# NPS; clinical pharmacological and psychopathological issues

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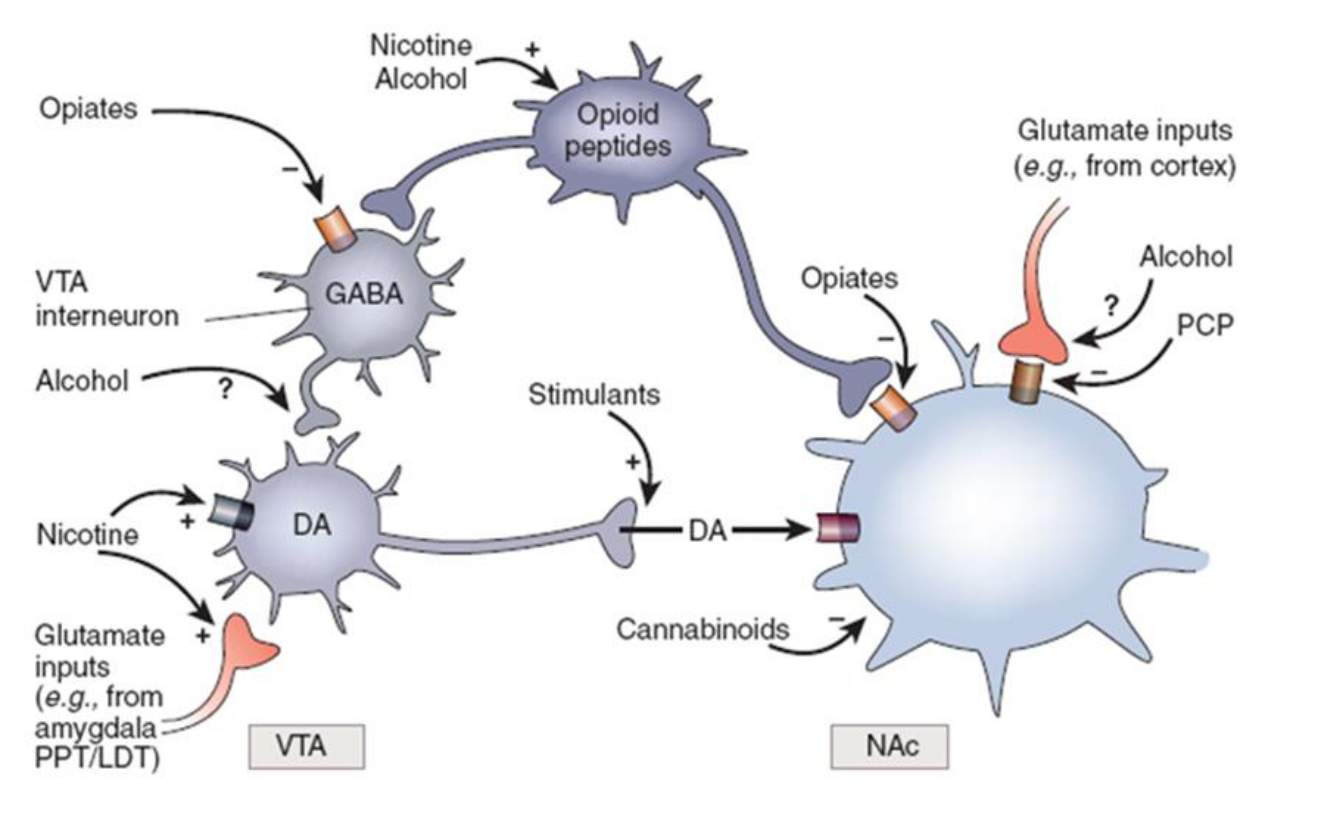
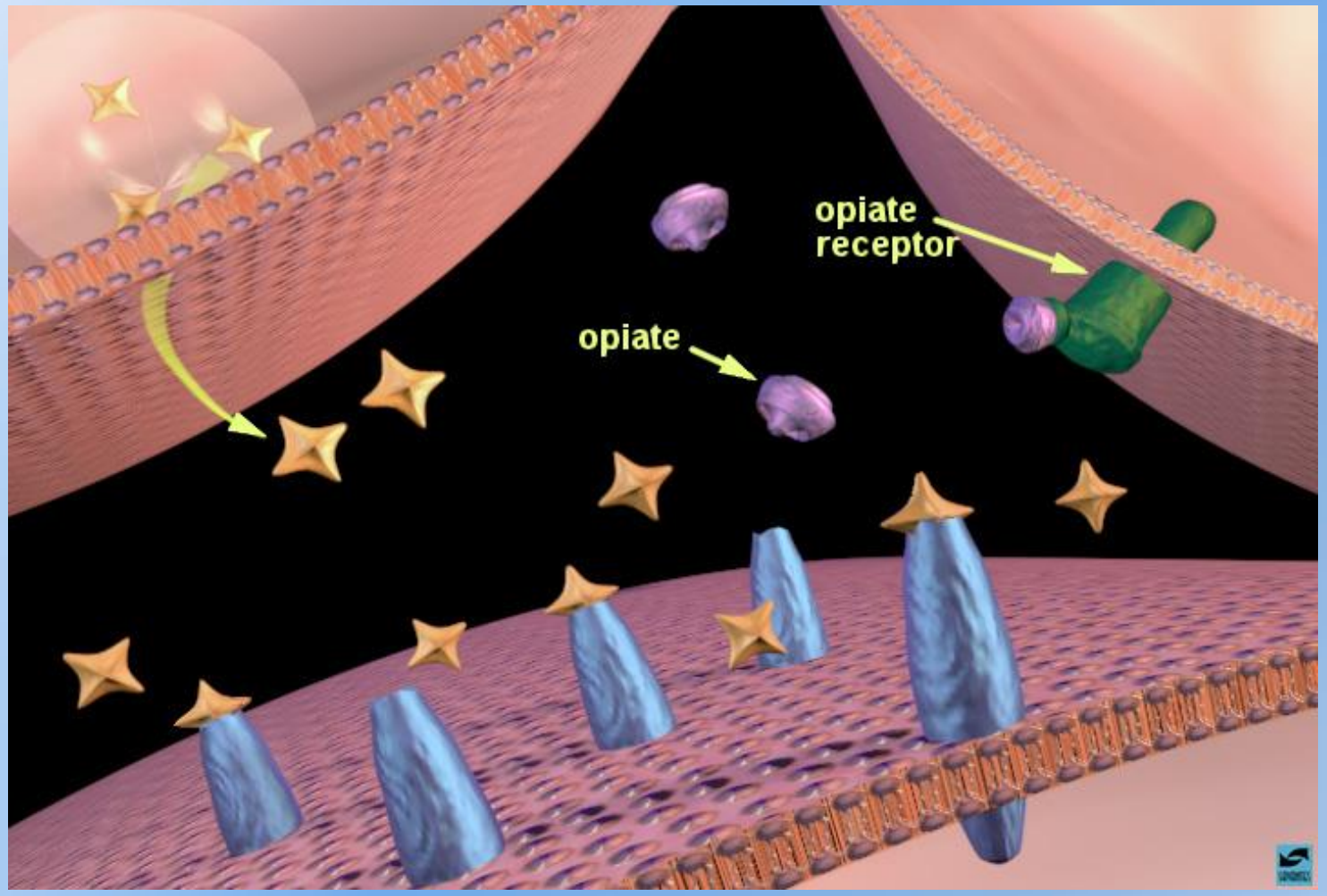
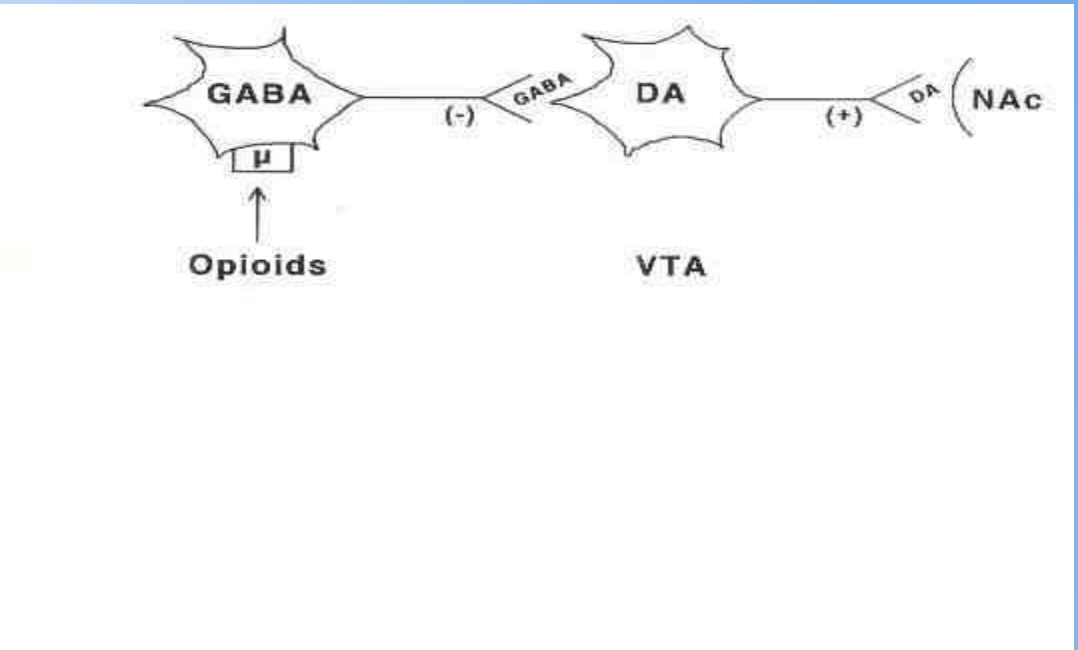
# Overall summary of misusing drugs' ph. dynamics



