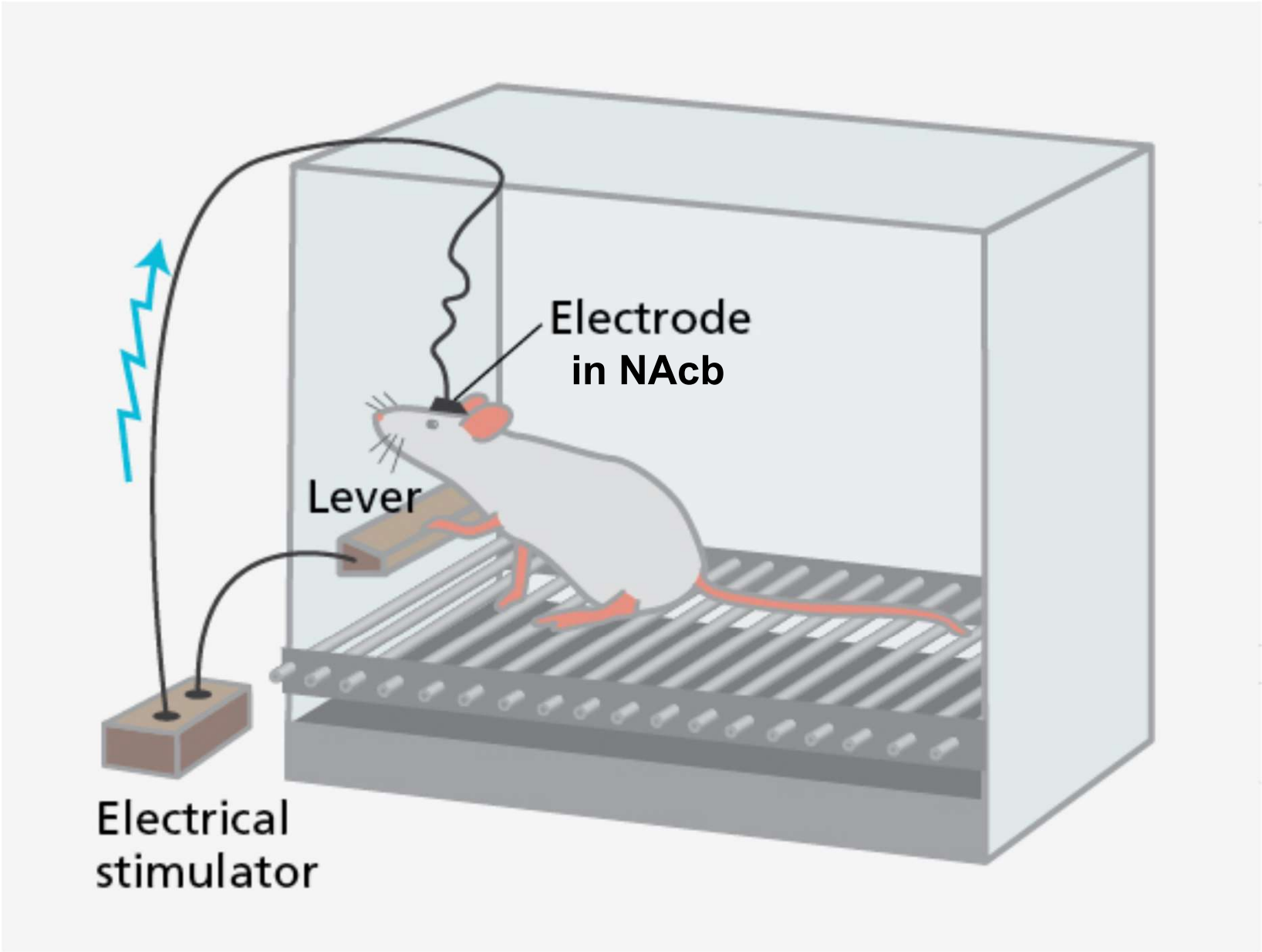
- **Synaptic neuroplasticity** is modified by drugs of abuse, therefore may contribute to development of **addiction.**

Identification of reward circuit

- **The involvement of the NAcb in pleasure/reward mechanisms** was first demonstrated by **Olds & Milner (1954),** working at McGill University, who implanted stimulating electrodes in the NAcb of a rat's brain, and trained the rat to press a lever to stimulate the NAcb, to release **dopamine** →pleasurable effect.

- **The rat stimulated itself repeatedly** to receive pleasurable effect, with no satiation, and excluding eating, drinking or sex. This endless reward-seeking activity is comparable to human drug addiction.

Reward circuit identified by brain stimulation

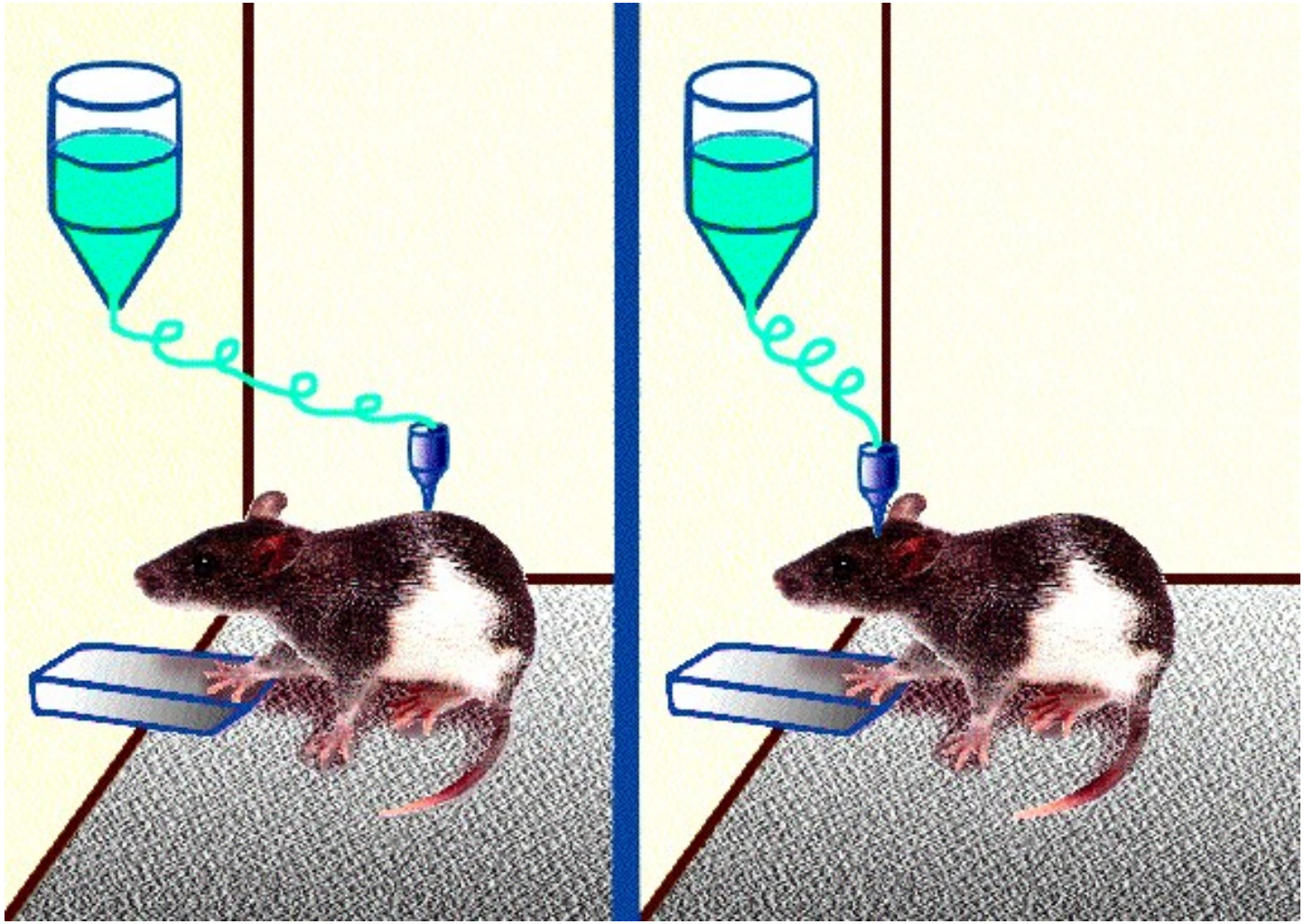


Identification of reward circuit

- Another effective means of studying brain reward systems in animals is to use either **systemic or intracranial administration** of addictive reinforcing drugs through surgically implanted catheters.

- Animals are trained to press a lever to obtain various i/v drug rewards, in a similar manner to electrical stimulation. **This provides another useful experimental animal model of human compulsive drug-taking behaviour.**

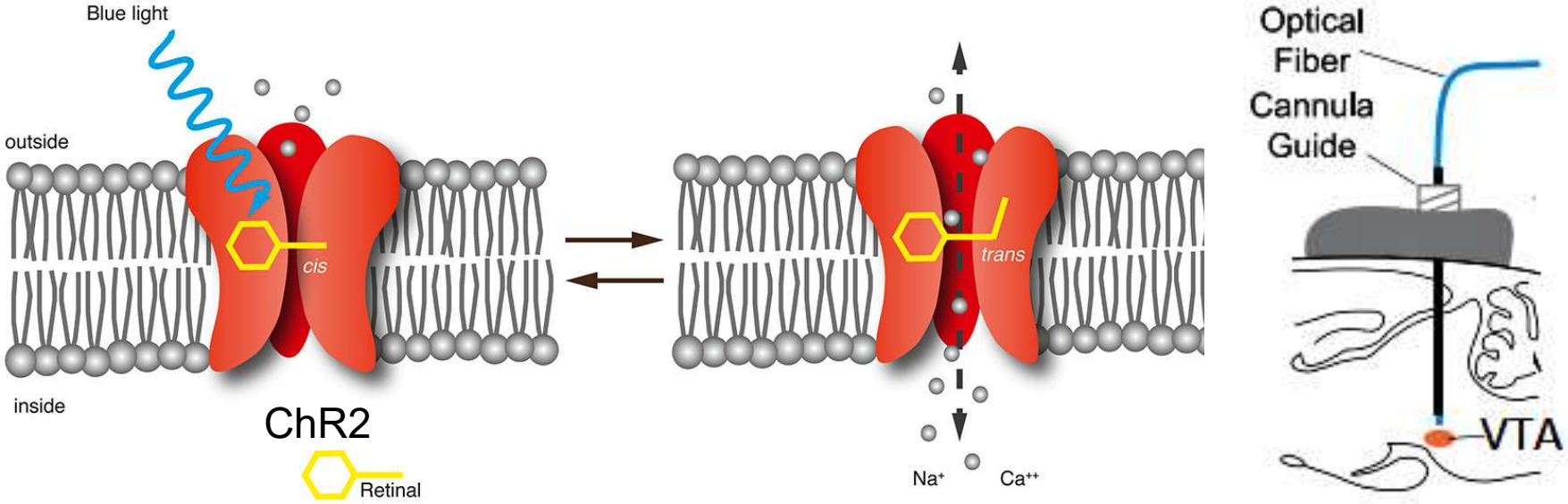
Reward: drug self-administration



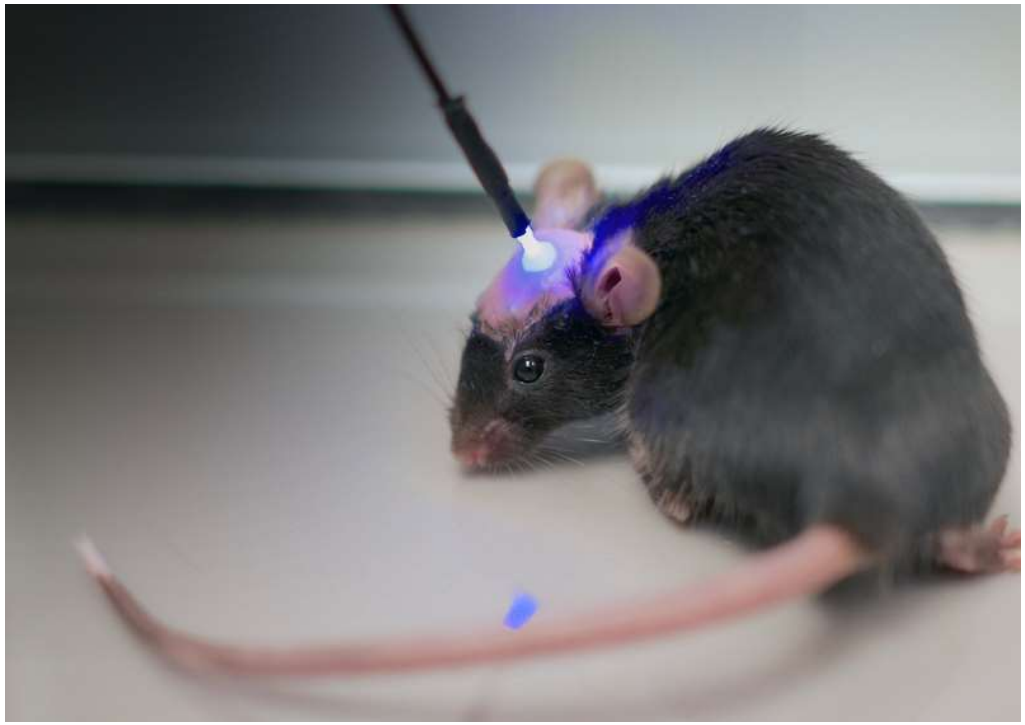
Rats can be trained to press a lever to self-administer strongly addictive agents *e.g.* amphetamine, cocaine or heroin, either i/v or directly into Nucleus Accumbens. 'Zippy' rats are particularly prone!

