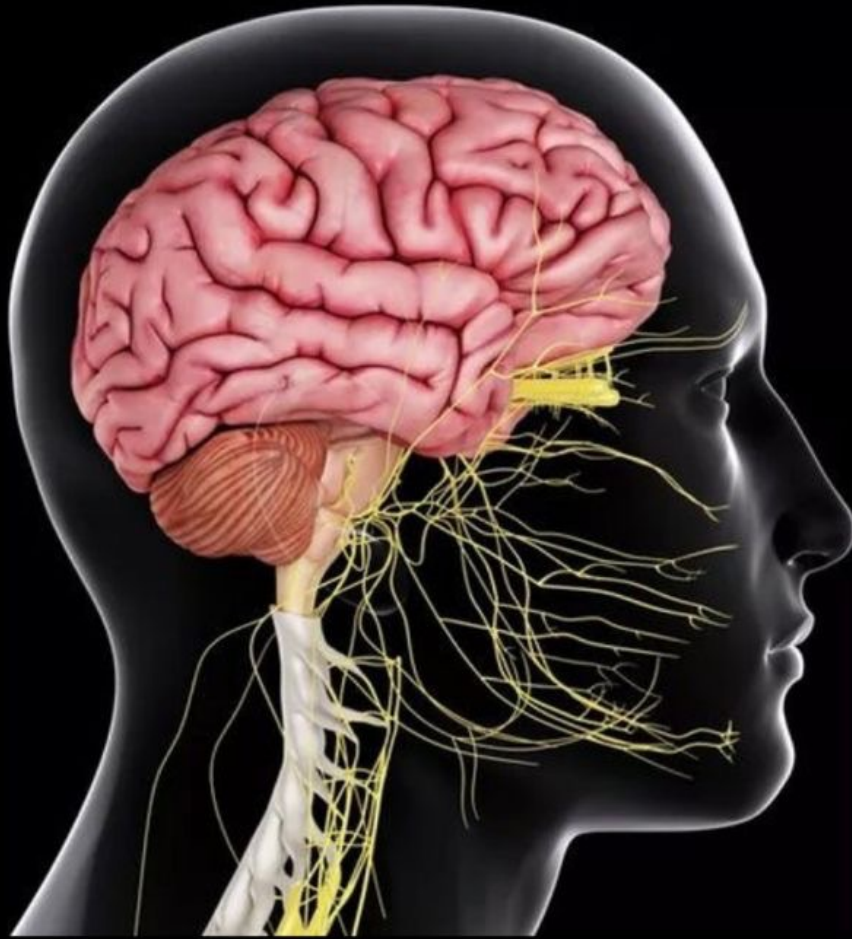




CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 9

DONE BY : Batool ALzubaidi

وَقُلْ رَبِّ زِدْنِي عِلْمًا

CNS Stimulants & Drugs of abuse



كوكايين



ممکن سجارة نيكوتين عادية او حشيش زي الميرجوانا

Ahmad Altarifi

D.D.S., Ph. D.

Marijuana is most abused substance in the united state, cocaine and heroine are also a big problem .. abuse is dynamic human pharmacologists in specific can synthesise drugs that can be abused for example fentanyl (opioid) which is a very potent drug (small dose of it can exert big effect due to high receptor affinity)