# OPIATES' BINDING TO OPIATE RECEPTORS IN THE NUCLEUS ACCUMBENS: INCREASED DOPAMINE RELEASE



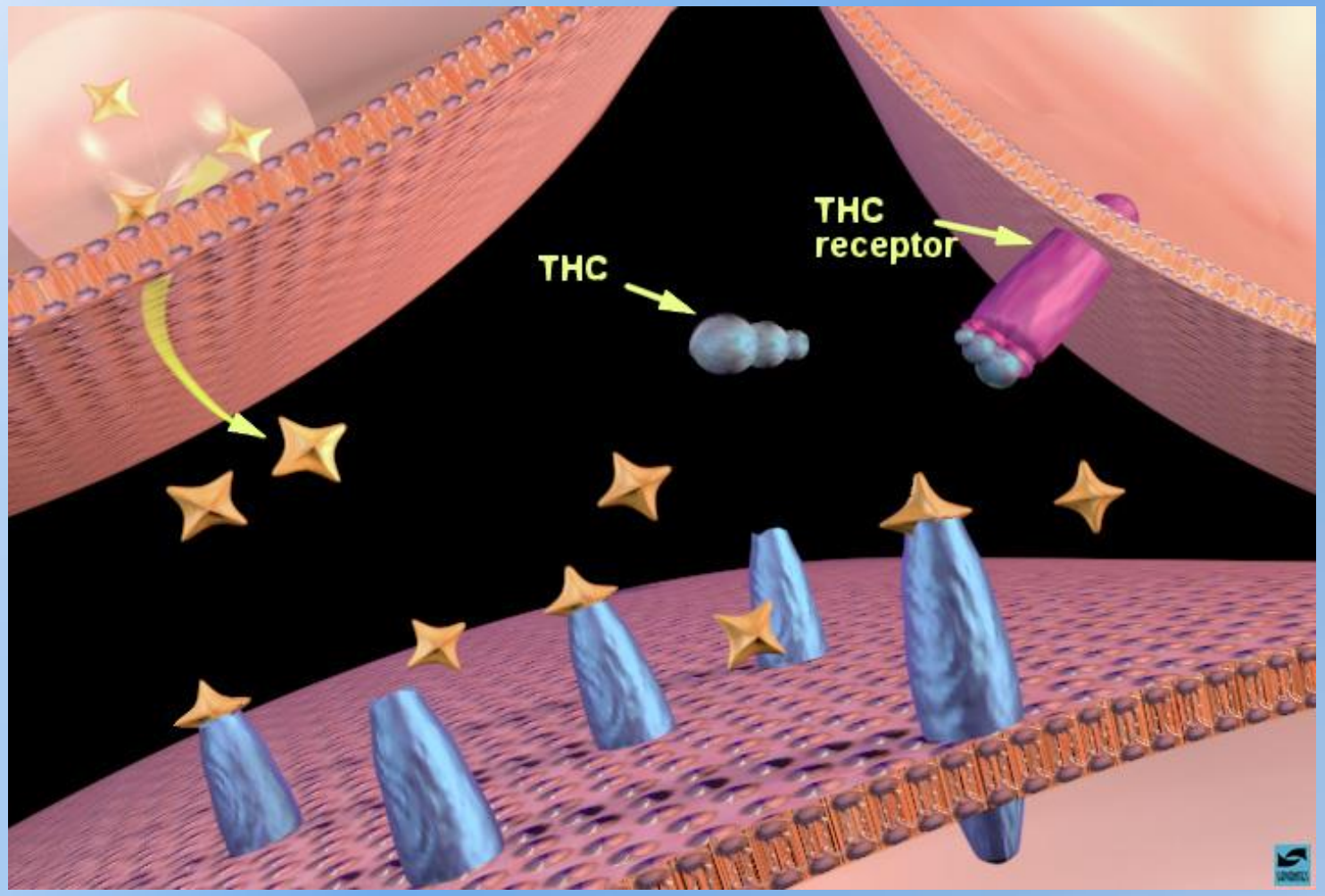
# DA NEURONS IN THE VTA AND OPIOIDS



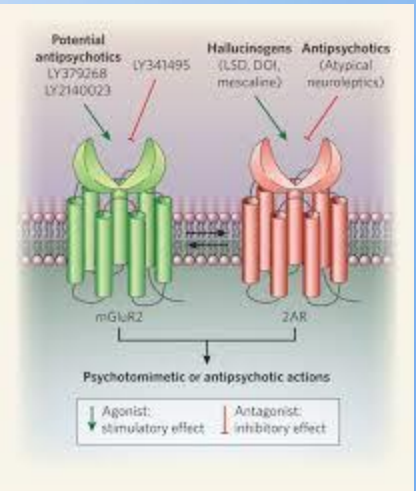

Schematic illustration of the way in which DA-containing neurons in the ventral tegmental area (VTA) are excited by opioids. GABA-containing interneurons are hyperpolarized by opioids acting at p-receptors. This results in decreased (-) GABA release and increased (+) firing and DA release of DA-containing neurons in the VTA towards the nucleus accumbens (NAc).

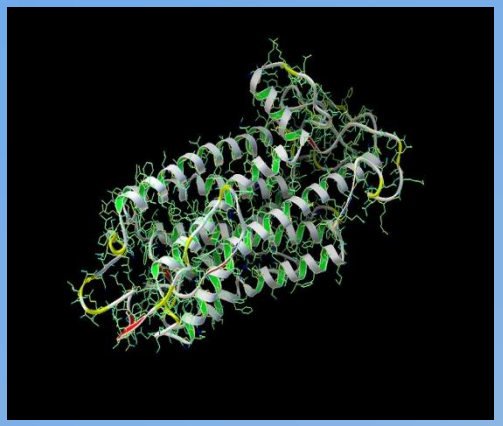
# THC BINDING TO THC RECEPTORS IN THE NUCLEUS ACCUMBENS: INCREASED DOPAMINE RELEASE; THE ROLE OF ANANDAMIDE AND 2-AG IN MODULATING DA RELEASE /PROTECTING FROM THE EMERGENCE OF PSYCHOTIC DISTURBANCES

THC INDUCES DOPAMINE RELEASE IN THE SHELL OF NUCLEUS ACCUMBENS ACTING ON CB1 RECEPTOR. THIS EFFECT MAY BE INDIRECT AND MEDIATED IN PART BY CANNABINOID REGULATION OF ENDOGENOUS OPIOID SYSTEMS IN THE VTA