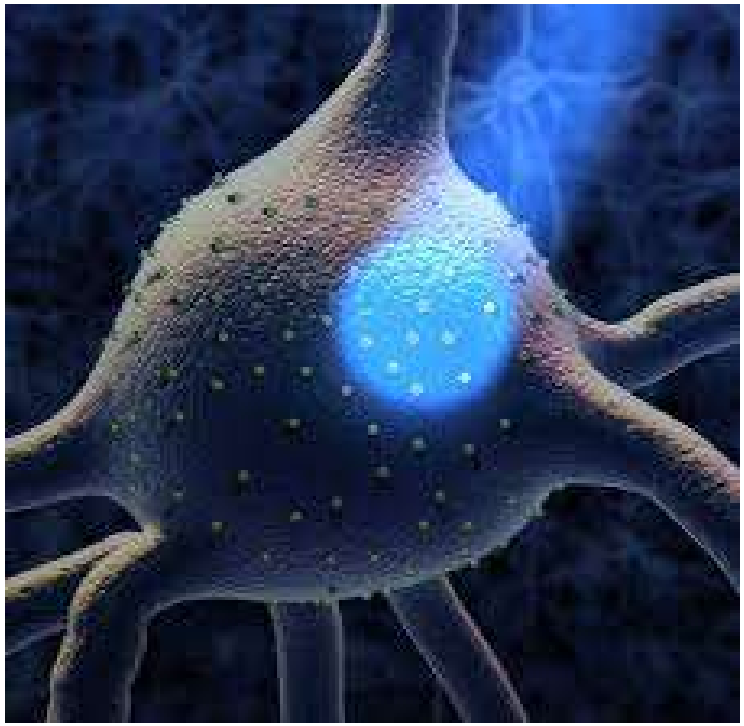
Identification of reward circuit

- More recently, the novel technique of ***optogenetics*** using ***channelrhodopsin-2 (ChR2)*** has been employed in order to selectively stimulate DA neurones in the VTA using a surgically implanted cannula carrying blue light laser illumination via an optical fibre.



Reward: blue light self-administration

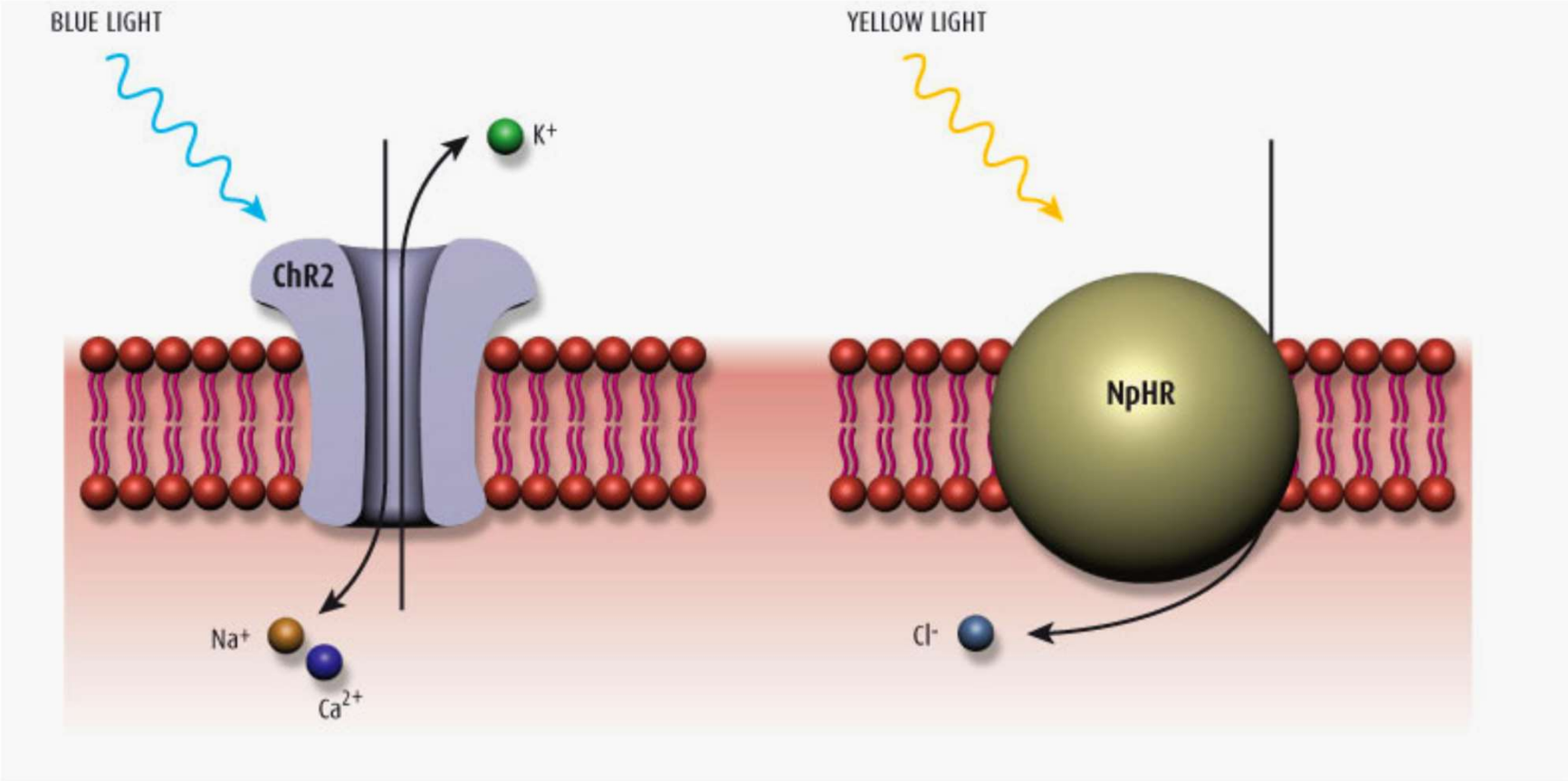




Animals are then trained to press a lever to self-administer the laser light stimulus. Following illumination with blue light (activation maximum 470 nm), ChR2 channels previously expressed selectively in the VTA DA neurones allow the entry of cations (mostly Na^+ and Ca^{2+}) into the cells, causing depolarization and DA release in the Nucleus Accumbens in a similar manner to electrical stimulation.

Pascole et al., (2015) Neuron, 88(5), 1054-1056.

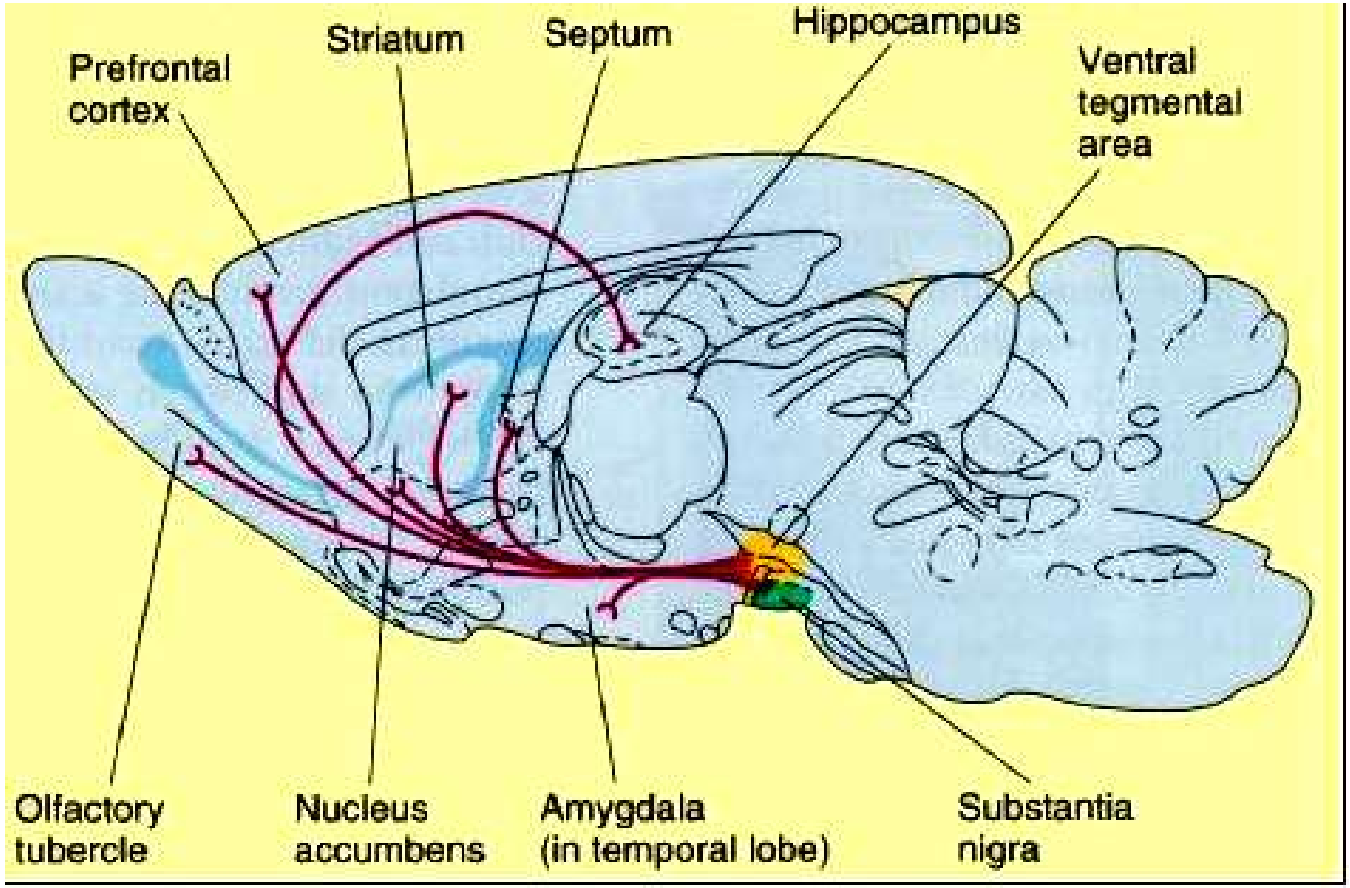
Optogenetics: *inhibition* of cell firing



Interestingly, the technique of optogenetics also allows you to *inhibit* the activity of neurone populations via the selective expression of the ***anion pump protein halorhodopsin (NpHR).*** Activation of the cells with yellow laser light (589 nm) then activates the pump so that Cl^- ions enter the cell causing *hyperpolarization* and *inhibition* of cell firing.

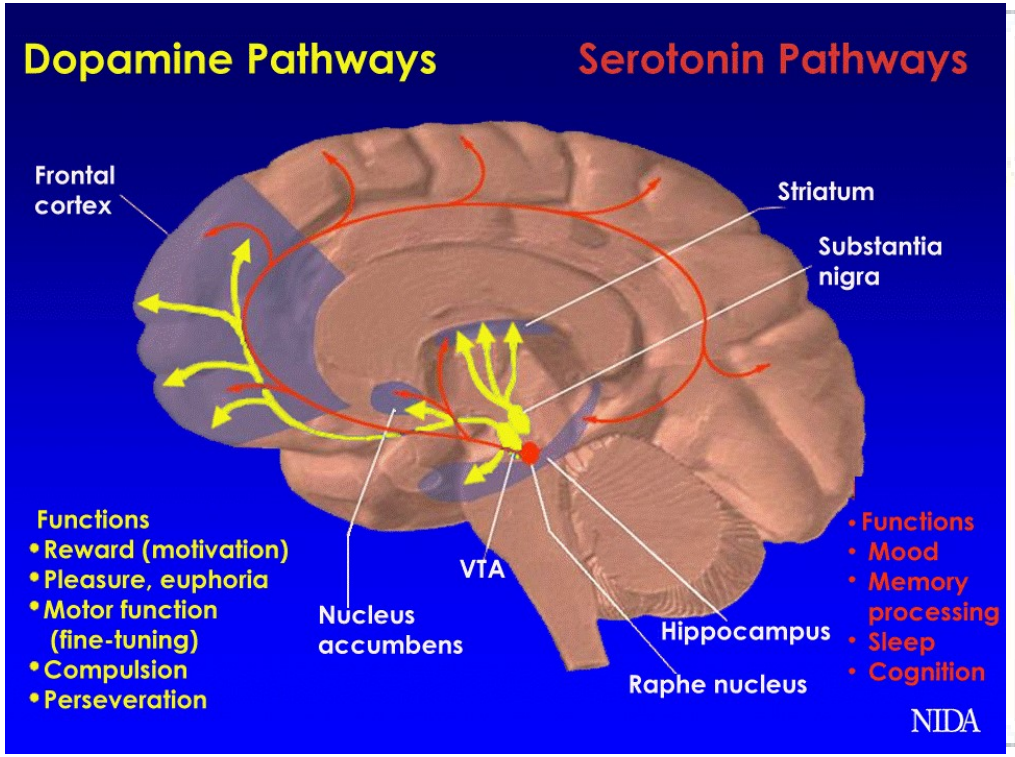
Other neurotransmitters

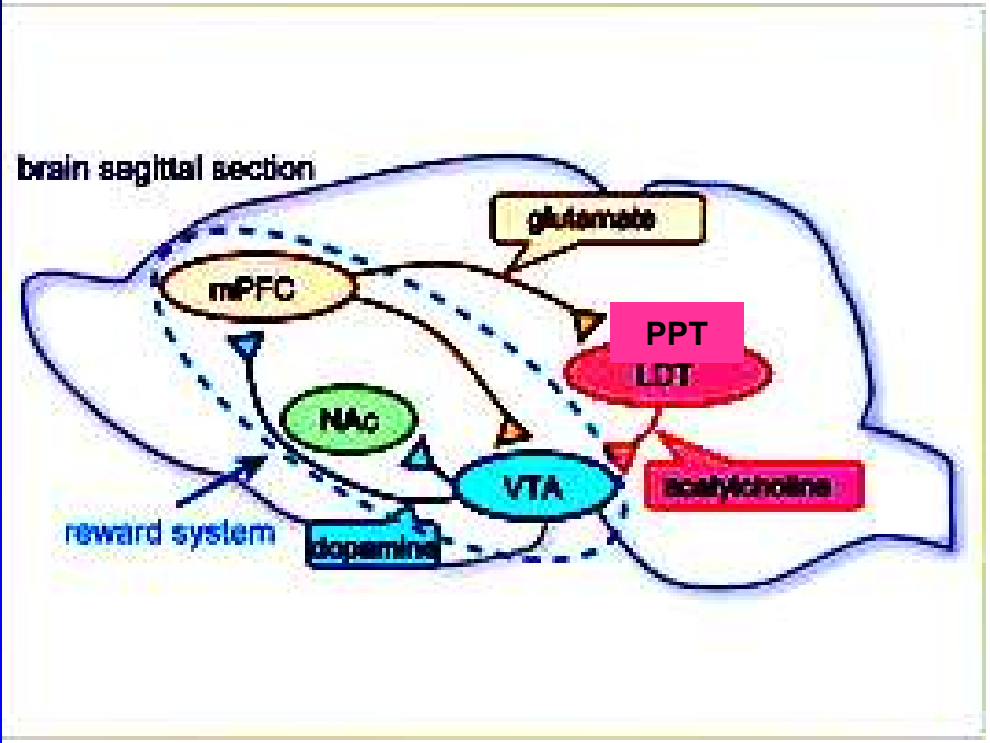
Other brain areas and neurotransmitters also have an important function in the brain reward circuitry *e.g.* the ventral pallidum, parabrachial nucleus, thalamus and limbic areas: amygdala, hippocampus and olfactory tubercle.