Most of abused drugs are stimulants, but in general anything can be abused

Stimulants vs. Depressants

Stimulants will increase the three of them

- Alertness
- Wakefulness
- Locomotion
- Examples

– Amphetamine

Stimulant

– Barbiturates

Depressants

– Opioids

Depressants

– Cocaine

Stimulant

– Benzodiazepine

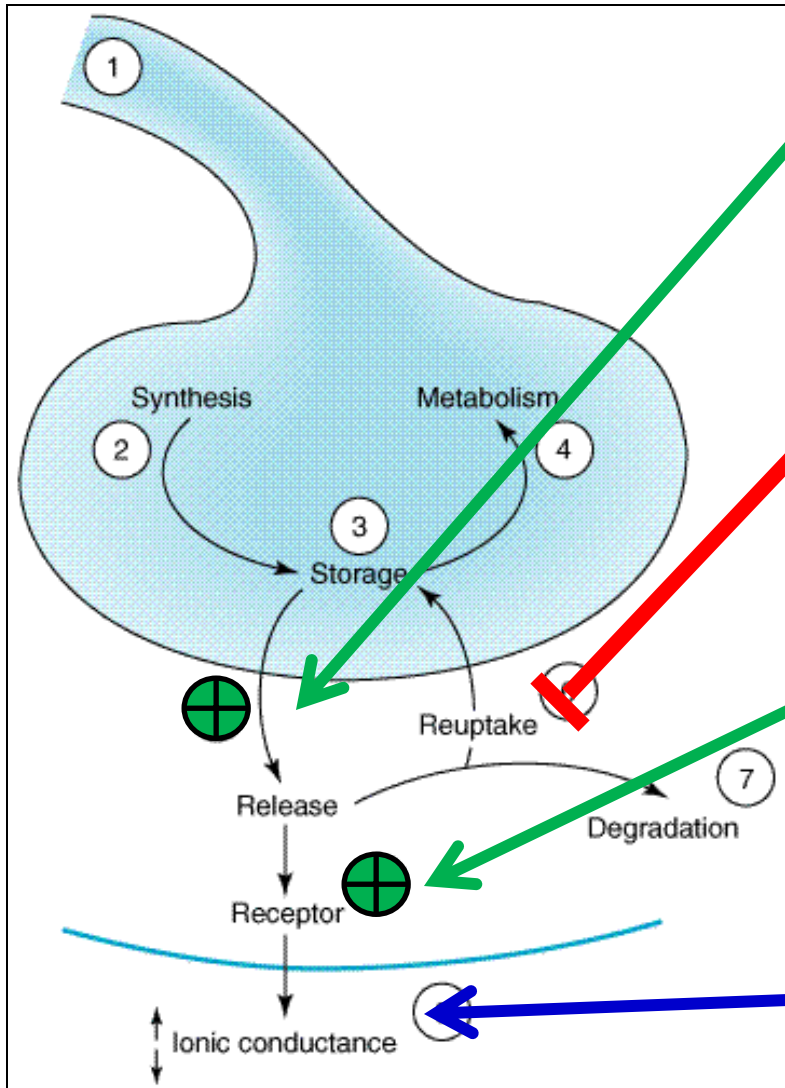
Depressants



Most abused drugs in Jordan in the last 10 years are cocaine and Captagon

Stimulants excite/stimulate the excitatory/stimulatory neurotransmitters

Excitatory Neurons



1) **Enhance Neurotransmitter release:**

- Amphetamine

2) **Inhibit Neurotransmitter Uptake:**

- Cocaine

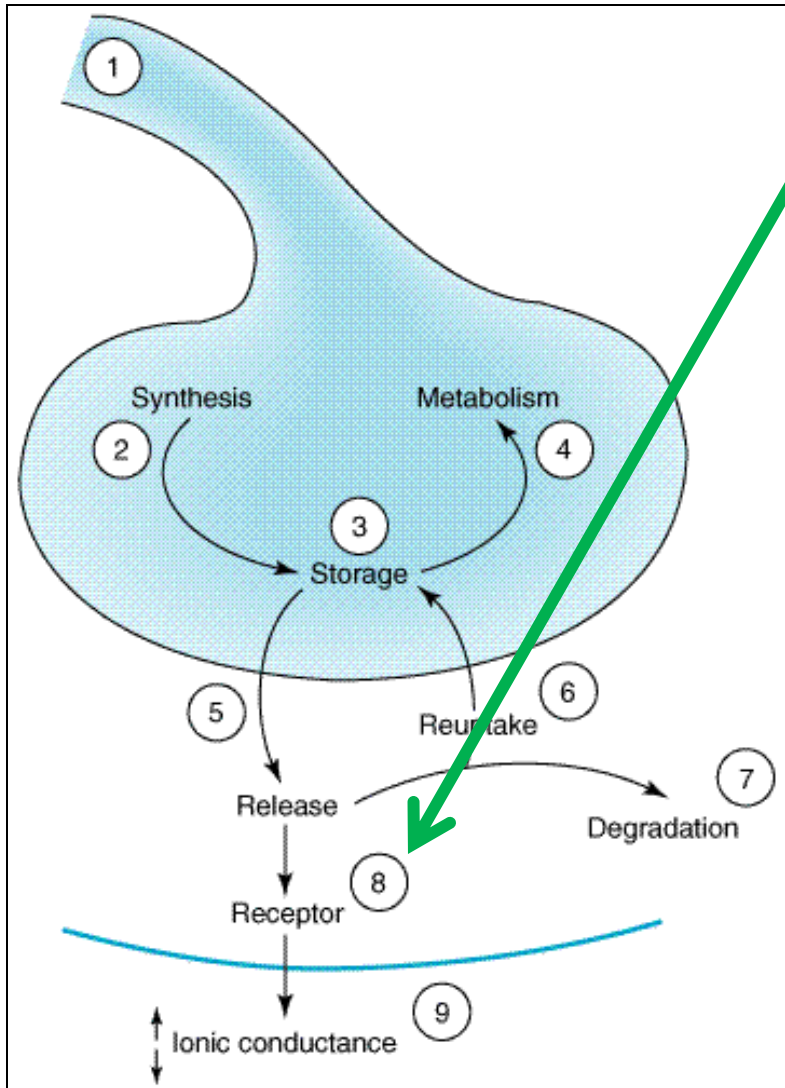
3) **Activate postsynaptic receptors**

- Nicotine

4) **Interfere with 2nd messenger**

- Caffeine

Inhibitory Neurons



1) Inhibit postsynaptic receptors:

- Strychnine (inhibit glycine receptors)

CNS Stimulants

They in general produce euphoria, decrease the feeling of sleepless, increase locomotion



Definitions

- **Drug abuse:**
 - A pattern of drug intake in which the user consumes the drug against its medical indication

Unnecessary use of the drug, taking the drug without medical advice

جارتنا ام محمد لما تاخذ antibiotic لانه عندها common cold هاد drug abuse



Definitions

- **Withdrawal symptoms:**
 - The emergence of unwanted signs and symptoms after cessation of drug intake



Definitions

- **Dependence:**
 - Compulsive drug using behavior in which the individual uses the drug to avoid unwanted side effects



If symptoms happen after you stop taking the drug following chronic use » patient is dependent on that drug

Definitions

1. *Something appears at human body, you can see the symptom*

- **Physiological Dependence:**

- Diarrhea
- Sweating
- Nausea
- Headache
- Hypertension
- etc



Definitions

2. More serious, needs behavioral therapy

• Psychological Dependence:

- Continuous drug intake for personal satisfaction.
- Emotional connection to the abused substance



و هاد الاشياء التي يعملوا عليه ابحاث و تجارب حاليا و بشوفوا ال
calcium channels المربوطة بال neurons التي رايحة من ال
hippocampus لل target بتزيد لما الواحد يوقف هدول الادوية و
بالتالي استخدم هاد الاشياء بانني اخفف ال dependence

ال physiological dependence comes first ب اول ٣ ايام ل اول اسبوع و
بعد اسبوعين there should be no physiological withdrawal symptoms

Definitions

- **Addiction**
 - Continuous repetition of a behavior despite adverse consequences.

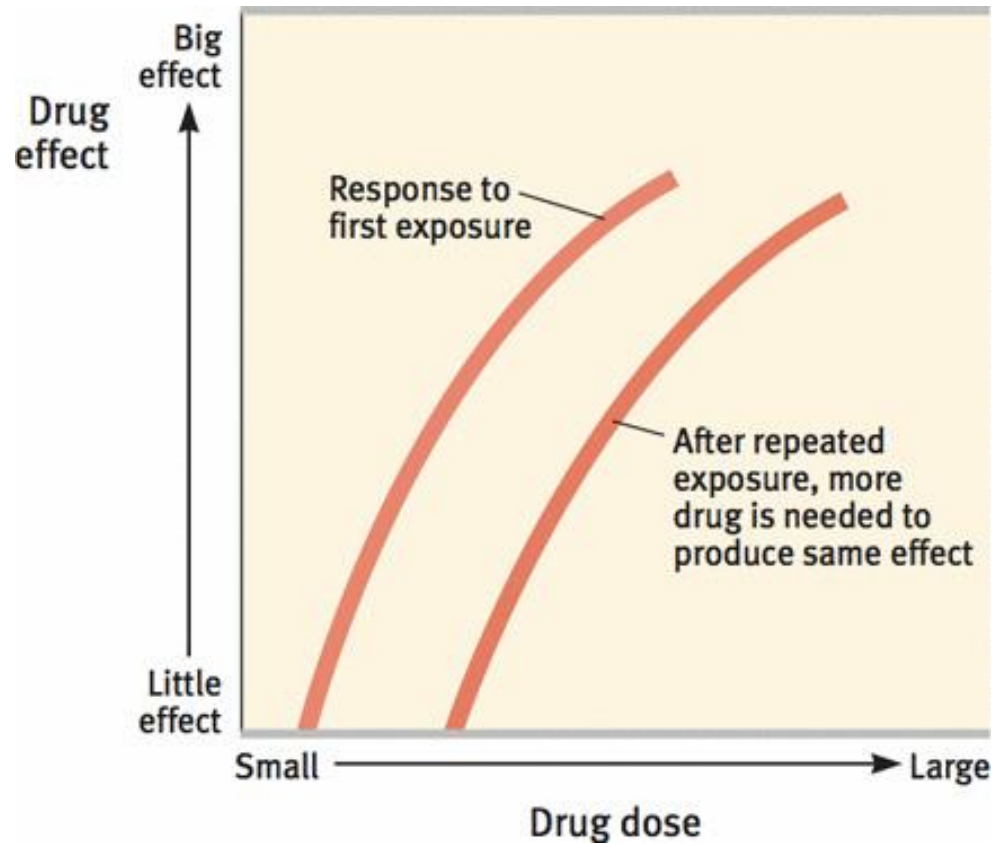


الناس الي بدخنوا هم عارفين
اثاره و سلبياته و مع هيك بدخن

ال consequences مش شرط يكونوا
على ال health ممكن على ال social
connections ممكن يطلق مرته مثلا
عشان حكته اترك الدخان، ممكن
بيطل يروح على الشغل، ممكن يصير
يسرق من اي مكان عشان يشتري
الاشي الي هو مدمن عليه