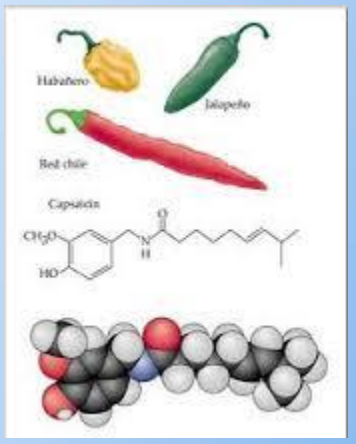


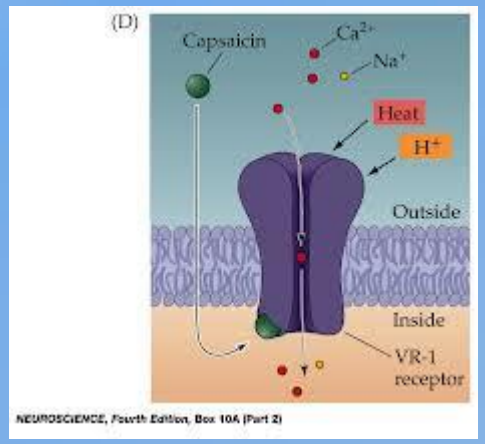
# THE 5-HT2A RECEPTOR

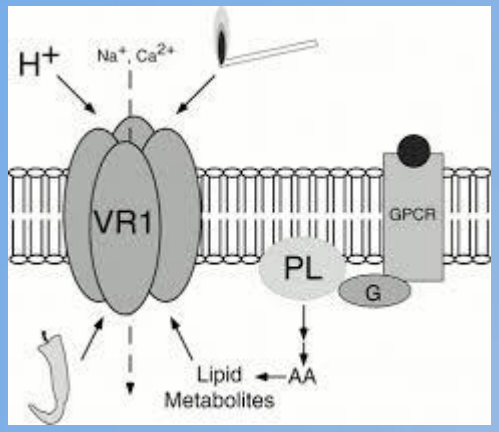


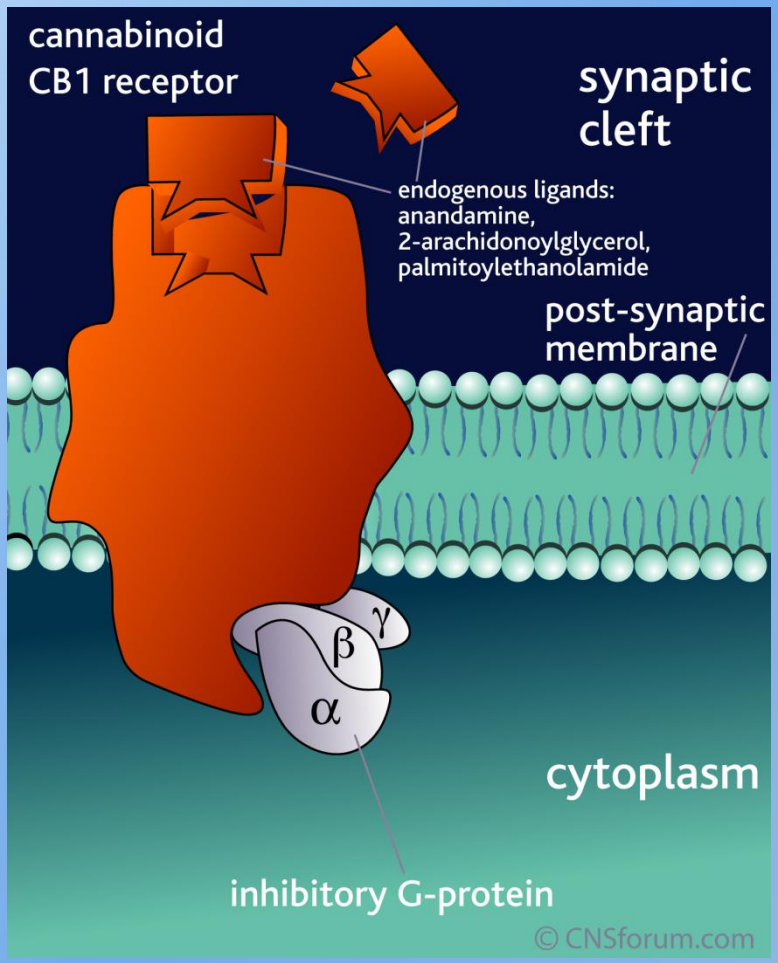