Other neurotransmitters

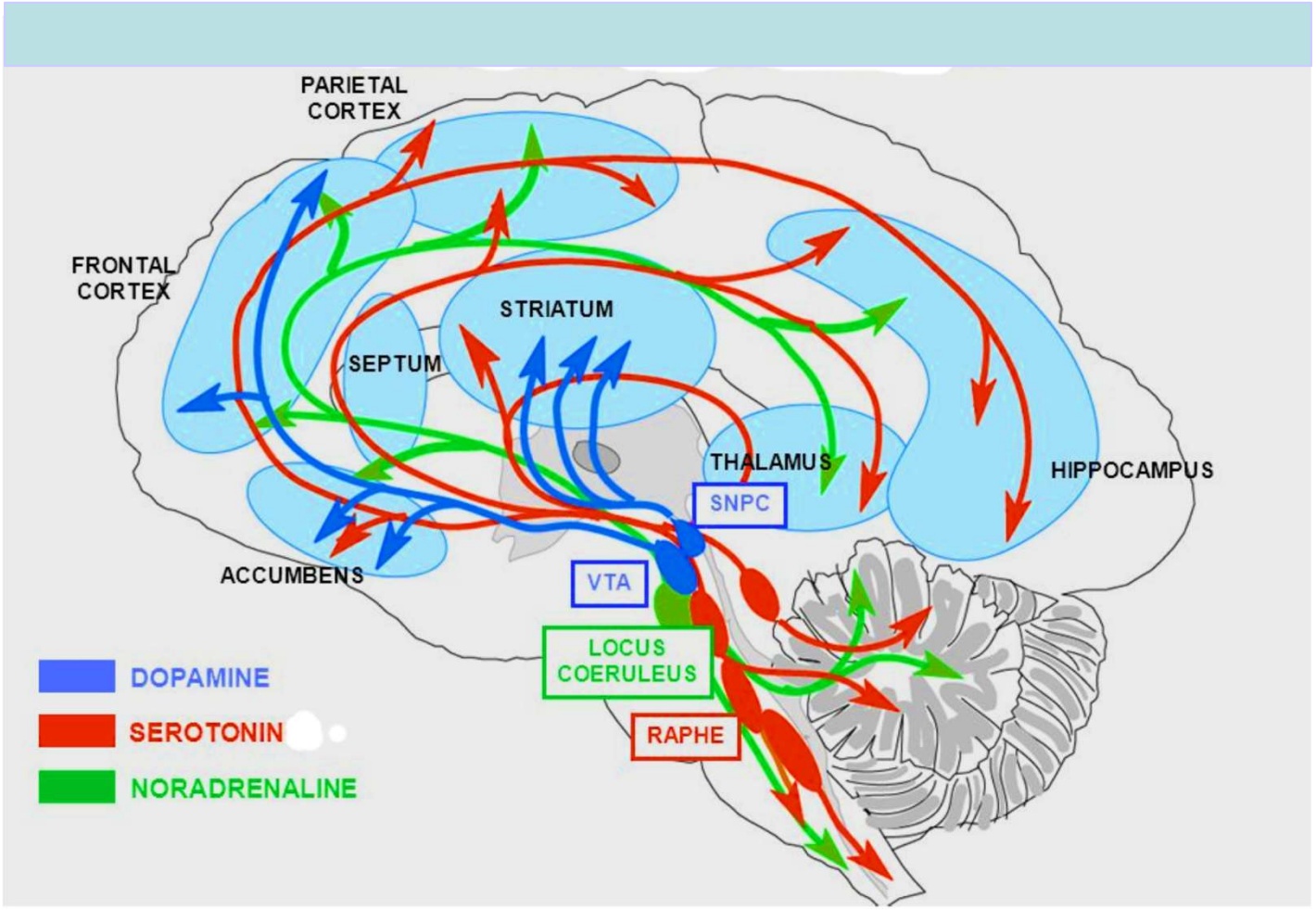
The brainstem *pedunculopontine nucleus* (PPT) **(ACh/glutamate systems),** *raphe nucleus* **(5HT system)** and *locus coeruleus* **(noradrenaline system)** also regulate the reward circuit. Other neurotransmitters include: GABA, ACh, glutamate, endogenous opioid peptides and endocannabinoids.





Other neurotransmitters

Noradrenergic neurones from the *locus coeruleus* innervate multiple areas including the nucleus accumbens, prefrontal cortex and hippocampus.



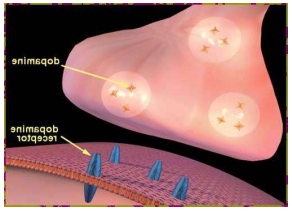
Mechanisms of addiction

- **Drug addiction (dependence)** may be defined as "the complex series of behaviours that start with casual/recreational use of a drug and ultimately lead to compulsive drug taking (craving), loss of control over drug intake, tolerance, withdrawal, and continued use despite adverse consequences".

- **Addiction represents a loss of control** over pleasurable and biologically useful events, and a gradual move over to behavioural abnormalites that can persist well after drug use is discontinued [motivational toxicity].

Mechanisms of addiction

- **Craving** – due to deteriorated dopamine function in the reward pathway: repeated drug use may **deplete dopamine stores in the mesolimbic reward circuitry** leading to the intense craving effect.
- **Initially** – casual or incidental drug use leads to increased dopamine and increased pleasure;
- **Over time** – reward function collapses and dopamine levels ↓ → depression + other *negative* affective states.



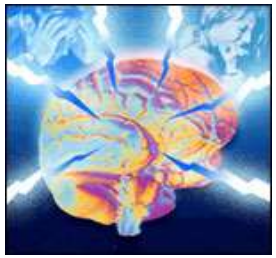
- **Adaptations in glutamate transmission from prefrontal cortex →NAcb, also associated with processes of craving and relapse.**

Mechanisms of addiction

- **Repeated use of drugs that affect the reward system** will lead to **tolerance** – more of the drug being required to produce the same effect.

- **This may reflect a moving 'set-point' level** for neurotransmitter release/receptor sensitivity in the reward circuitry.

- **Prolonged exposure** to a psychoactive compound→semi-permanent adjustment of the reactivity of the circuit to a different higher homeostatic level.



Mechanisms of addiction

- **Withdrawal –** a manifestation of physical changes in the brain in response to prolonged drug exposure - **change in brain equilibrium** – metabolism, receptor availability/sensitivity, gene expression, responses to environmental stimuli - a form of drug-induced neural plasticity]; morphological changes also occur.

- **Addicts are not now abusing drugs to create pleasure,** but to prevent painful/uncomfortable side effects of not using them. Withdrawal reflects fact that brain equilibrium takes times to readjust back to pre-addiction level; **in some individuals, 'normality' may never be fully achieved.**

How do drugs of abuse act?

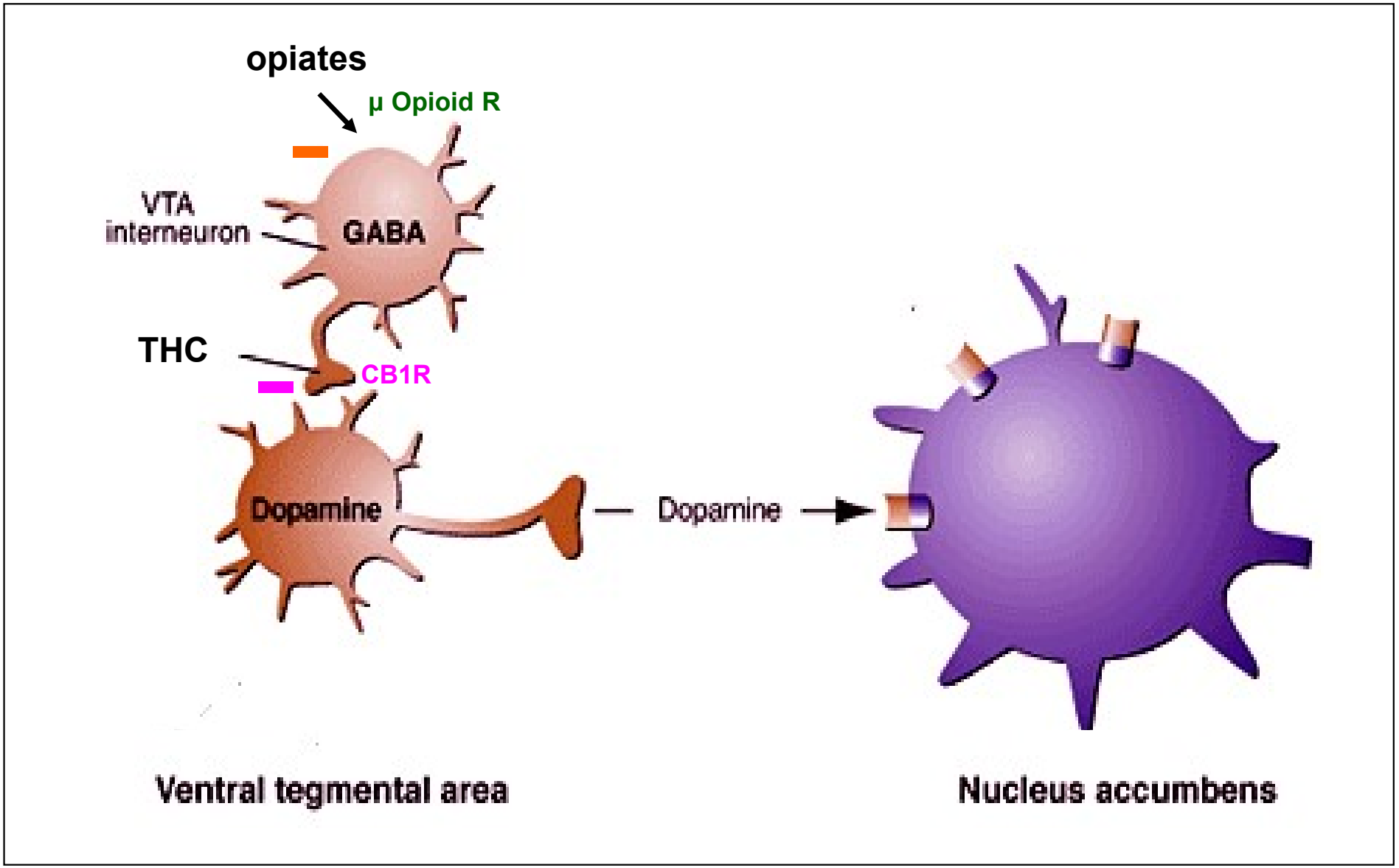
- **Opiates (morphine, heroin)** and **cannabis (tetrahydrocannabinol [Δ^9-THC]),** act on ***μ*-opioid** and **cannabinoid CB_1** receptors respectively, located on local GABAergic interneurones in the VTA.

- **Activation of opiate receptors hyperpolarizes, the VTA GABA interneurones, while activation of presynaptic CB_1 receptors inhibits GABA release through inhibition of Ca^{2+} channels;** the VTA dopaminergic projection neurones are therefore indirectly **disinhibited.** Activation of *μ*-opioid and CB_1 receptors on GABAergic neurones in the NAcb can also cause some disinhibition at the dopaminergic nerve terminals.