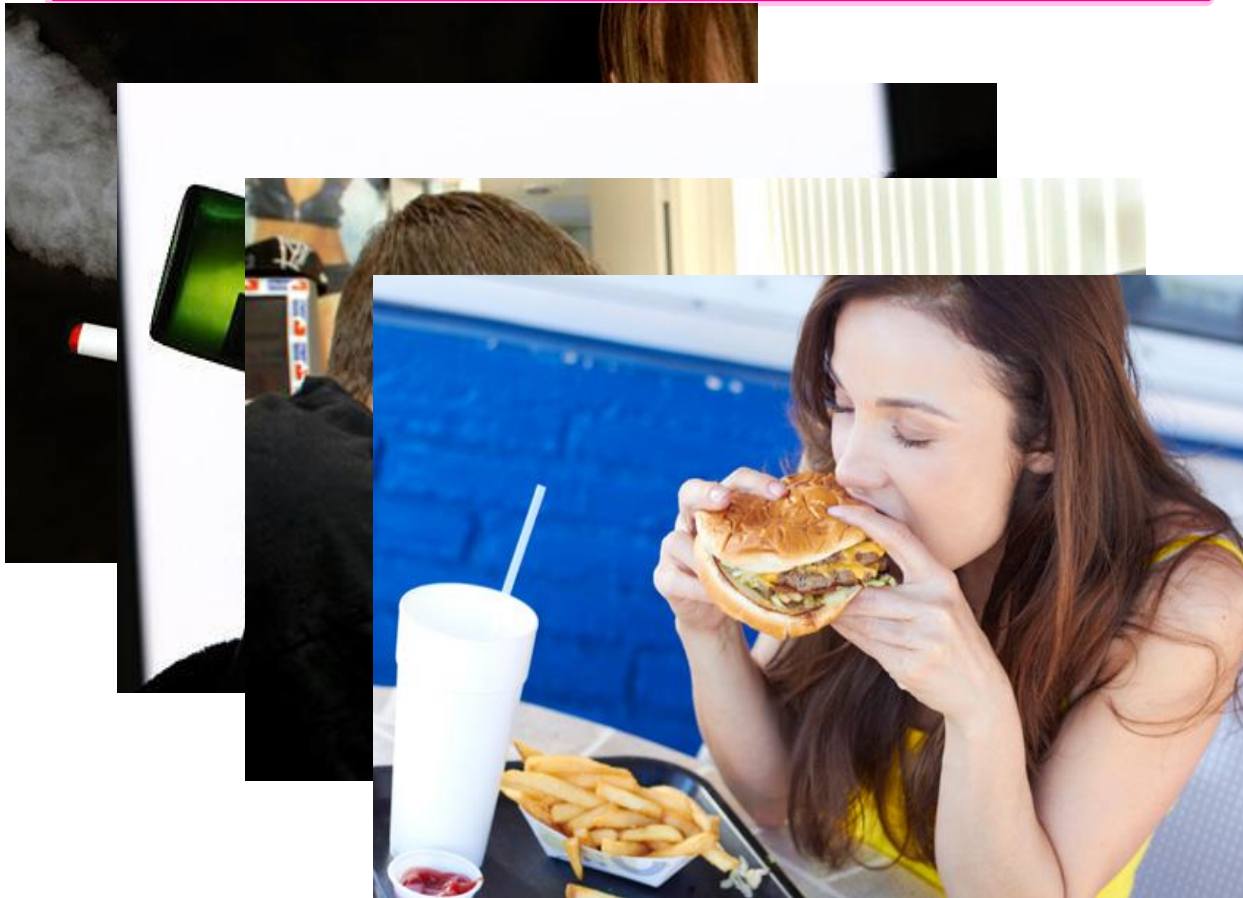
Definitions

- Tolerance

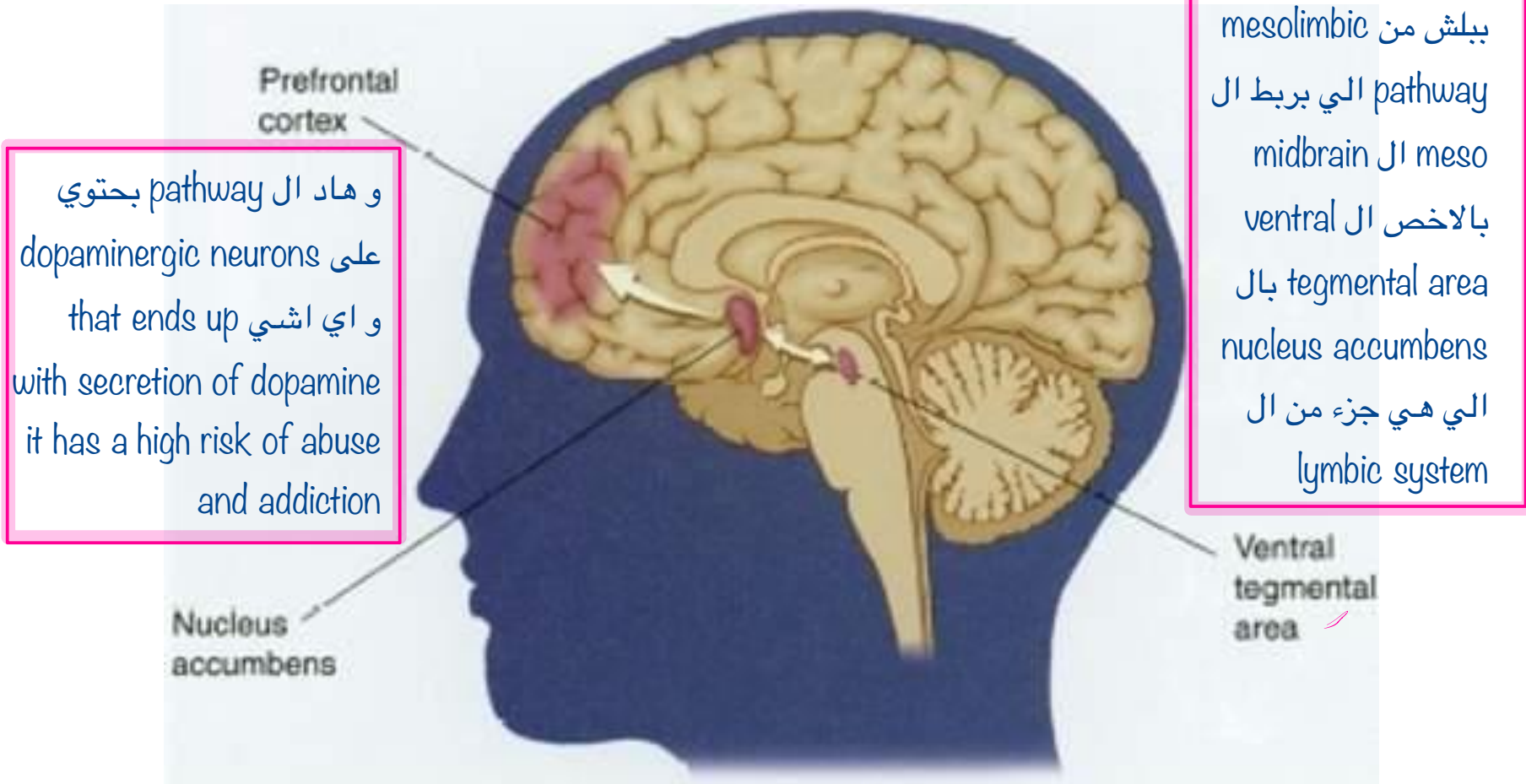


Examples of Addiction?

Smoking, nicotine, alcohol, opioids, eating, video games, social media



Mesolimbic Dopamine Pathway



بعض ال dopaminergic neurons بوصولوا ال prefrontal cortex ال وظيفتها ال recognition and disson

Examples

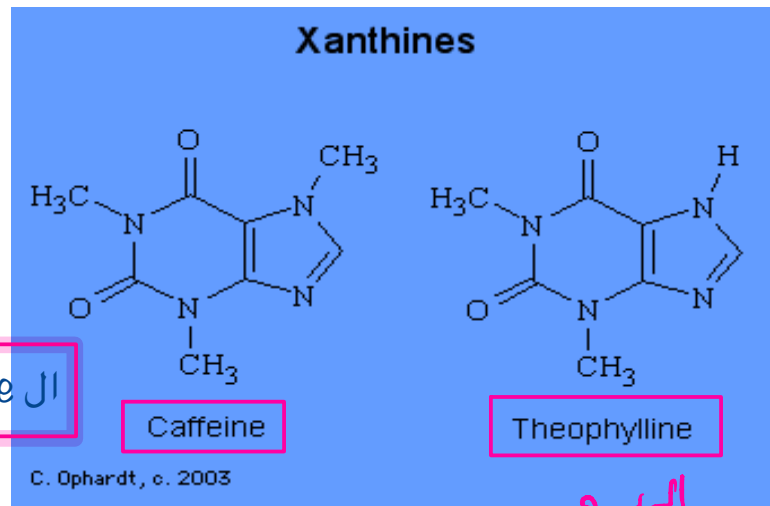
- Patient feels pain.