# THE VANILLOID RECEPTOR



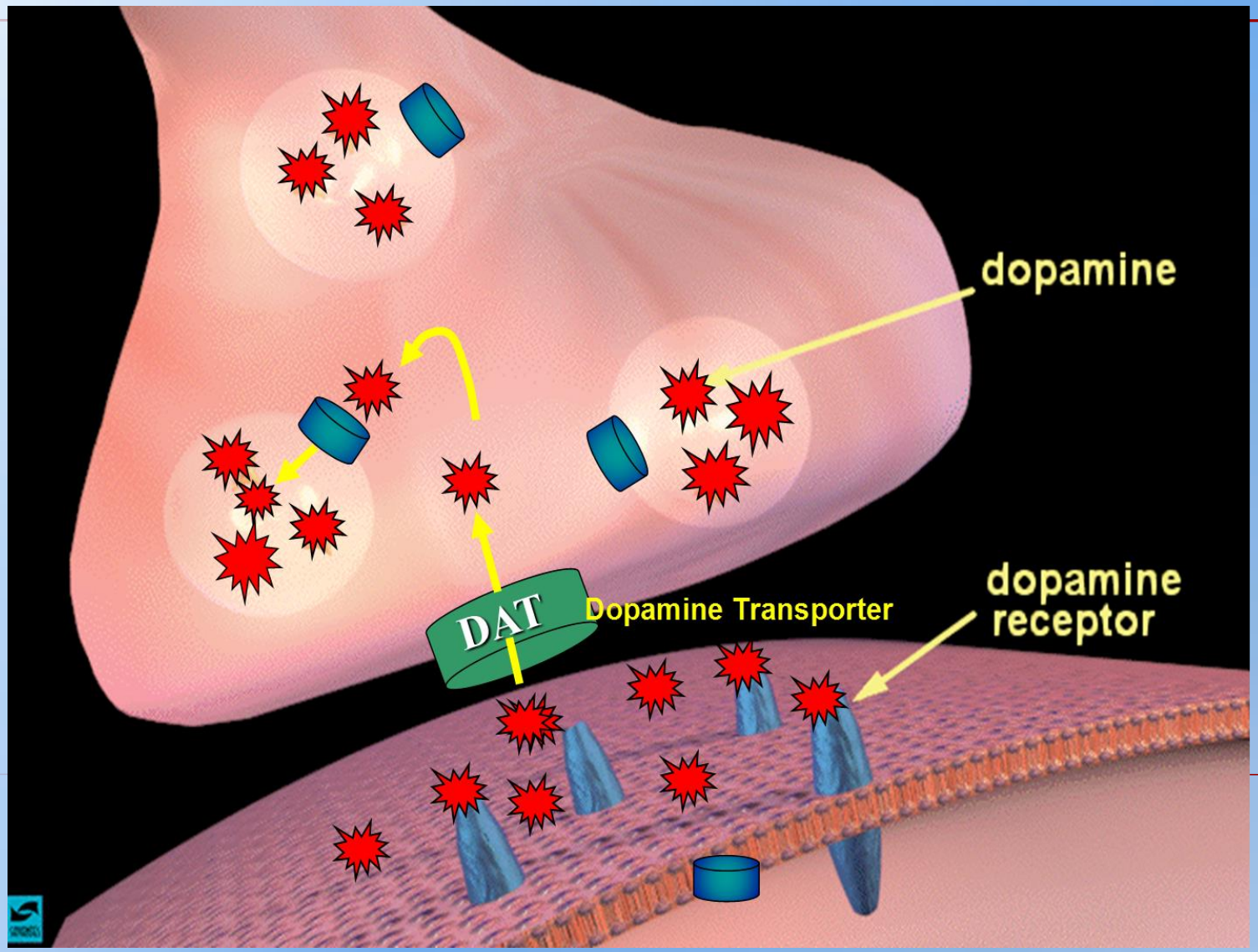



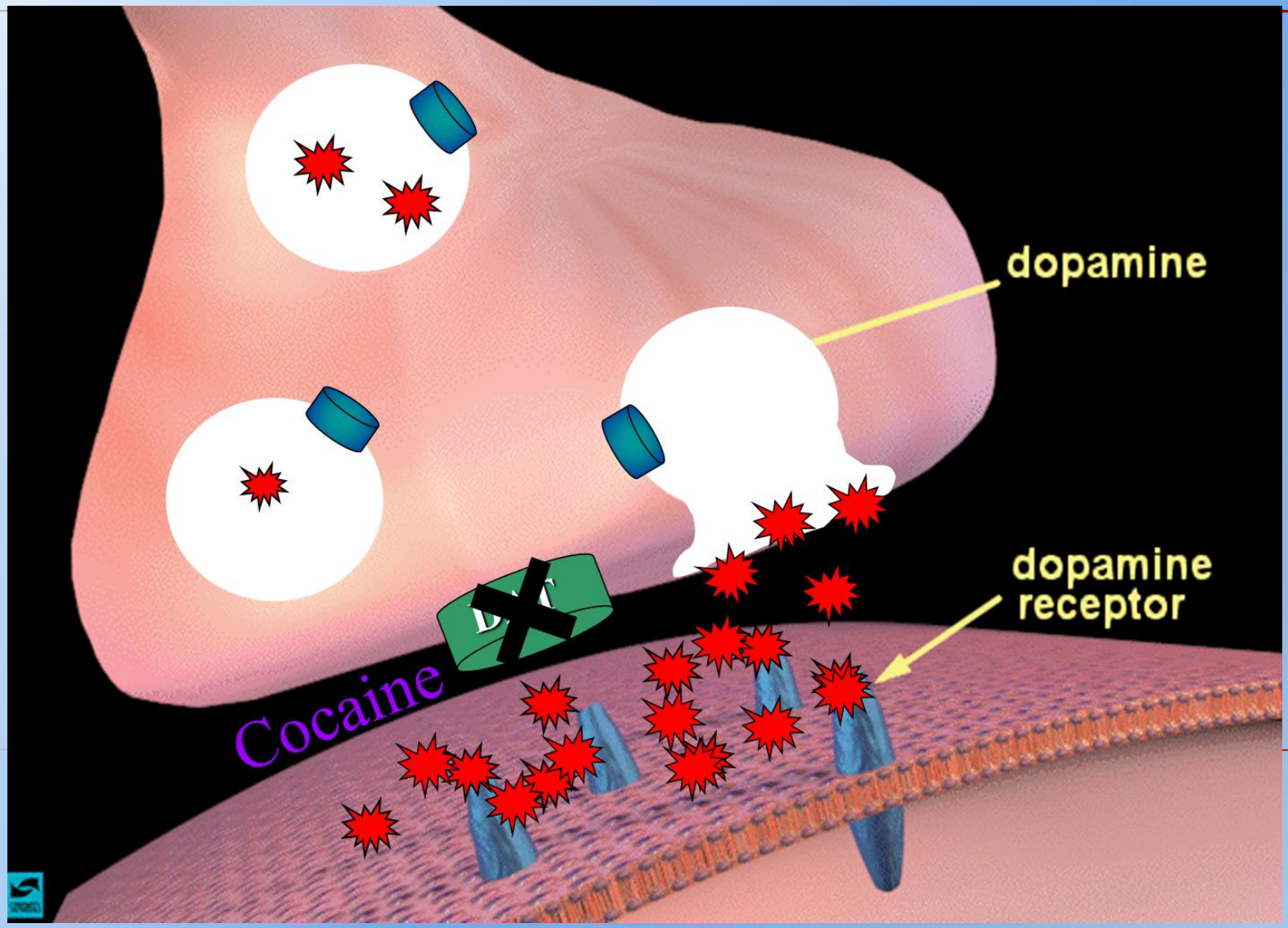
# CB1 RECEPTOR



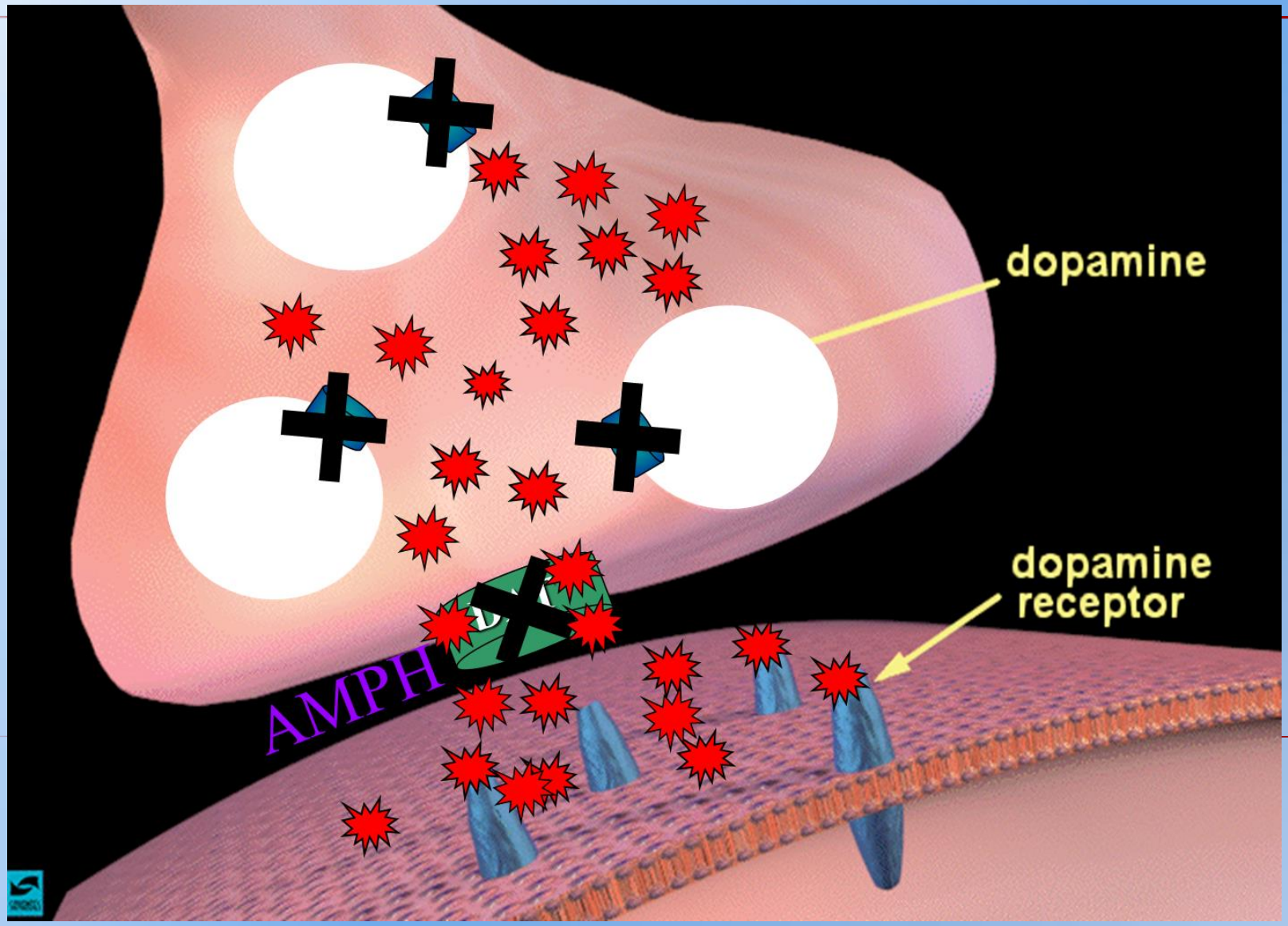
# Mechanism of action of cocaine/most synth cathinones/1