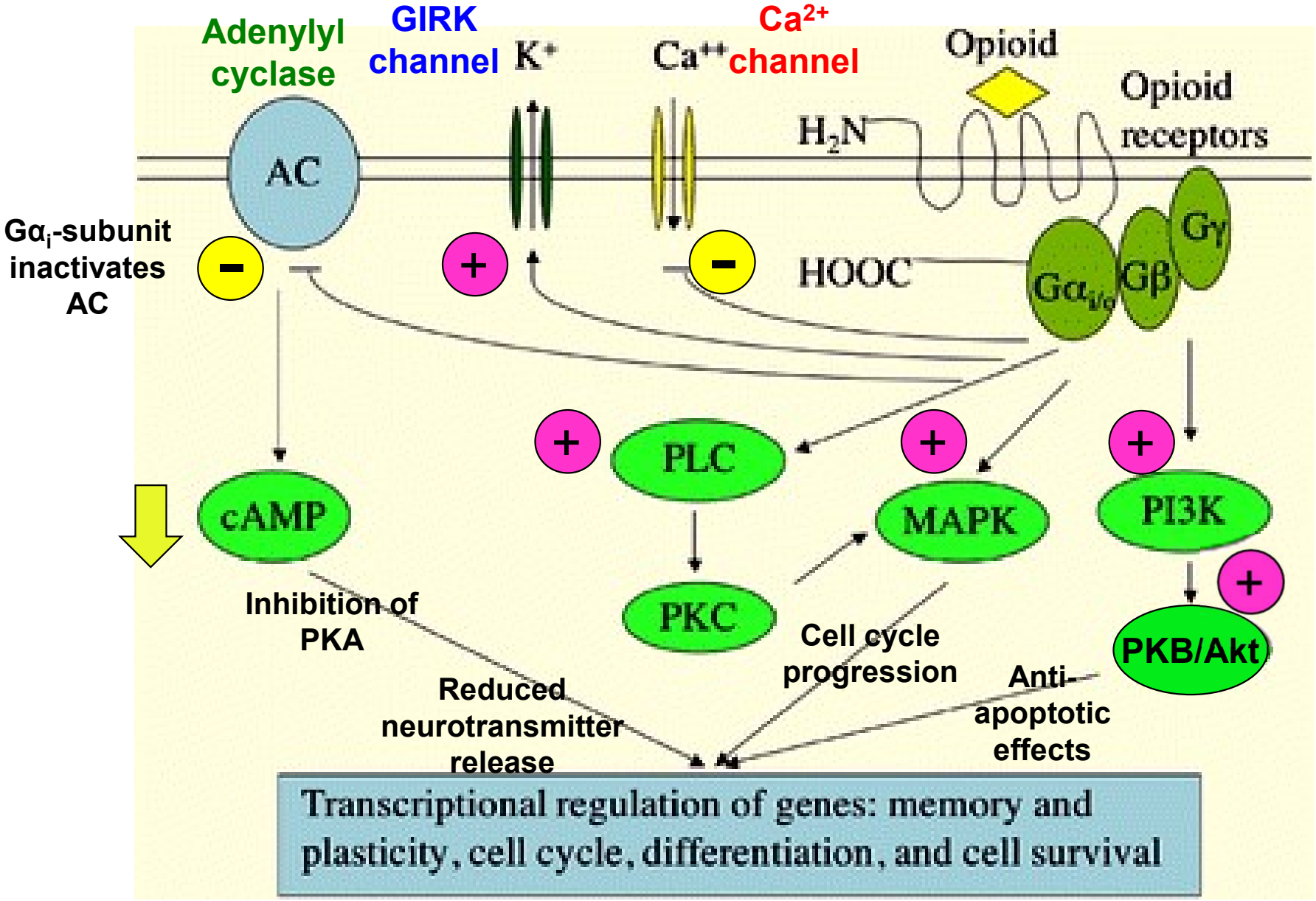

Take a
Break!

How do drugs of abuse act?

How do drugs of abuse act?



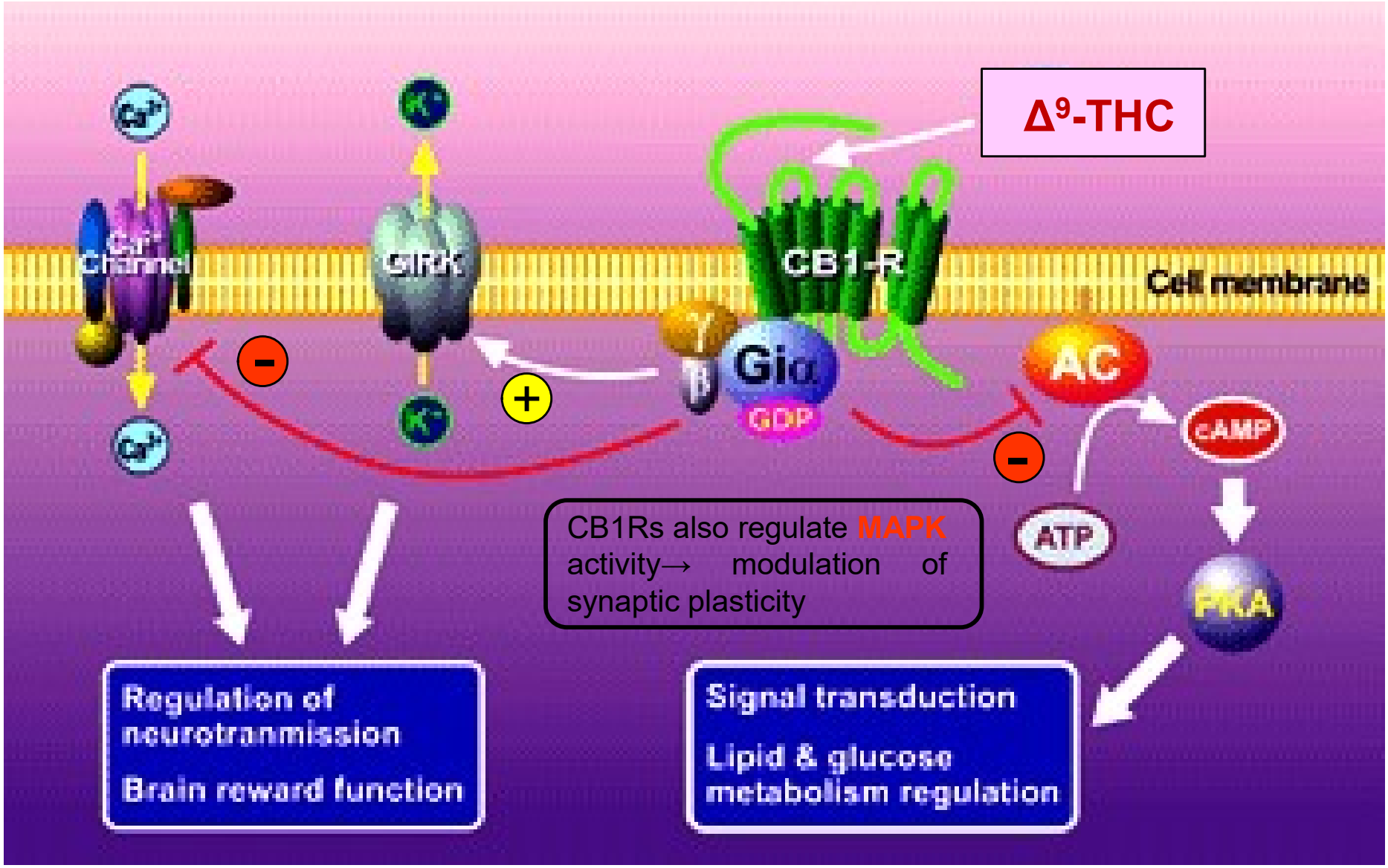
How do drugs of abuse act?



MAPK: mitogen-activated protein kinase

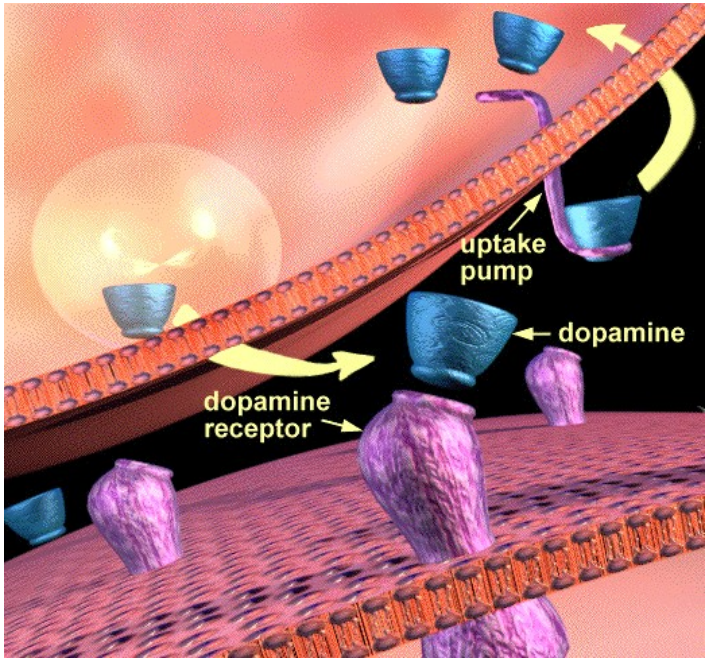
PI3K: Phosphatidylinositol 3-kinase

How do drugs of abuse act?



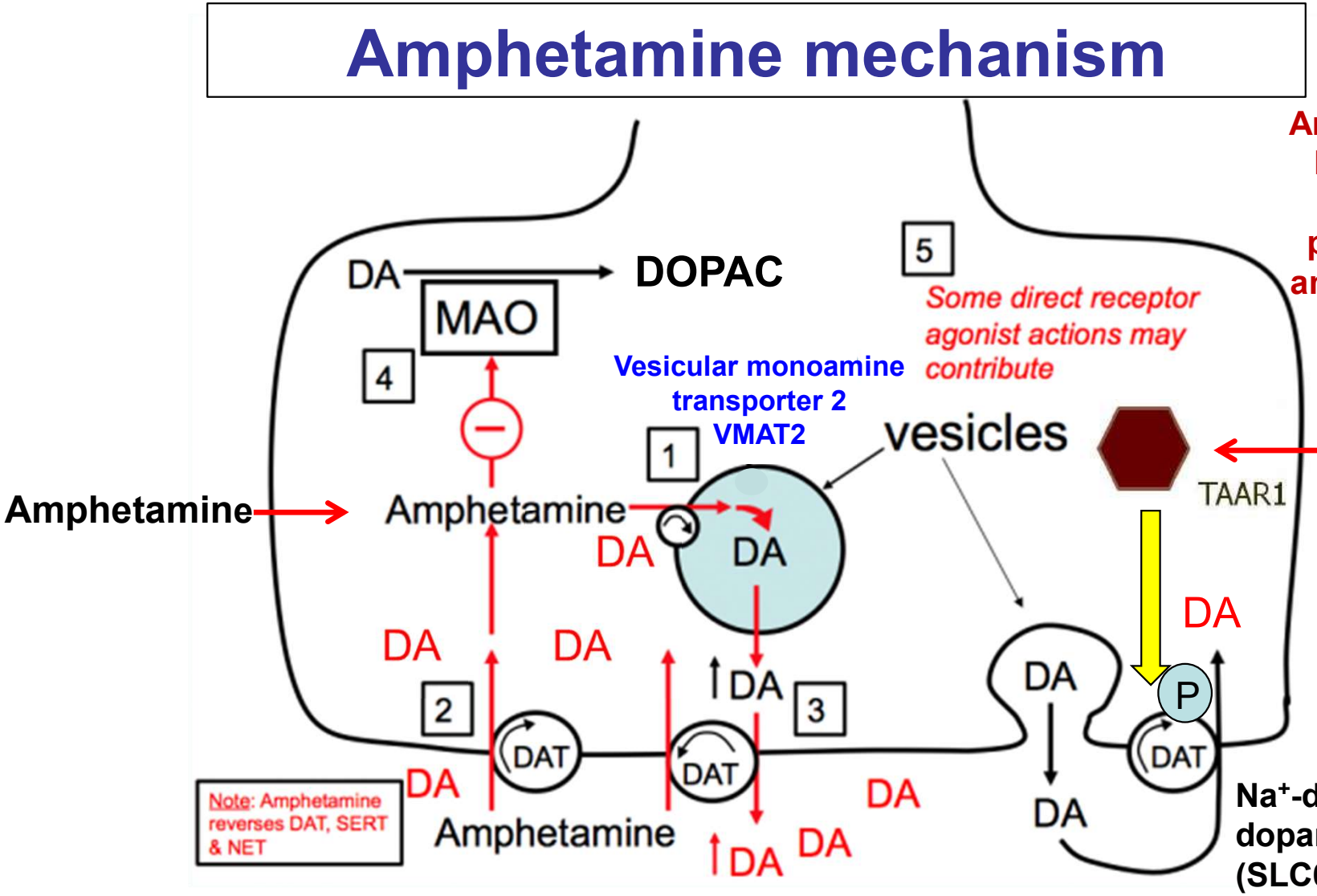
How do drugs of abuse act?

- **Amphetamines** and **cocaine** amplify the mesolimbic dopamine signal through different mechanisms. Amphetamines act indirectly in the NAcb by releasing dopamine from presynaptic terminals. Cocaine increases extracellular dopamine levels in the NAcb by blocking the **presynaptic dopamine transporter (DAT).**



How do drugs of abuse act?

Amphetamine mechanism



Amphetamine also binds to TAAR1 leading to phosphorylation and internalization of the DAT.