Methylxanthines

- Improve alertness and enhance wakefulness and mental performance

ال stereotype اي حدا بياخذ الدوا المعين هاد راح يصير معه نفس ال behaviour

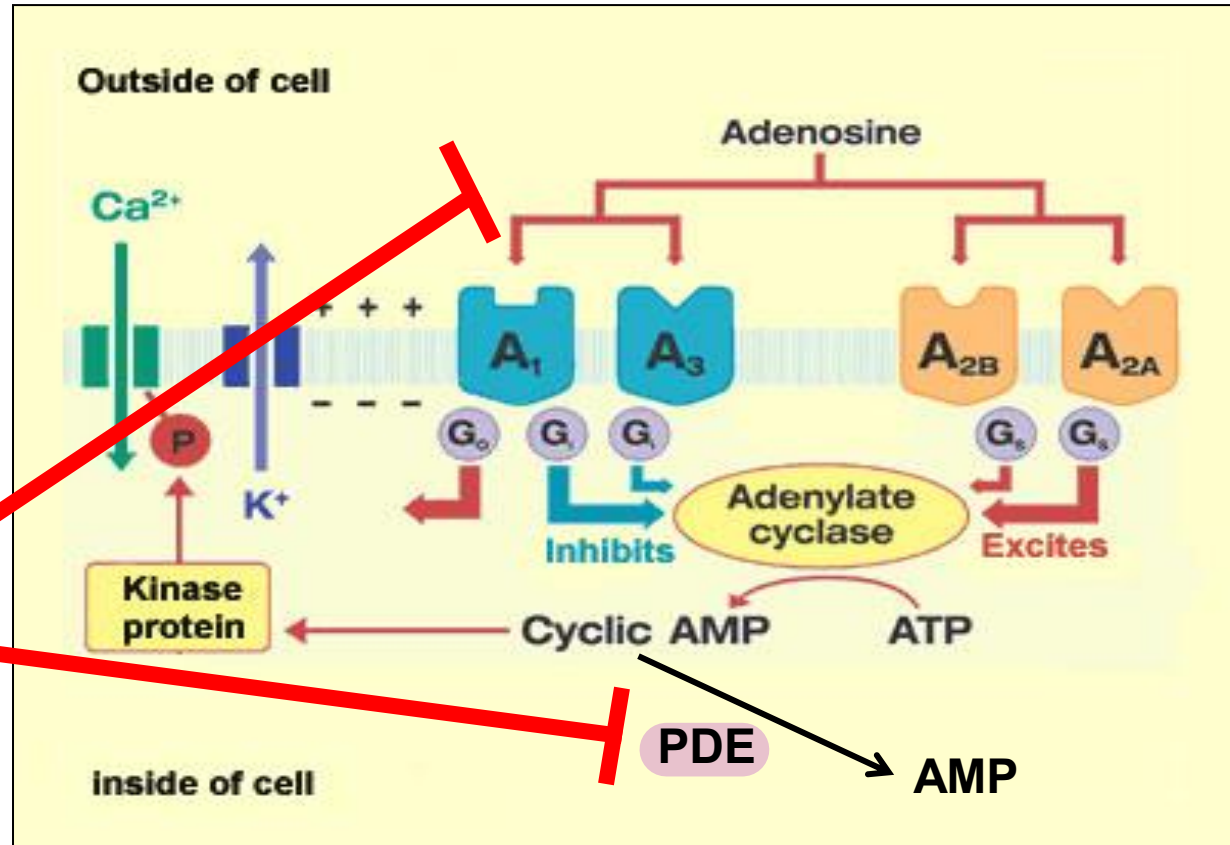
- No stereotyped behavior or psychosis even in large doses
- Act by inhibition of adenosine receptors and PDE.



Methylxanthines

Inhibits inhibitory receptors » excitation

Caffeine



PDE = Phosphodiesterase

Methylxanthines

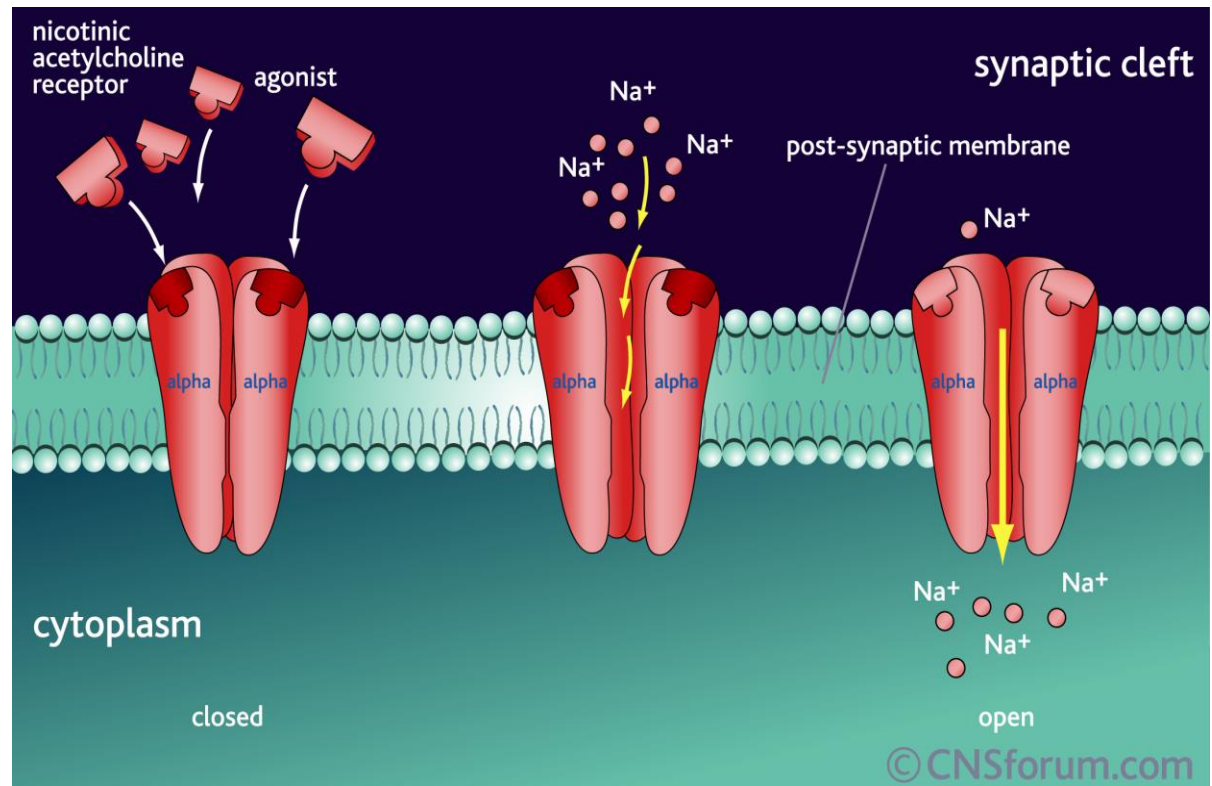
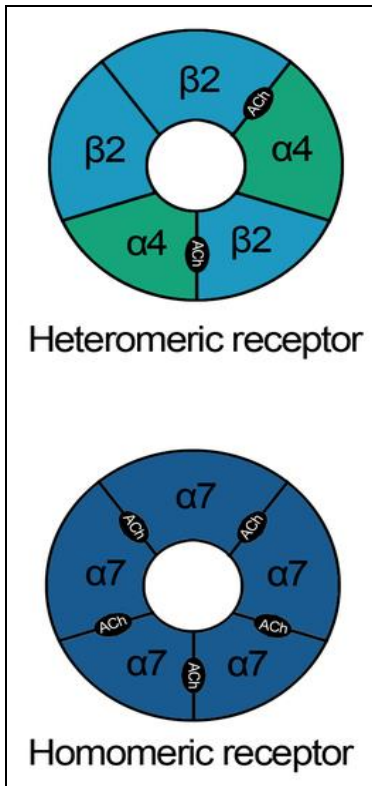
- CNS:
 - Low dose:
 - High dose:
 - Tremor, anxiety insomnia, nervousness, cardiac stimulation and arrhythmia.
 - Withdrawal:
 - Lethargy, fatigue, and headache.