# Mechanism of action of cocaine/most synth cathinones/2



# Mechanism of action of amphetamines/PIAs/other stimulants



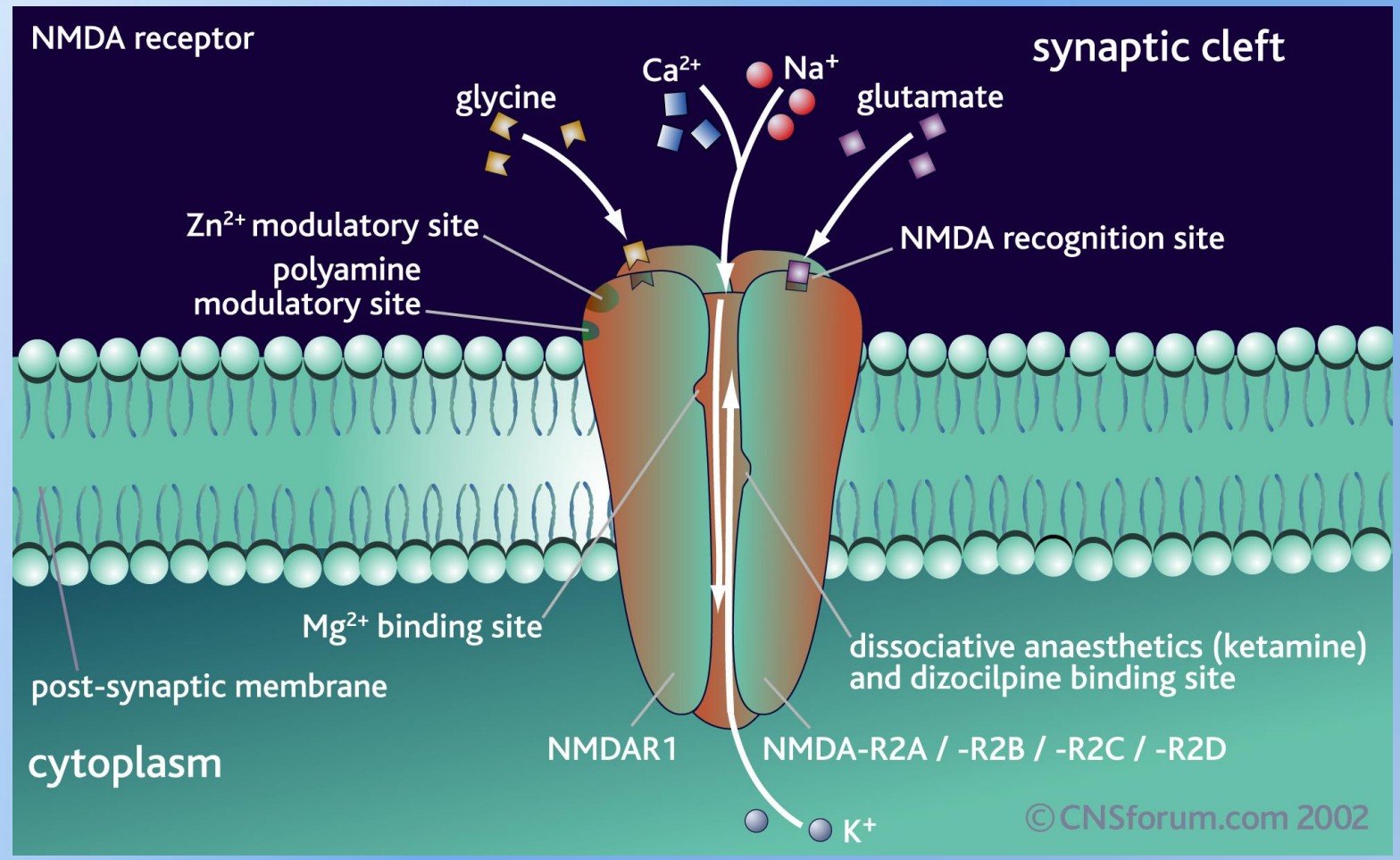
## Mechanism of action of cocaine/synth cathinones

- It binds to and competitively inhibits the functioning of the DA transporter, increasing the duration of action of DA being released into the synaptic cleft.
- It similarly affects 5-HT and NA transporters.