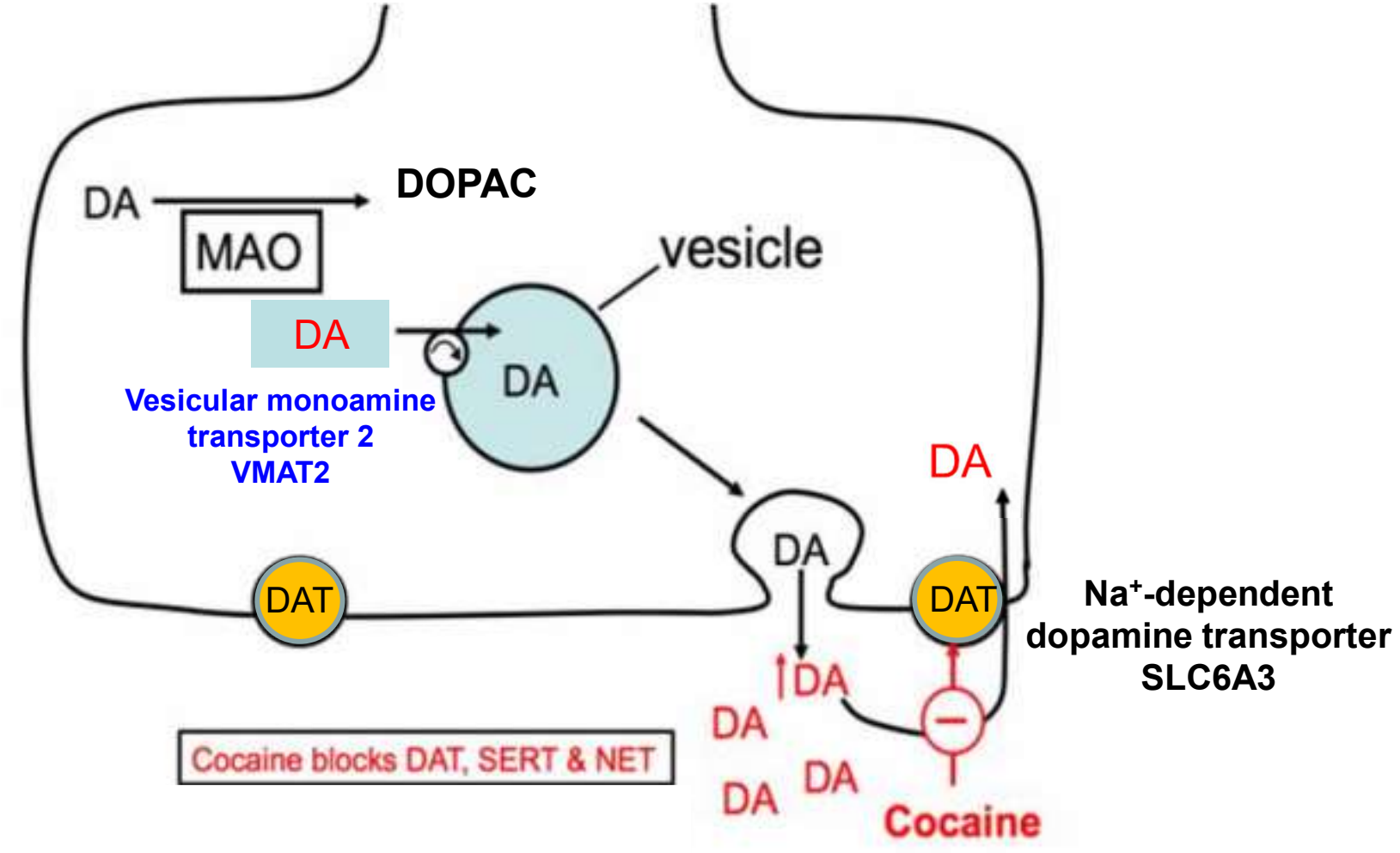
Na^+-dependent dopamine transporter (SLC6A3) transports 2 Na^+ and 1 Cl^- for each DA molecule so is *electrogenic.*

DOPAC: 3,4-Dihydroxyphenylacetic acid

TAAR1: Trace amine-associated receptor 1

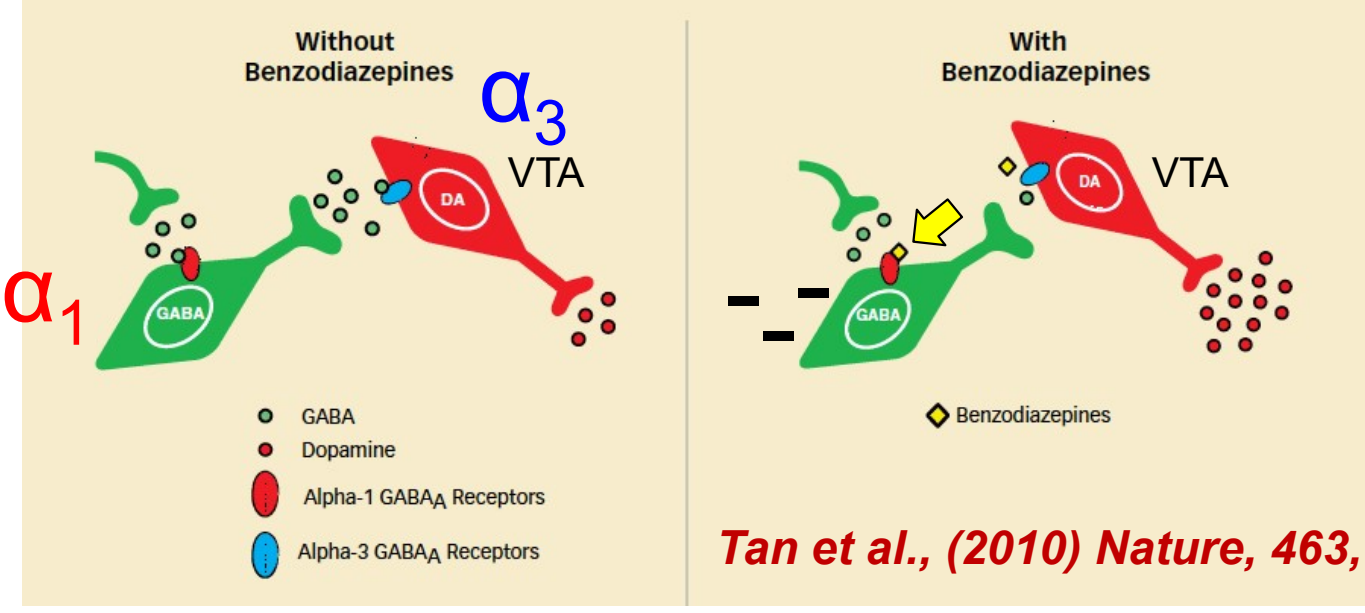
How do drugs of abuse act?

Cocaine mechanism



How do drugs of abuse act?

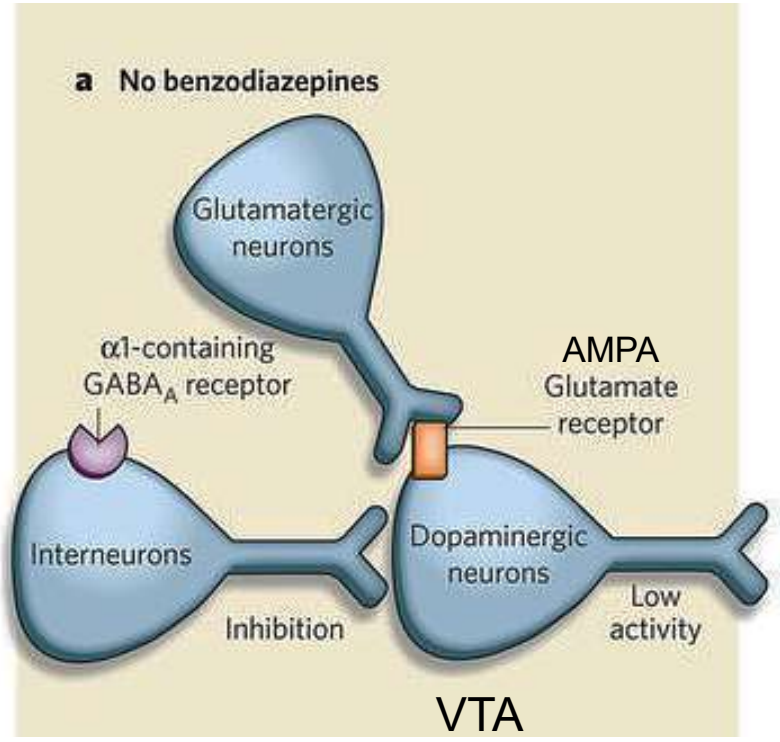
- **Benzodiazepine** anxiolytics are also known to be highly addictive. It is now believed that BDZs induce addiction by modulating the function of local inhibitory interneurones in the VTA, preferentially possessing **α-1-type $GABA_A$Rs**. VTA neurones possess **α-3-type $GABA_A$Rs which are insensitive to BDZs.** Enhancing effects of locally released GABA on α-1-type interneurones *reduces* GABA release onto VTA dopaminergic neurones, hence their firing rate *increases* with a consequent increase in DA release in the *nucleus accumbens*.

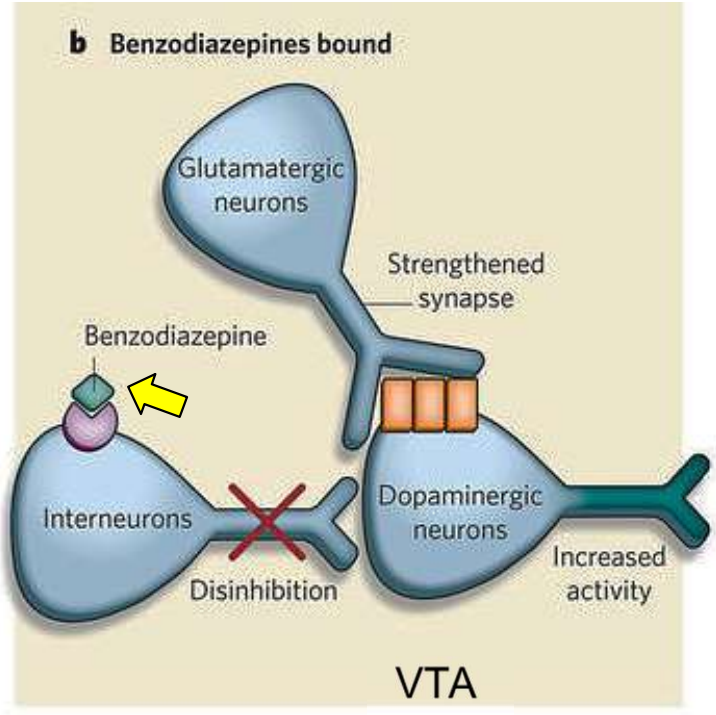


Tan et al., (2010) Nature, 463, 769-774.

How do drugs of abuse act?

- **Benzodiazepines:** Increasing the firing activity of VTA DA neurones by this mechanism also strengthens the VTA's glutamatergic synapses by promoting insertion of new (Ca^{2+} permeable, GluA2-lacking) AMPA receptors into the membrane of the dopaminergic VTA neurones. This adaptive effect may form the fundamental basis for the addictive properties of all drugs of abuse.

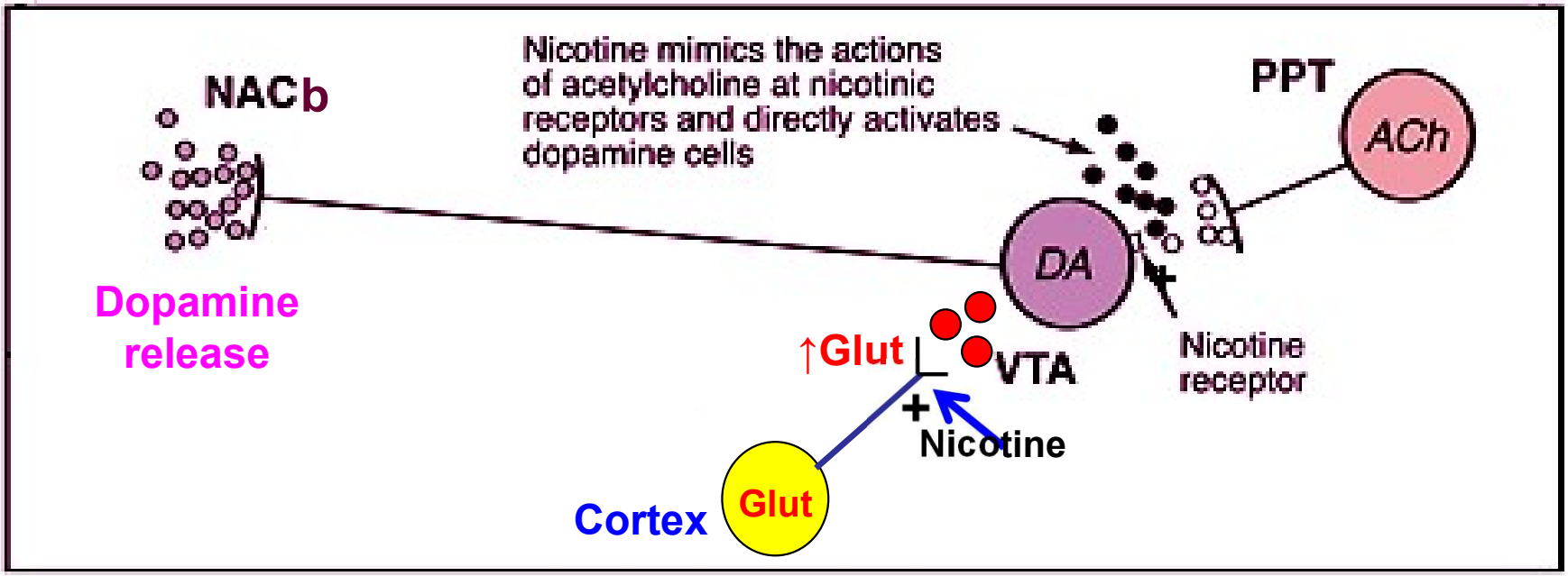




How do drugs of abuse act?

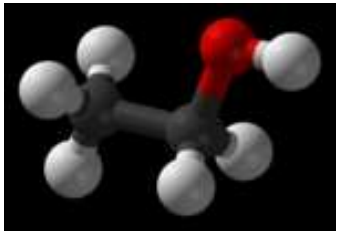
- **The positive reinforcing effects of nicotine** are also believed to be due to activation of the mesolimbic dopamine projection, acting via cholinergic nAChRs located somatodendritically on dopaminergic VTA neurones to increase their firing rate and to release dopamine directly in the *nucleus accumbens*.