Nicotine

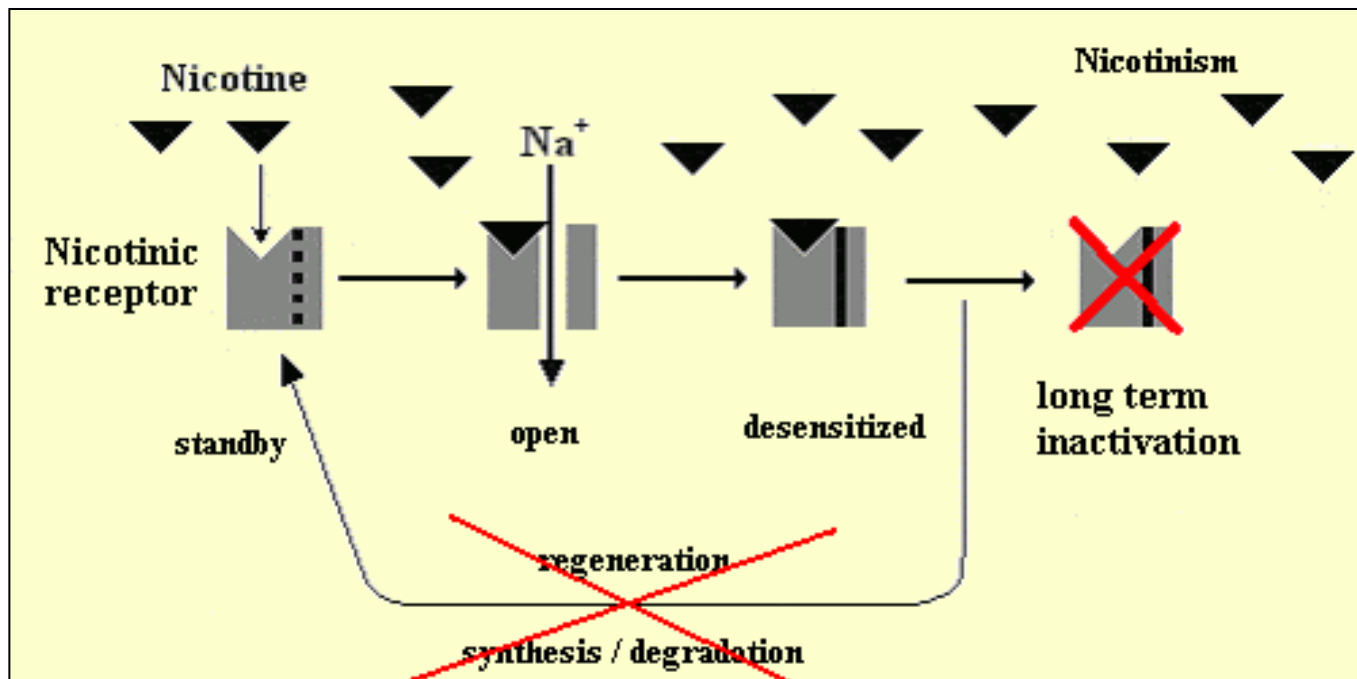
- Is the active ingredient of tobacco.
- Second only to caffeine as the most widely used CNS stimulant.
- Second only to alcohol as the most abused substance. (in US)
- Low doses stimulate and high doses block the ganglia.
 - Why?

ال target تا ع ال nicotine هو ال nicotinic receptors الموجودين بال ganglia, brain, neuromuscular junction
عشان هيك بزبطش تكون تدخن و تلعب رياضة لانه في خاصية بهاد ال receptor اسمها ال desensitisation

Nicotinic Receptors



Nicotinic Receptors (Desensitization)



بفترة النوم بس يصير washing out and metabolism لل nicotine راح
يخف ال desensitisation و الصبح اول ما يصحى بصير بده يدخن

Nicotine

- Is the active ingredient of tobacco.
- Second only to caffeine as the most widely used CNS stimulant.
- Second only to alcohol as the most abused substance. (in US)
- Low doses stimulate and high doses block the ganglia.

– Why?

ال acetylcholine بحفز ال contraction بالعضلات هو الي بكبر العضلات ف اذا
انفرز ال acetylcholine و ال receptor desensitised راح يكون ال contraction قليل

- Q: What is the difference between nicotine and Acetylcholine?

Effects of nicotine

- Low dose:
 - Euphoria, arousal, relaxation, and improvement of attention, learning, problem solving and reaction time, anxiolytic.
- High doses:
 - Respiratory depression and severe hypotension.

Nicotine

- Nicotine is an appetite suppressant .
- Physical and psychological dependence.
- Withdrawal:
 - Irritability, anxiety, restlessness.
 - Headache and difficulty in concentration
 - Insomnia, weight gain (?).
- Withdrawal symptoms could be relieved by: ↘
 - Transdermal patches
 - Chewing gum
 - Varenicline: Partial agonist. ??
 - Bupropion:?

بختلف شو تختار حسب الشخص
هل هو fast or slow metabolizer

يعني يرتبط بال receptor بس ما بعمل full activation ف يقلل ال
desensitisation و بنفس الوقت ما بنتج عنه withdrawal symptoms

Cocaine

- Chewing, intranasal snorting, smoking IV.
- Acts by inhibition of catecholamines uptake especially dopamine.

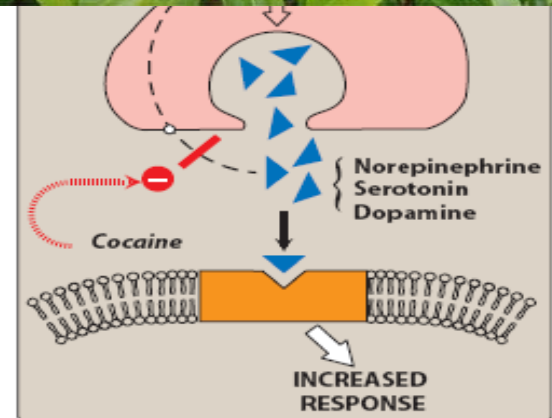
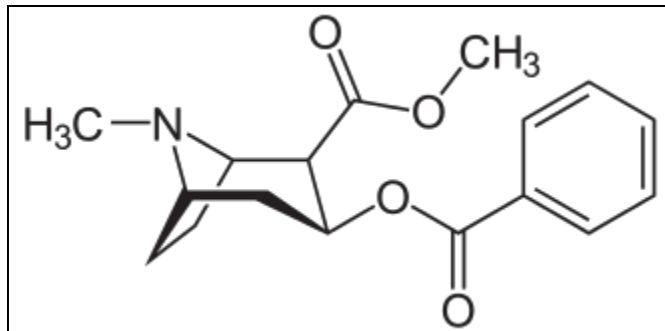


Figure 10.6
Mechanism of action of cocaine.

Cocaine

- Produces euphoria, self-confidence, mental alertness for short period.
 - Produces tolerance, physical and psychological dependence.
- Overdose:
 - death from arrhythmia, seizures, respiratory depression
 - severe hypertensive episodes which can lead to MI and strokes, and hyperthermia.

Cocaine

highly abused and يصف انه
addictive و لكن الة استخدامات طبية

- Therapeutic use:
 - Local anesthesia (esp. ENT and eye)
 - Vasoconstrictive effect
- Pharmacokinetics:
 - Fast onset of action (susceptibility of overdose)
- Withdrawal:
 - Depression of mood (anhedonia)
 - Apathy, irritability.