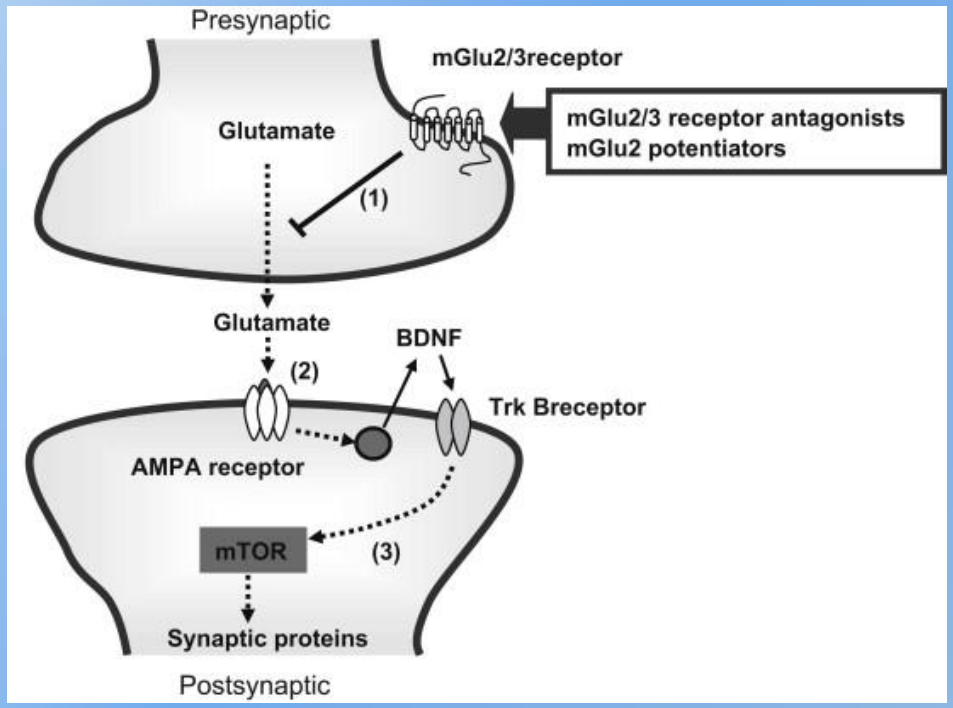
## Mechanism of action of amphetamines/other stimulants

- It potentiates DAergic and other types of monoaminergic neurotransmission by acting as a substrate for monoamine transporters.
- It causes *reverse transport* of DA, 5-HT and NA from the terminals, hence *permanent axonal degeneration*.