PPT= Pedunculopontine nucleus



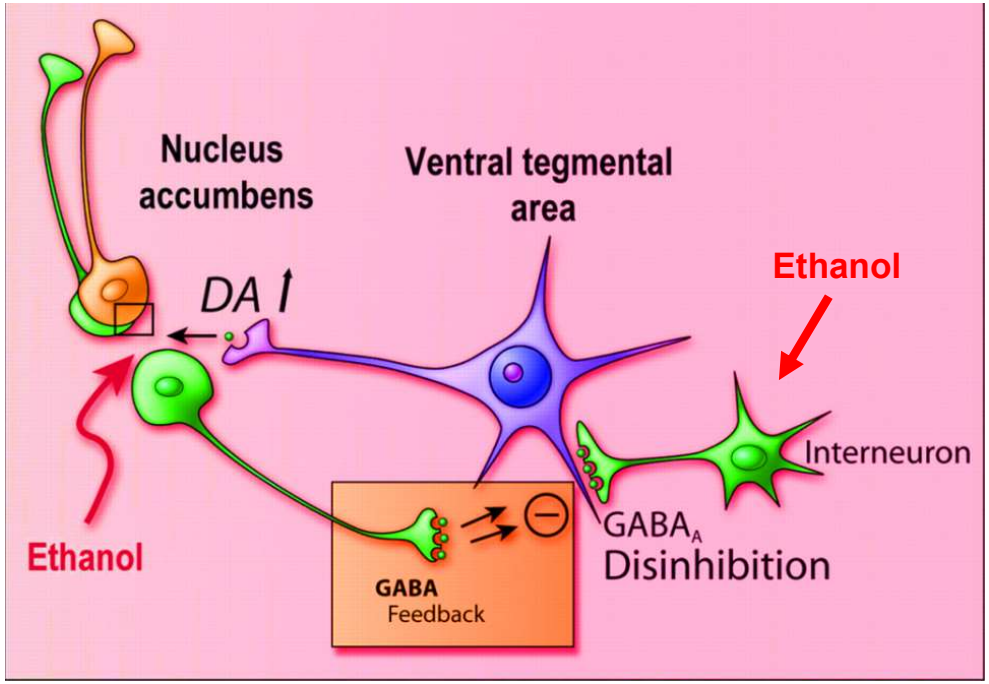
How do drugs of abuse act?

- **Alcohol (ethanol):** despite much research, the exact mechanism by which alcohol exerts its excitant/depressant effects in the brain is still not clearly understood. At a mechanistic level, alcohol has **8 principal molecular targets in the brain (concentration dependent):**
- **$GABA_A$ receptor** (+ve allosteric modulation)
- **NMDA receptor** (-ve allosteric modulation)
- Glycine receptor (+ve and –ve allosteric modulation)
- AMPA/kainate(glutamate)receptor(-ve allosteric modulation)
- nACh receptor (+ve and –ve allosteric modulation)
- $5\text{-}HT_3$ receptor (+ve allosteric modulation)
- L-type Ca^{2+} channel blocker
- GIRK (K^+) channel opener



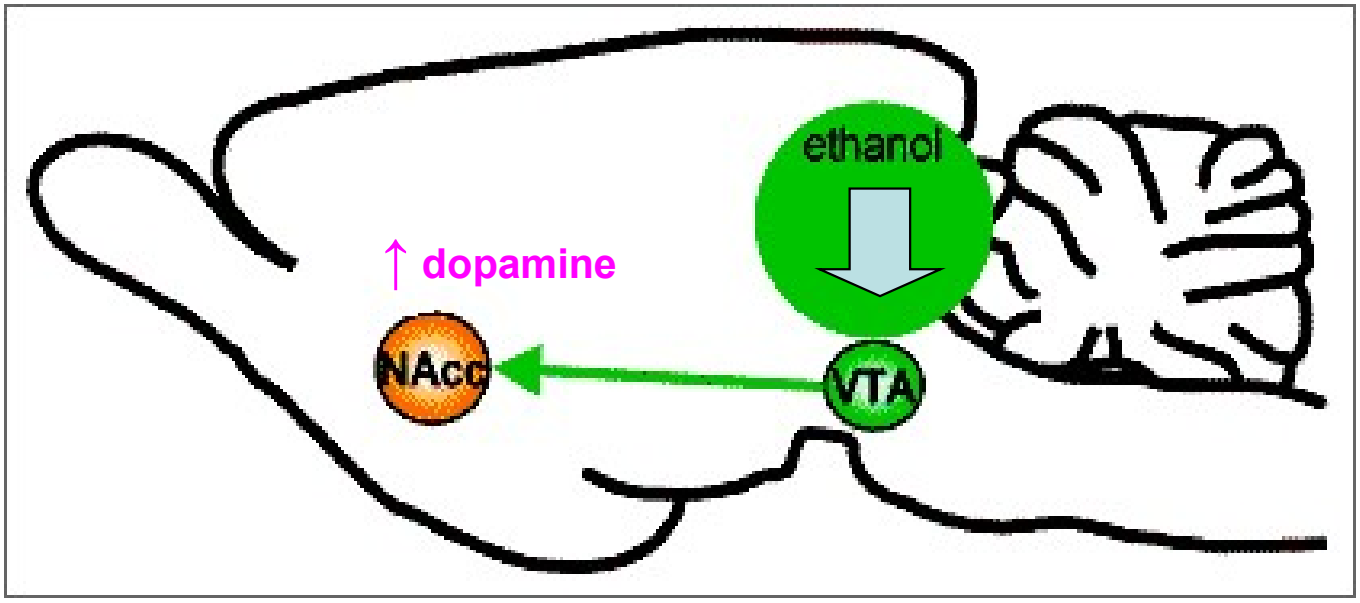
How do drugs of abuse act?

- **Alcohol (ethanol)** ultimately affects the mesolimbic pathway to release **dopamine** in the NAcb, but its mechanism of action is complex: by facilitating $GABA_AR$ function directly, it inhibits GABAergic interneurone transmission in the VTA thereby ***dis-inhibiting*** (*i.e.* exciting) VTA neurones. It also inhibits glutamate inputs from the cortex to the NAcb.



How do drugs of abuse act?

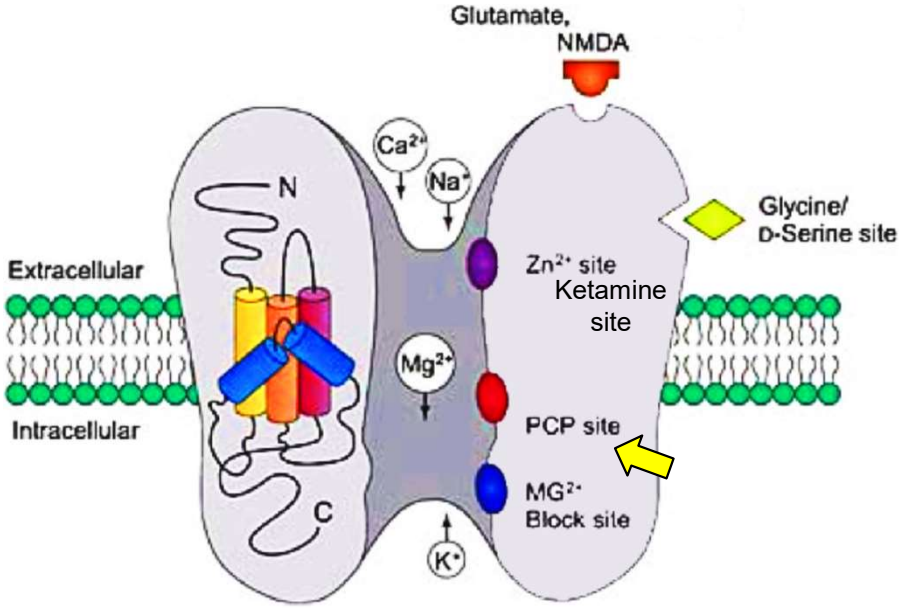
- **Alcohol also activates a neuronal loop in the NAcb involving anterior VTA nAChRs,** →increase in firing rate of dopaminergic VTA neurones → ↑dopamine levels in the nucleus accumbens.



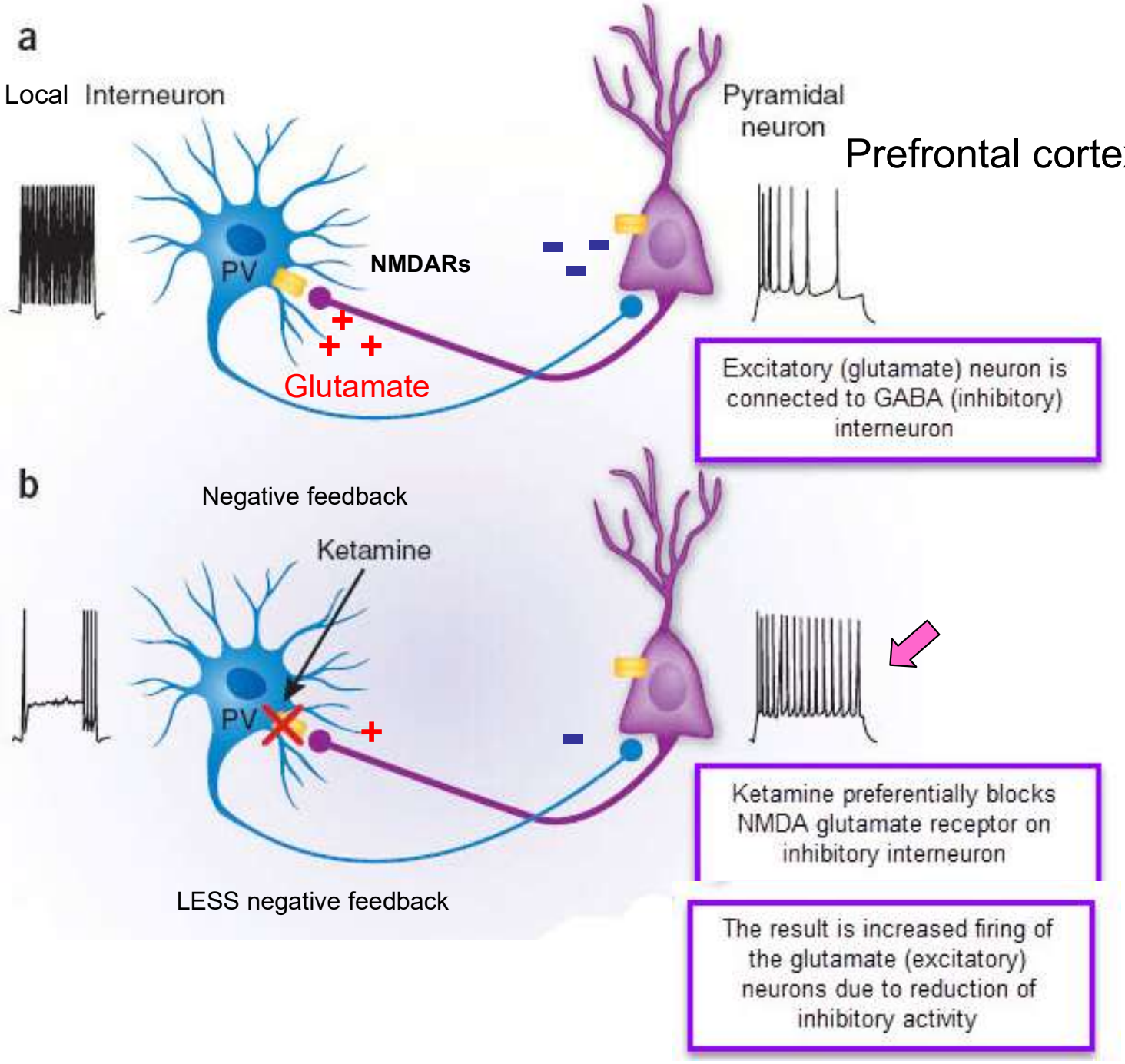
- **Alcohol may also activate endogenous opioid and endocannabinoid pathways** converging on the NAcb.

How do drugs of abuse act?

- **Phencyclidine (PCP)** and **ketamine** block NMDARs, but their effect to release dopamine in the NAcb is indirect. PCP and ketamine activate the mesolimbic pathway through a mechanism in the prefrontal cortex. Blockade of NMDA receptors on local inhibitory GABA interneurones, results in *disinhibition* of the local cortical circuit, →overall cortical excitation thereby **activating descending excitatory glutamate release in the VTA→ excitation →↑DA release.**



How do drugs of abuse act?

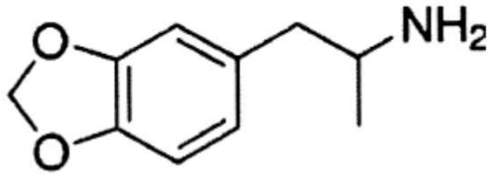


How do drugs of abuse act?

- **Ecstasy (MDMA) –** (being an amphetamine derivative) releases DA in NAcb indirectly by exciting DA neurones in the VTA through 5HT receptors. Ecstasy primarily ↑5HT release in the VTA directly by binding to the serotonin transporters, causing them to work in reverse, thereby releasing 5HT into the synapse and also by inhibiting reuptake. Ecstasy also releases DA (and 5HT) in the NAcb. It has a weaker effect on dopamine reuptake.