Schedule 2

مشهد من فيلم بحكي عن طيار بكون مدمن كحول و لما بده يصحى عشان طيارته بياخد كوكاين

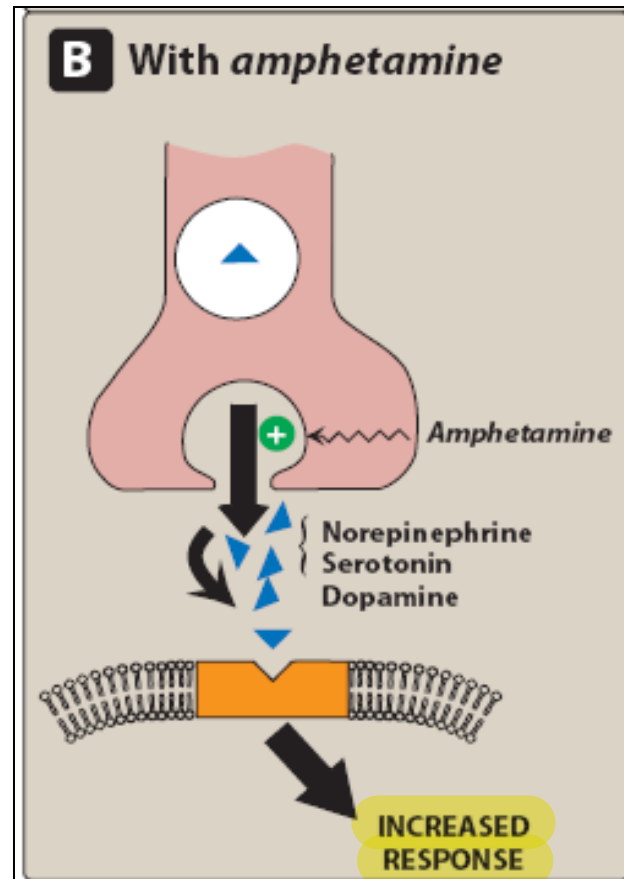
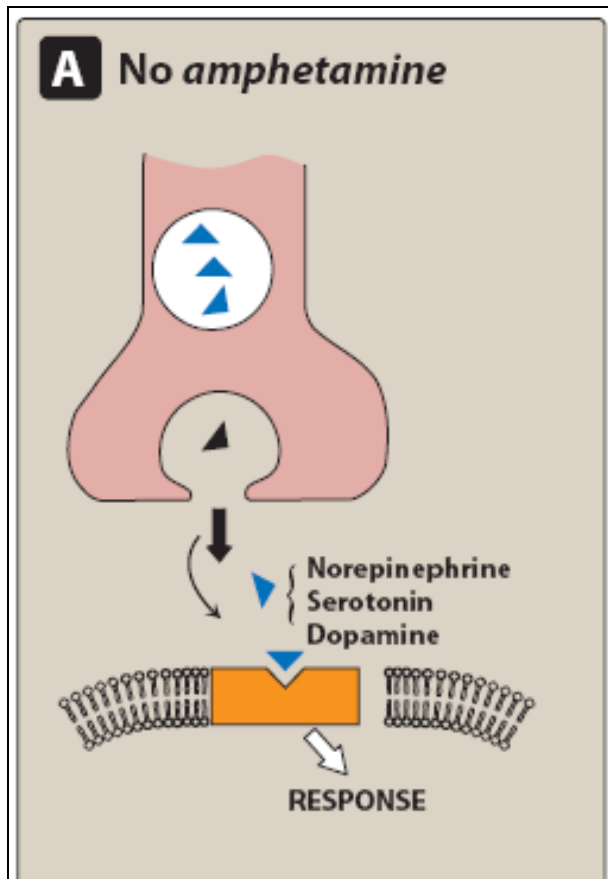


Flight

Amphetamines

- D-amphetamine, methamphetamine and methylphenidate.
- Main effects:
 - Similar to cocaine
 - Increase motor activity
 - Euphoria and excitement
 - Anorexia
 - Stereotyped and psychotic behavior – after prolonged use.
- The effects are mainly due to release of NE & Dopamine.

Amphetamine (MOA)



Amphetamines

- Therapeutic uses:

- ADHD

- Narcolepsy

Sudden sleep

في بروتين اسمه snare خدول بكونوا موجودين على ال
membrane و هاد الي بهاجمه البوتوكس و بعمله inhibitione

- Longer effect than Cocaine

- Tolerance to the stimulant effect develops rapidly.



CNS Hallucinogens

- Psychotomimetic Drugs
- Produce profound changes in thought patterns and mood
 - Delusion; illusion; hallucination
- Examples:
 - LSD يُصنّف انه highly abused and addictive و ما اله استخدامات طبية | schedule 1
 - MDMA (Ecstasy)

Hallucinogens

- Affect thoughts, perceptions and mood with no marked psychomotor stimulation or depression.
- Mood change is very complex “not euphoria nor depression”.
- They do not produce dependence.

Hallucinogens

- Mechanism of actions:
 1. Interfere with 5-HT (serotonin):
 - a. 5-HT₂ agonists as LSD
 - b. 5-HT uptake inhibitors as: Methylene DioxyMethAmphetamine(MDMA).
 2. Antagonist at NMDA receptors
 - Glutamate receptors
 - Phencyclidine
 3. Activate cannabinoid receptors
 - Marijuana

LSD

Lysergic acid diethylamide



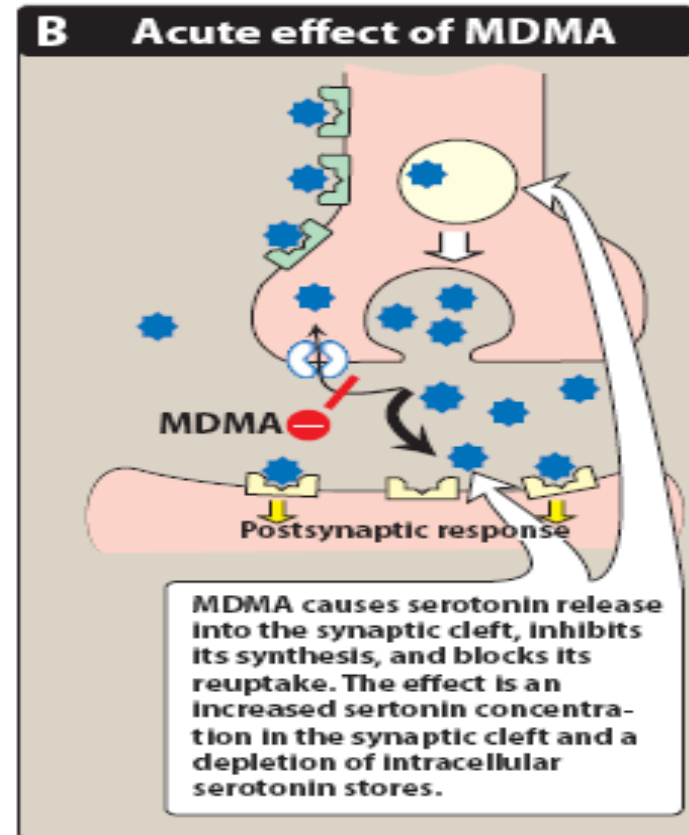
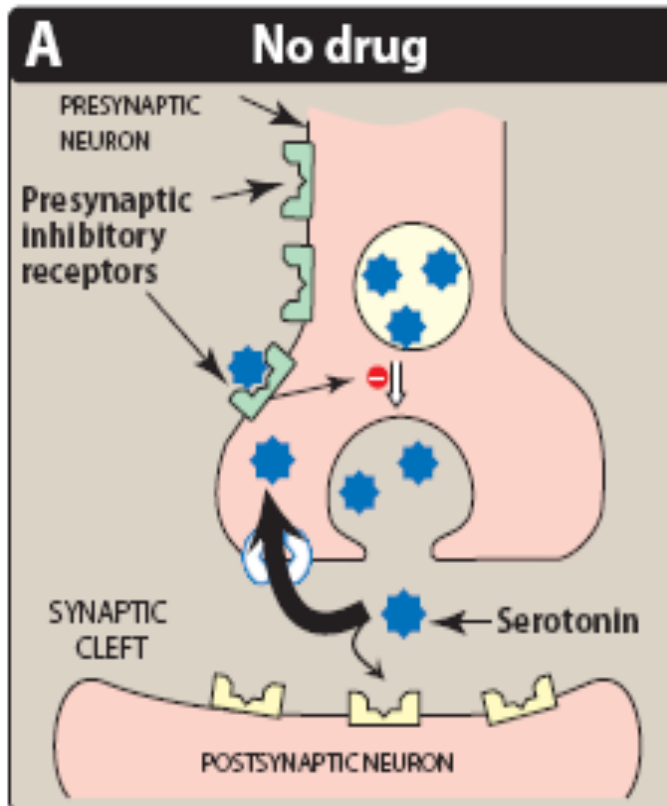
LSD

- 5-HT₂ Receptor agonist.
- Potent and long duration of action (5-12 hrs)
- Effects:
 - Hallucination with brilliant color
 - Alteration of mood
 - Sympathomimetic:
- High doses may produce psychotic changes

MDMA(ecstasy)

- Methylendioxyamphetamin
- Widely used as “party drug”.
- Has severe long term psychotic effect.
- Effects:
 - Sympathomimetic
 - Sense of well-being, euphoria, empathy.
 - Serotonin syndrome
 - Teeth and jaw grinding