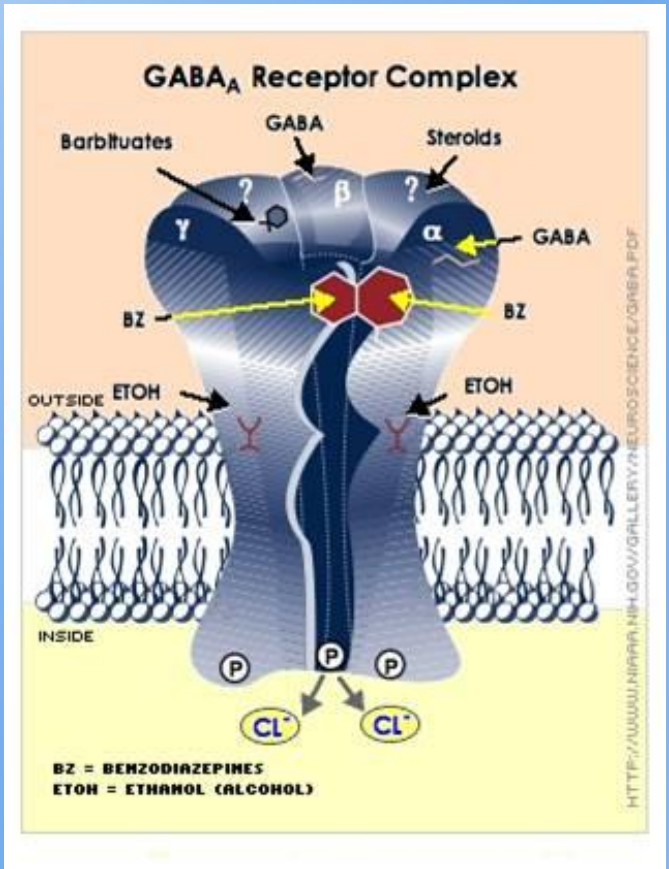
# PCP-LIKE DRUGS; NMDA RECEPTORS' NON COMPETITIVE ANTAGONISTS



# PCP-LIKE DRUGS; MGLU2/3 RECEPTOR ANTAGONISTS

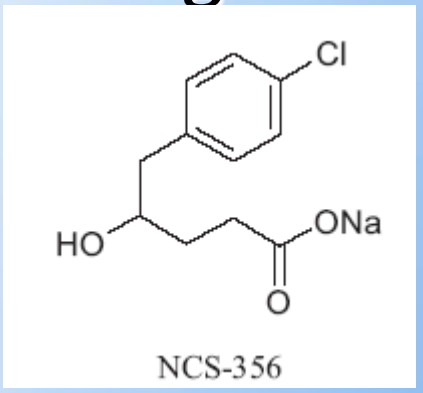


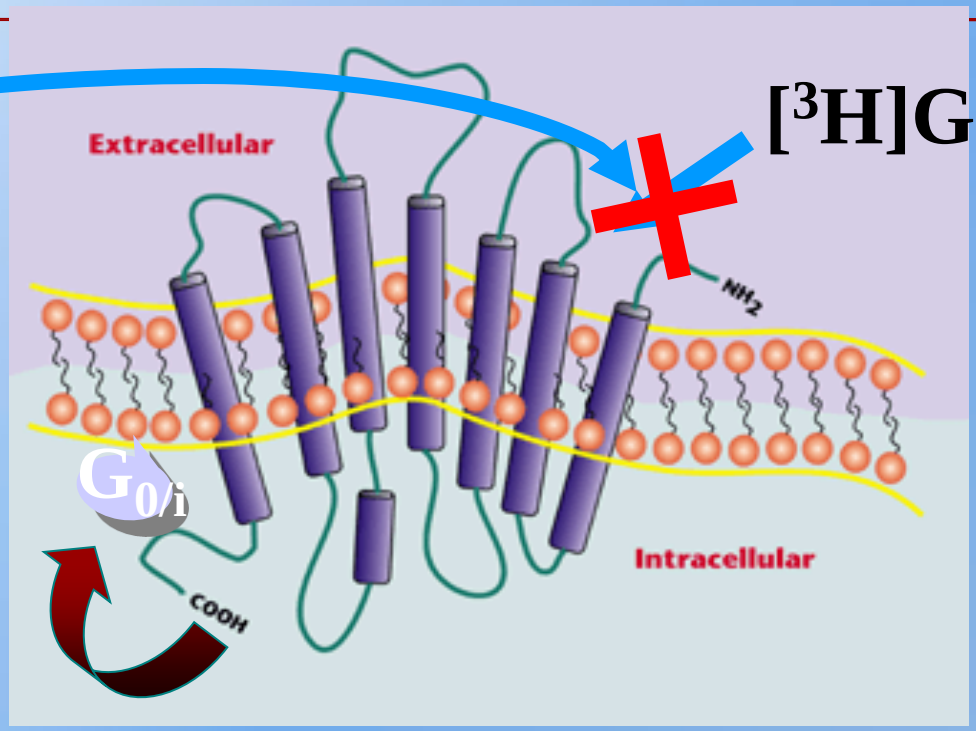
# $GABA_A$ RECEPTOR



# GHB RECEPTOR

**NCS382 antagonist**




**[$^3$H]GHB**

**$K_{d1}$=30-580 nM**
**High affinity GHB binding site**

**$K_{d2}$=2,3-16 µM**
**Low affinity GHB binding site**

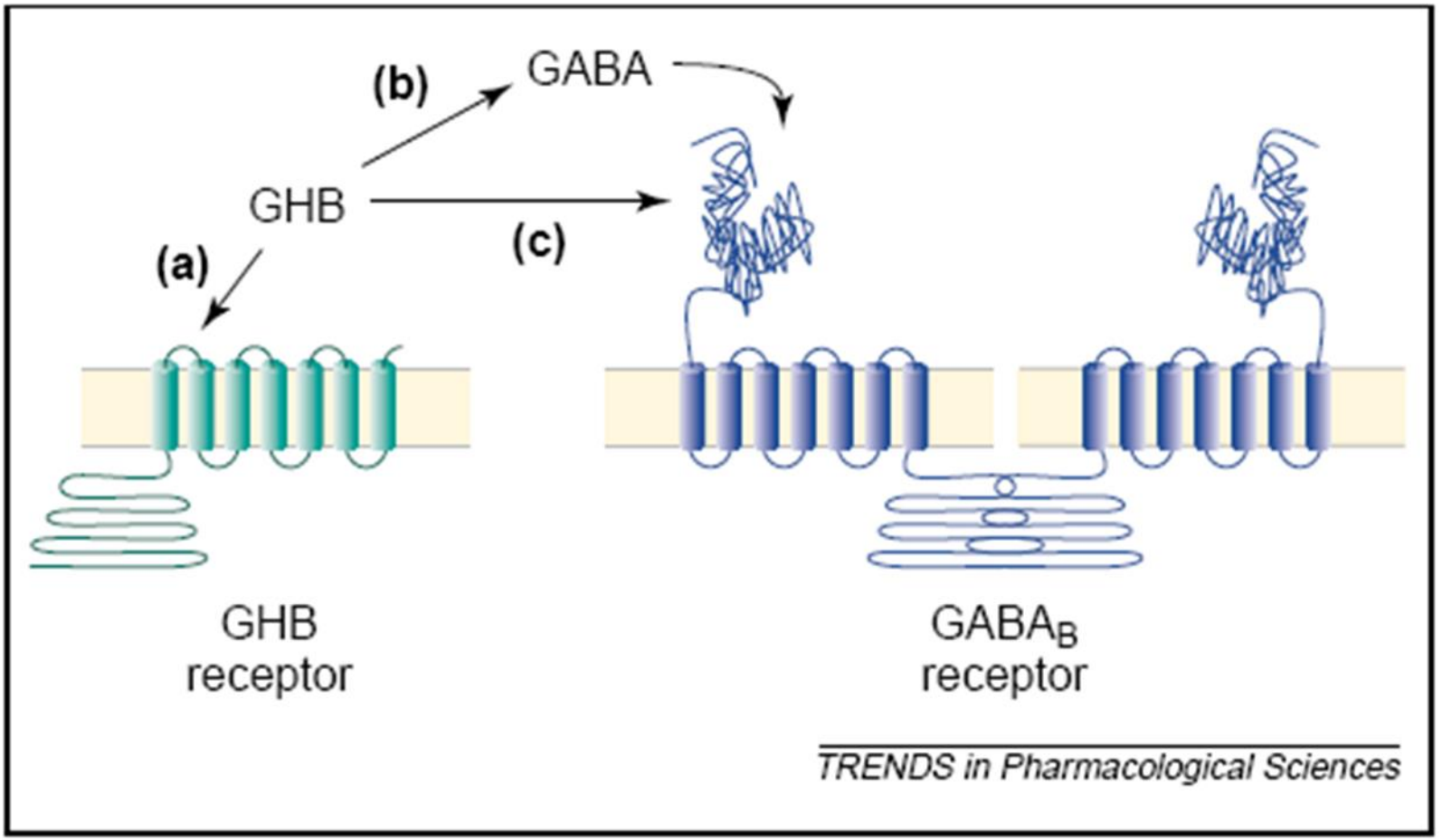



**Figure 1.** γ-Hydroxybutyric acid (GHB) has multiple mechanisms of action in the brain. **(a)** Physiologically relevant concentrations (1–4 μM) of GHB activate at least two subtypes of the GHB receptor: NCS382-sensitive and -insensitive subtypes [11]. **(b)** In addition to binding to the GHB receptor, at supra-physiological concentrations (high micromolar to low millimolar) a sufficient quantity of GHB might be metabolized to GABA, which then activates the $GABA_B$ receptor [7]. **(c)** At supra-physiological levels, GHB itself might bind to the $GABA_B$ receptor [12].

# RISK OF PSYCHOPATHOLOGICAL DISTURBANCES/PSYCHOSIS AND INVOLVEMENT OF THE FOLLOWING PATHWAYS/RECEPTORS....

- DA (agonists)
- CB1;vanilloid (partial/full agonists)
- 5-HT2A (agonists)
- Glutamate: NMDA and mGlu2/3 (antagonists)
- Mu, delta, and k opioid (agonists)

***Clozapine*** *: CB1 receptor antagonism; delta agonism; 5-HT2A antagonism;* mGlu2/3 agonism