MDMA

- **Mechanism of action: releasing agents for <u>mainly serotonin (SSRA)</u>, than dopamine, norepinephrine**

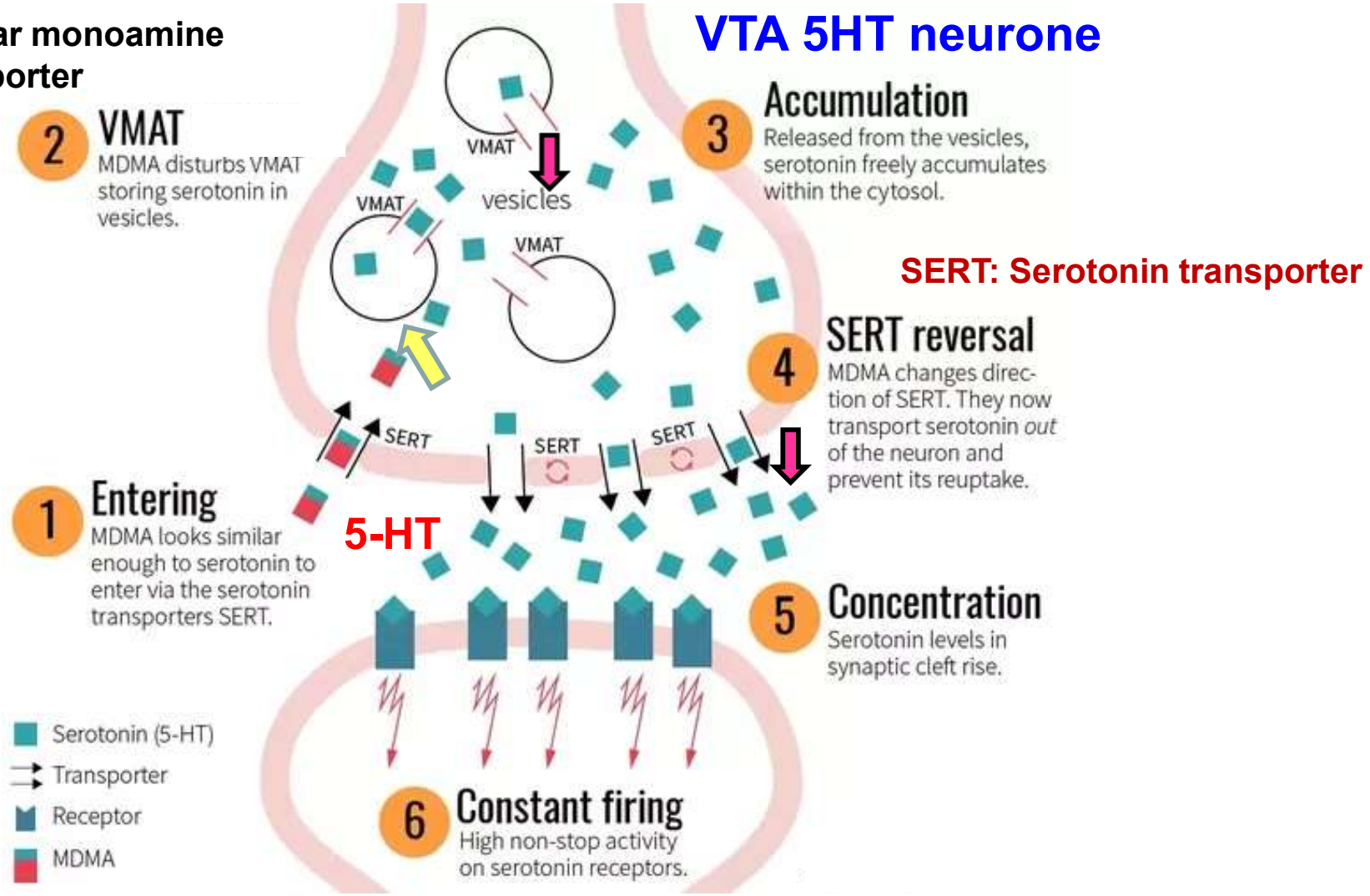


- **enter neuron via carriage by the monoamine transporters (DAT, SERT); inhibit VMAT... (like Meth).**

How do drugs of abuse act?

Ecstasy mechanism

VMAT: Vesicular monoamine transporter



Central opioid receptors and addiction

- It is now clear that although **dopamine** is a key neurotransmitter in the central pleasure/reward system, it is not the only neurotransmitter that is involved.

- In particular, **the endogenous opioid system** is believed to be significantly involved in the central processes of motivation and reward, and in the modulation of the reward circuits. Opioid receptors and peptides are abundantly expressed the reward pathways: **VTA, nACb, PFC, hypothalamus and amygdala.** Thus, it is considered likely that common opioid mechanisms may be involved in mediating the addictive properties of the various DOAs.

Central opioid receptors and addiction

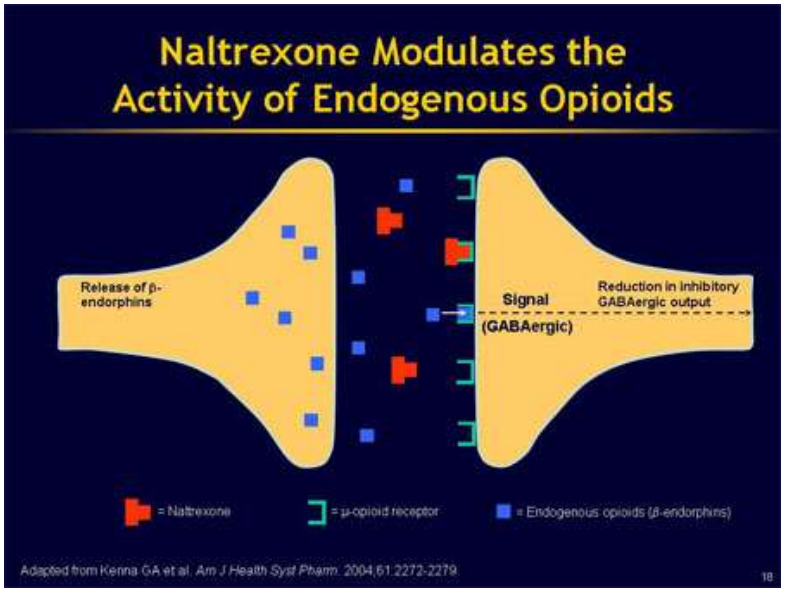
- This therefore opens the possibility of **the central endogenous opioid receptor system** being a useful target for DOA addiction medication in the future.

- There is already some therapeutic benefit in using opioid receptor antagonists *e.g.* **naltrexone** and **nalmefene *(Selincro)*** in the management of not only opiate addiction, but also in reducing craving in alcohol addicts that drink more than 7.5 units a day.

Central opioid receptors and addiction

- There is also some experimental and clinical evidence that opiate receptor blockers can block **cocaine, amphetamine, nicotine** and **cannabis**-induced reward, therefore opening the possibility of **the central endogenous opioid receptor system** being a generally useful target for DOA addiction medication in the future.

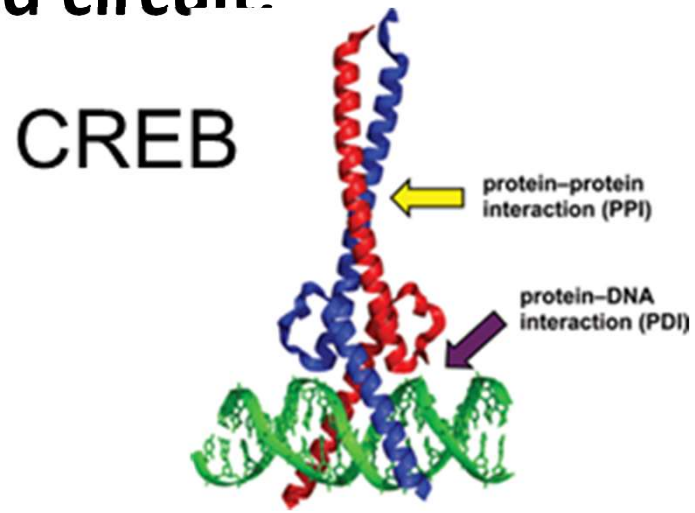
- Further research and clinical trials in this area are clearly necessary.



Molecular mechanisms

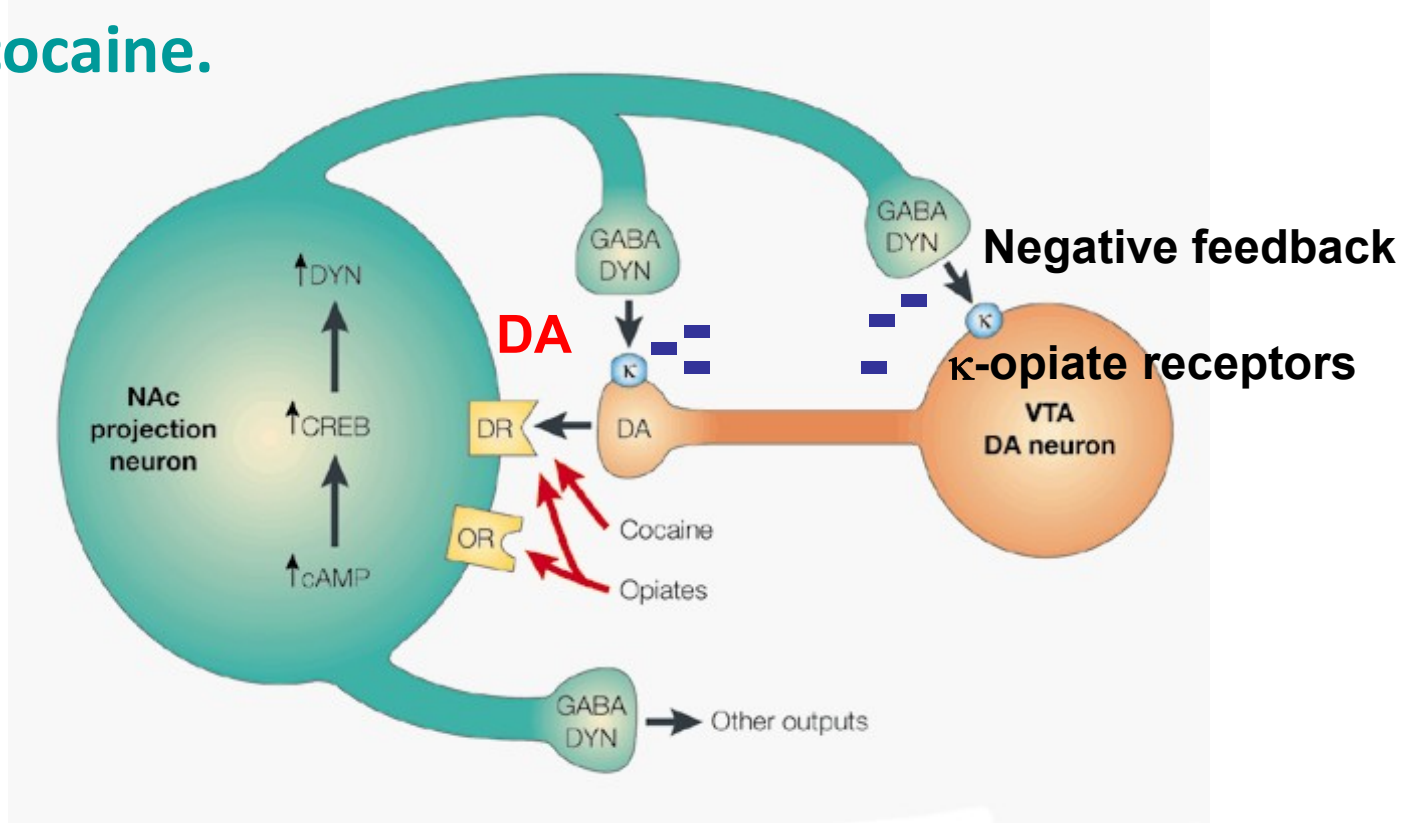
Chronic drug administration ↑production of two nuclear transcription factors in the NAcb: CREB (cAMP response element-binding protein) and **ΔFosB.**

CREB is upregulated by ↑cAMP and PKA activation (CREB phosphorylation at ser 133) – after CREB dimerization and movement to nucleus (binding to DNA cAMP response element – CRE) **it codes for proteins that *suppress* the reward circuit.**



Molecular mechanisms

- One such protein is the opioid peptide **dynorphin.** ↑Dynorphin synthesis and release from NAcb – (GABAergic) projection neurones *inhibits* VTA neurones, acting on *κ*-opiate receptors → **this ultimately *reduces* rewarding effects of opiates or cocaine.**



***Upregulation* of interneuronal dynorphin synthesis by CREB**

Molecular mechanisms

- **Upregulation of CREB protein** by infusing a modified herpes simplex viral vector [HSV-CREB] into the brains of rats or mice contributes to depressive-like and aversive states.

- **Downregulation of CREB protein** using a mutated vector [HSV-mCREB] has the opposite effect.

- **CREB activation** could thus contribute to the mechanism of tolerance induction. However, **activation of CREB, is not long lasting** therefore unlikely to mediate more stable behavioural abnormalities of addiction.

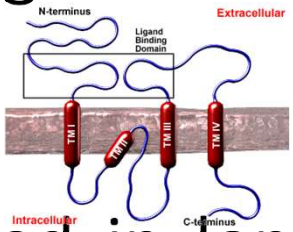
Molecular mechanisms

- **ΔFosB, is a highly stable member of the Fos family of transcription factors,** dimerizes with **jun-D** to form **AP-1 (activator protein-1)** which then reacts with AP-1 sites on DNA to alter transcription of target genes.

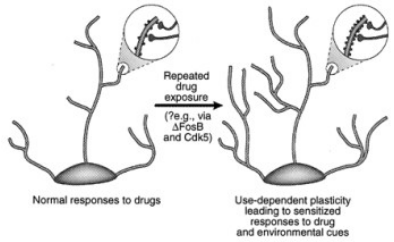
- **ΔFosB** may be involved in **more longer-lasting biochemical changes in the Nacb,** persisting after cessation of drug taking – development of a state of drug *hypersensitivity* and *increased compulsion* towards rewarding behaviour.

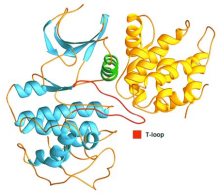
Other molecular effects

- **↑GluR1 and GluR2 expression** in the NAcb occurs after repeated drug (morphine/cocaine) exposure – this may be linked with drug hypersensitivity and ΔFosB upregulation.

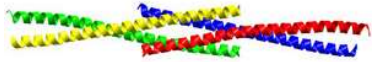


- **↑Cdk5 (cyclin-dependent kinase-5)** – involved in long-term increase in dendritic branches and spines in NAcb and PFC – behavioural drug sensitization?