MDMA (MOA)



Marijuana



Marijuana

- Hashish or Cannabis sativa.
- The active ingredient is THC (Tetrahydrocannabinol)
- Effects:
 - Produce euphoria?
 - Disinhibition
 - Uncontrollable laughing
 - Enhance appetite Medical application
 - Change in time perception
- Alcohol potentiates these effects.
- Uses:
 - Agonist: Antiemetic; appetite enhancer.
 - Antagonist: Obesity

Marijuana (MOA)

يصنع postsynaptically بعدين برجع على
CV1 or CV2 receptors و يرتبط ب
synapses و يعمل
presynaptically و بعمل
inhibition to the
release of neurotransmitter

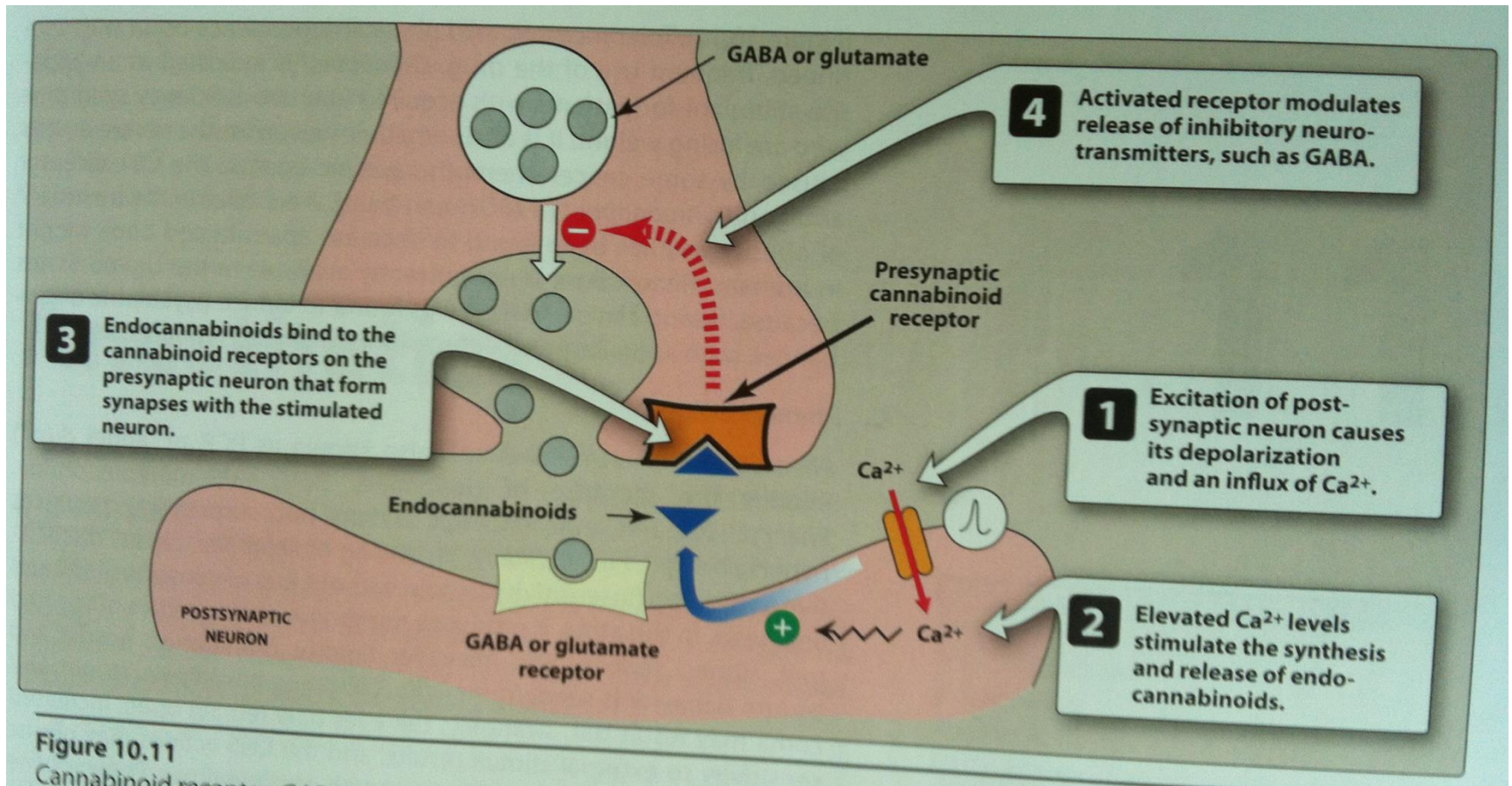


Figure 10.11

Cannabinoid receptor

Others?

- Captagon?



- Joker?



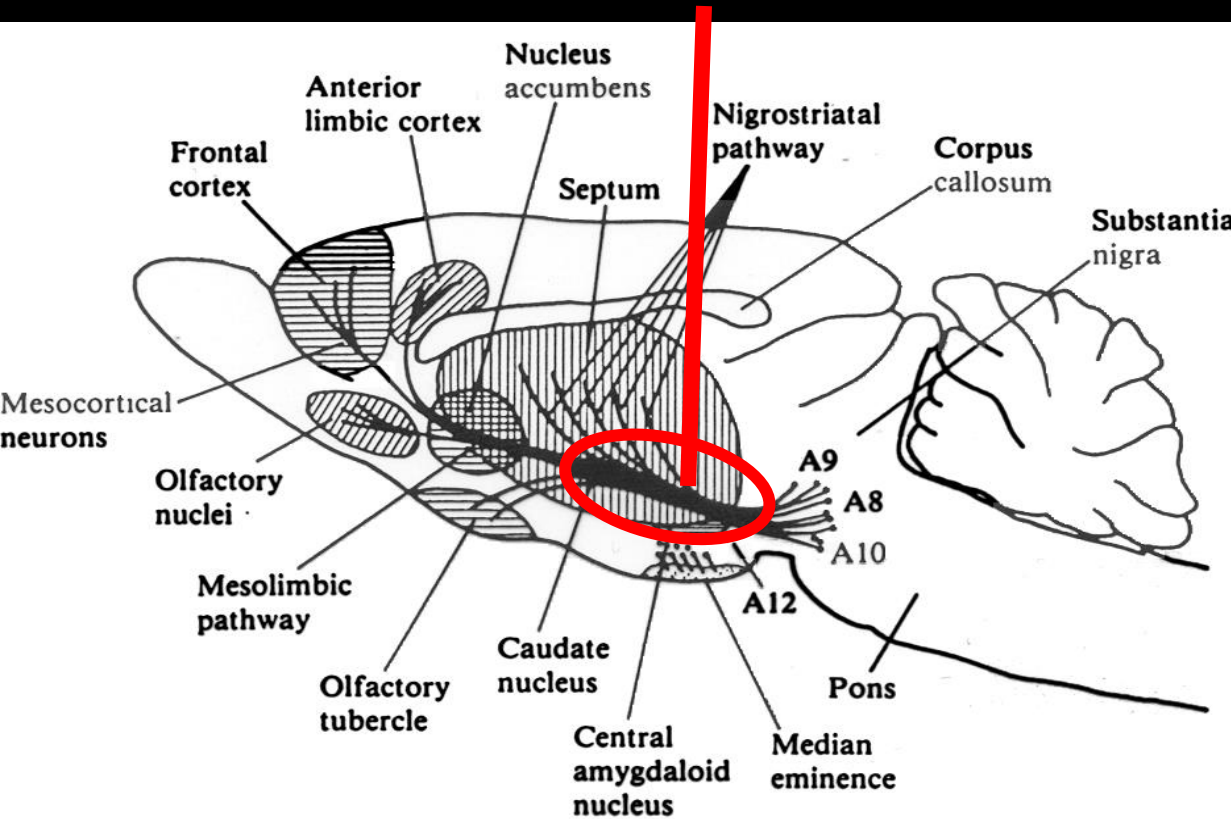
Videos

- Mouse party
 - <http://learn.genetics.utah.edu/content/addiction/mouse/>
- Spiders on drugs
 - <http://www.youtube.com/watch?v=sHzdsFiBbFc>
- Drugs and driving
 - <https://www.youtube.com/watch?v=bWLksTAnuFE>