- **↑Other proteins associated with craving and relapse** – the **cystine-glutamate exchanger**, the **activator of G protein signaling 3 (AGS3),** and **Homer** (a synaptic scaffolding protein).



Other molecular effects

- **CART (Cocaine- and Amphetamine-Regulated Transcript)** is a neuropeptide found mostly in the VTA, ventral pallidum, amygdala and striatum, associated with drug abuse and addiction. Within the NAc are neurones containing CART peptide, which interact with the mesolimbic dopaminergic system. Changes in the concentrations of CART peptide in the NAc **blunt dopamine- and cocaine-mediated behavioural effects, also some of the behavioural effects of amphetamine and ethanol thus may be useful in treating addiction.** The exact mechanism of these protective effects is not clear.

- **Hypothalamic CART** is also involved in feeding (anorexigenic), stress and the regulation of the endocrine system.

Deep brain stimulation

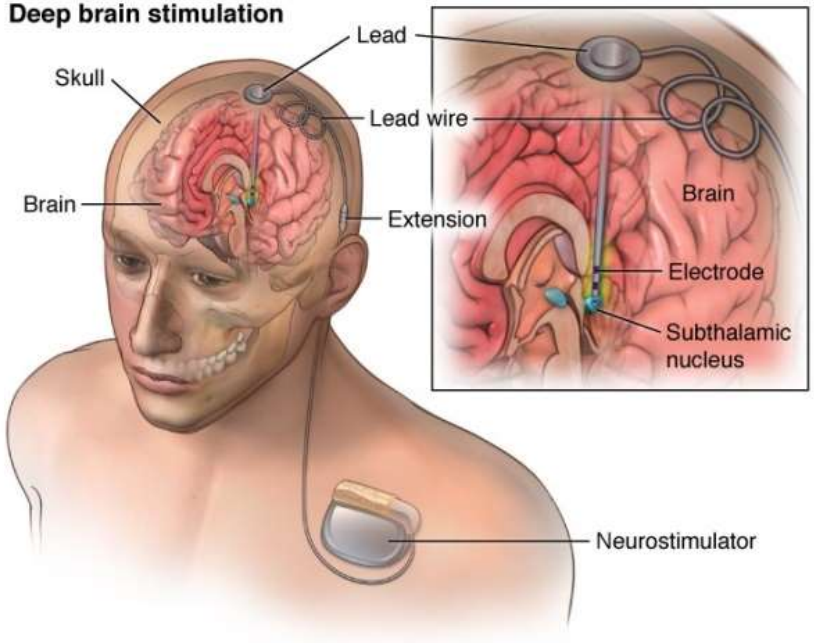
- **Deep Brain Stimulation (DBS)** of certain brain areas *e.g.* the *thalamus* or *subthalamic nucleus* has been shown to be effective in treating tremors in Parkinson's Disease patients.

- **DBS can also be effective in treating other CNS disorders** *e.g.* Tourette's syndrome, OCD, epilepsy and also major drug-resistant depression.

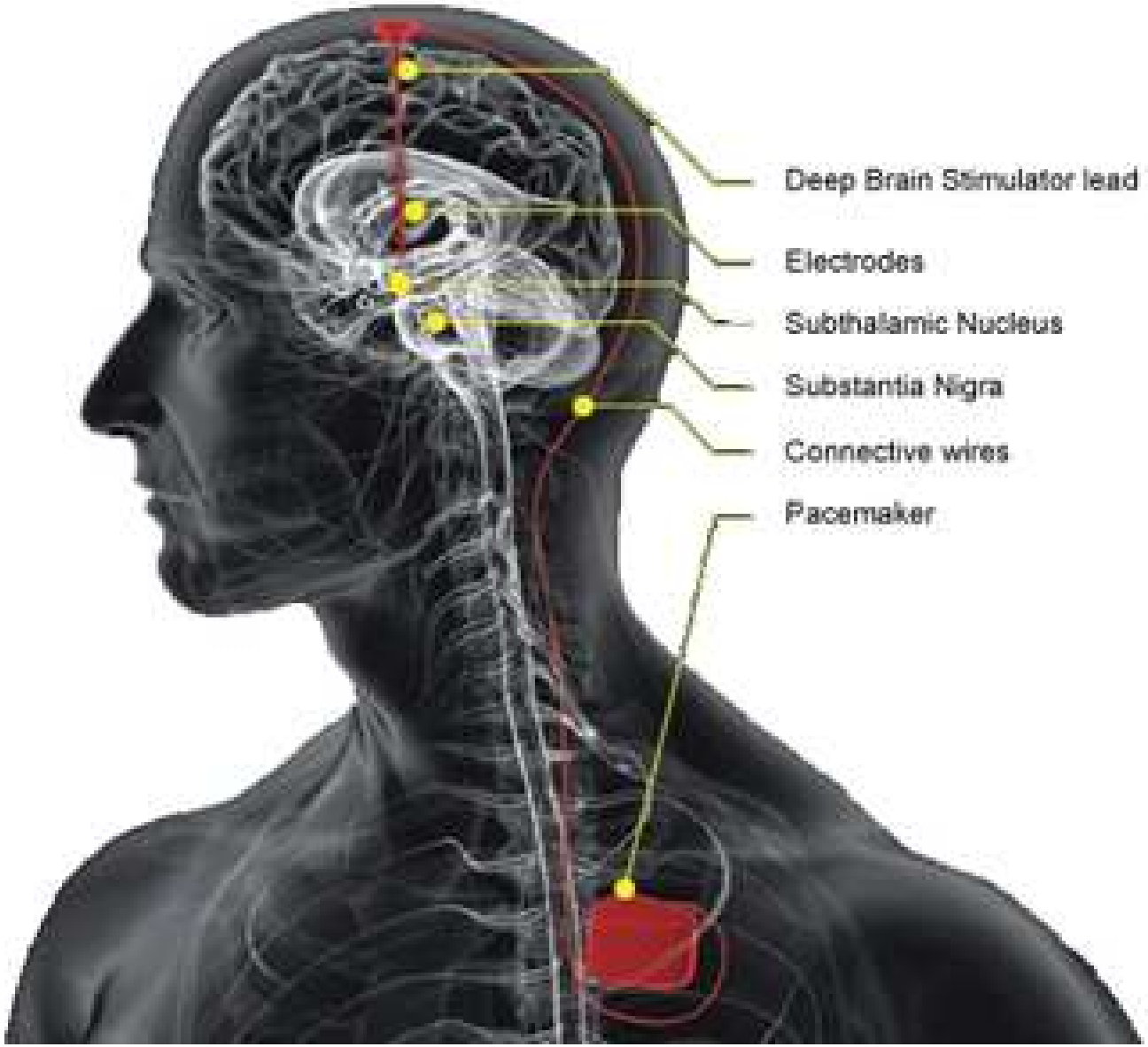
- **More recently, DBS of the *nucleus accumbens shell (NAcbs)*** has been used to treat alcohol addiction and also for reducing craving in nicotine, heroin and cocaine addicts respectively, with minimal side effects.

How is DBS applied?

- **Chronic DBS** is applied through fine stimulation electrodes implanted into the brain of the patient under general anaesthesia.
- **DBS is then chronically applied** through a pulse generator implanted under the skin below the collarbone or in the abdomen.
- **Patient assessments of quality of life** can be made 1, 6, and 12 months post-surgery.



How is DBS applied?



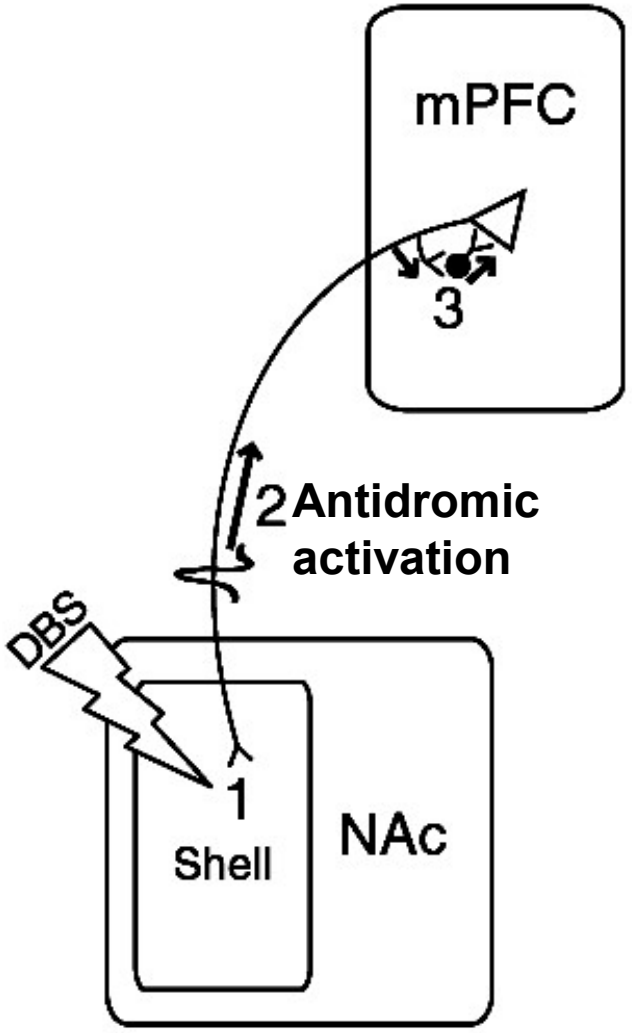
How is DBS applied?

- **Despite evidence of the effectiveness of DBS in a variety of CNS disorders** the underlying mechanism(s) involved in DBS remains uncertain.

- **Based on rodent DBS experiments** it has been suggested that NAcbs stimulation antidromically activates GABA interneurones in the medial prefrontal cortex (mPFC) which then inhibit cortico-accumbal glutamatergic projection neurones.

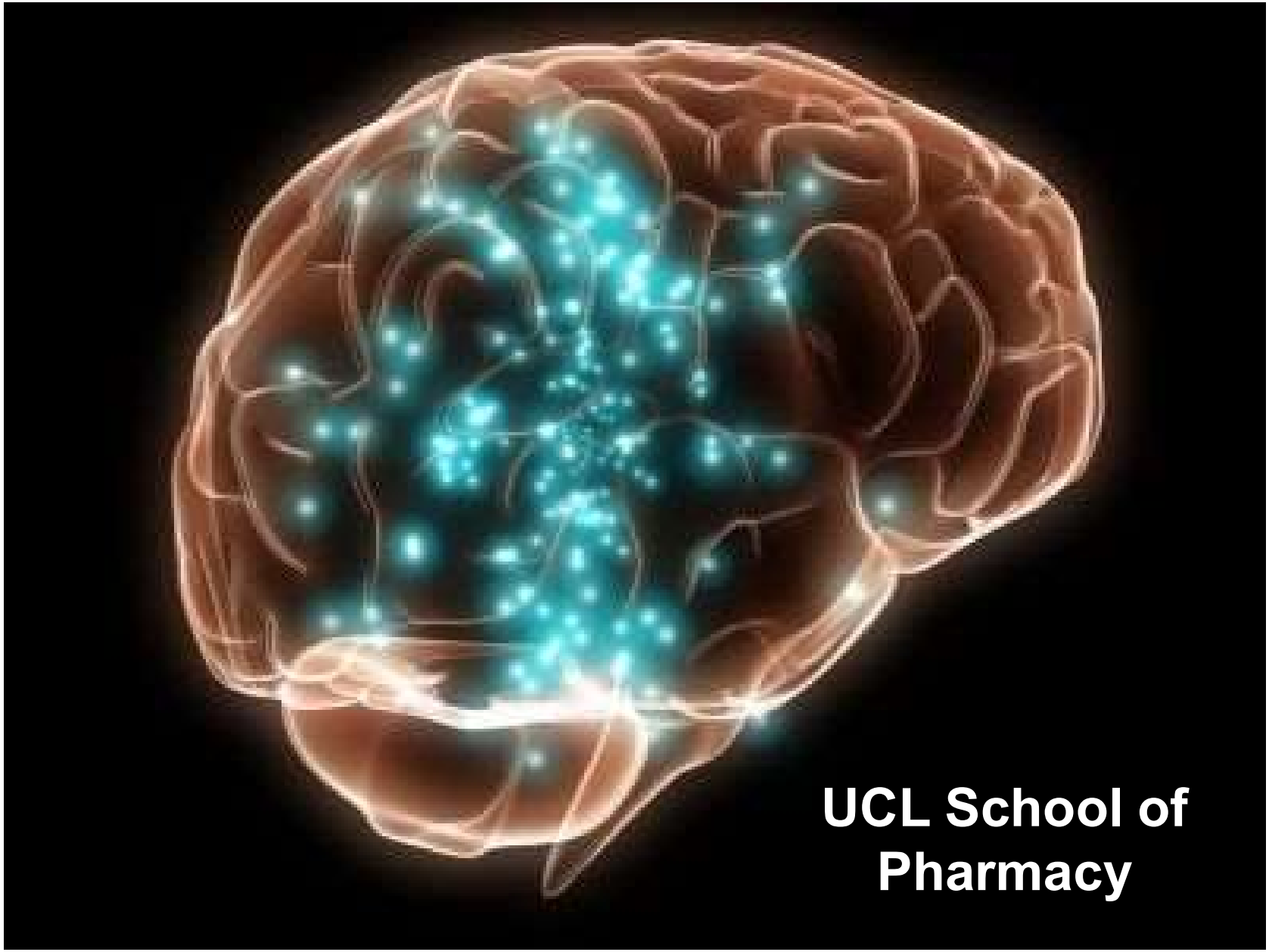
- **How this equates to a decrease in addiction is unclear.**

Mechanism of action of DBS



Release of GABA from local interneurones = decreased activity of cortical glutamate projection neurones

A mechanism, whereby DBS of the *nucleus accumbens shell (NAcs)* indirectly influences neuronal activity in the *medial prefrontal cortex (mPFC).*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