Thank you



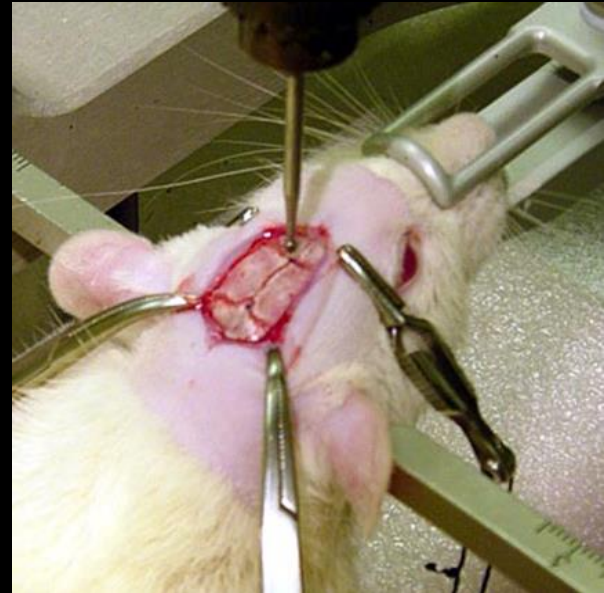
Mesolimbic pathway contains dopaminergic neurons



- Electrode implanted in the Medial Forebrain Bundle.(MFB)

Electrode Implantation

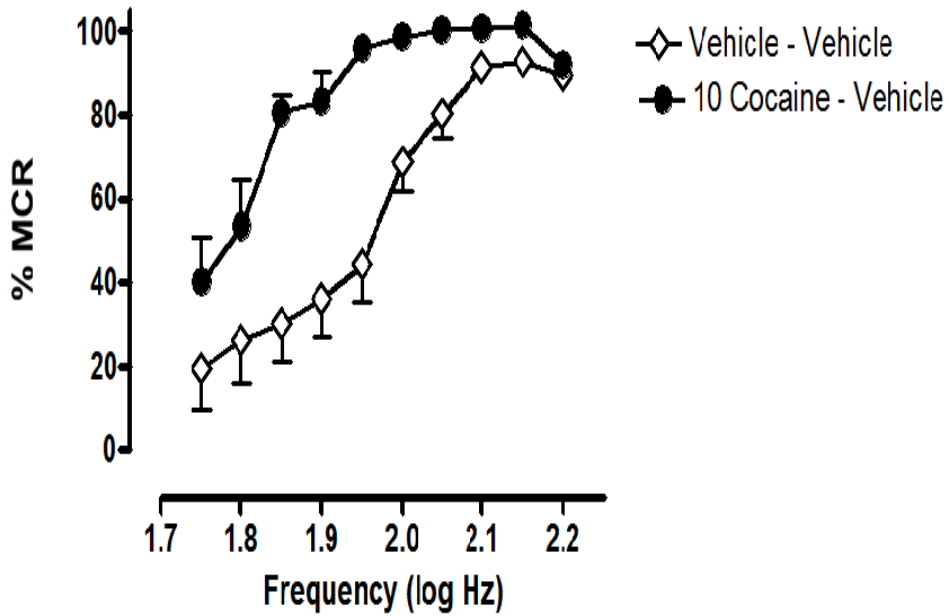
- Electrode implanted in the MFB
- Using the stereotax
- Coordinates:
 - M/L : 1.7 mm from Bregma
 - R/C: 2.8 mm from Bregma
 - D/V: 8.8 mm from Skull surface
- ICSS training



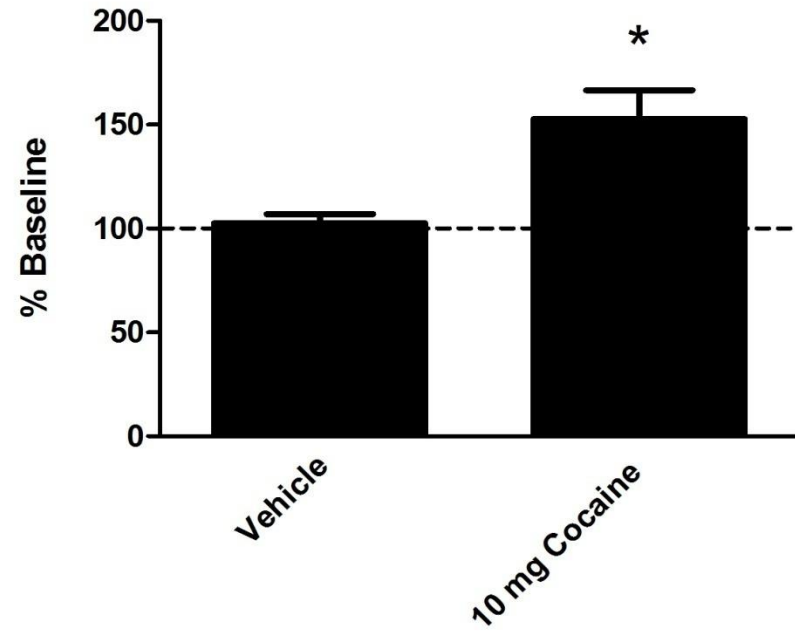


Cocaine

Cocaine and Vehicle Effects

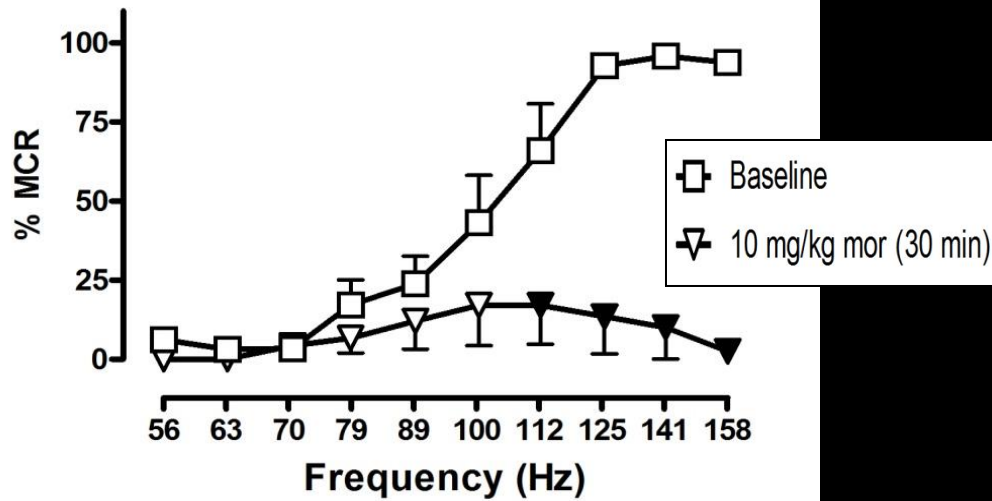


Total reinforcers



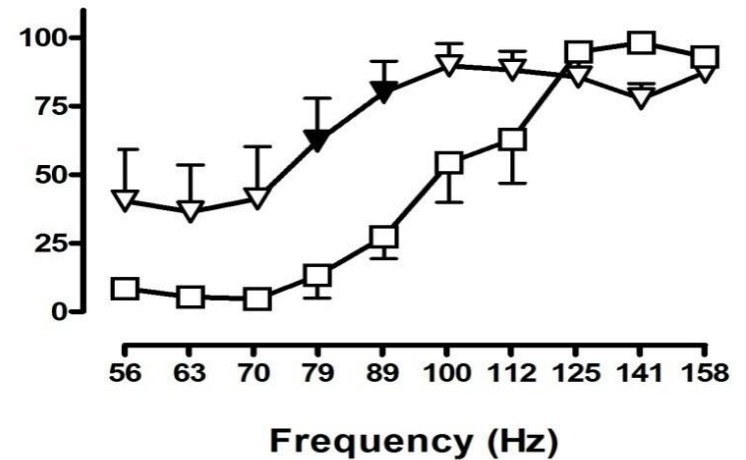
Morphine

Acute



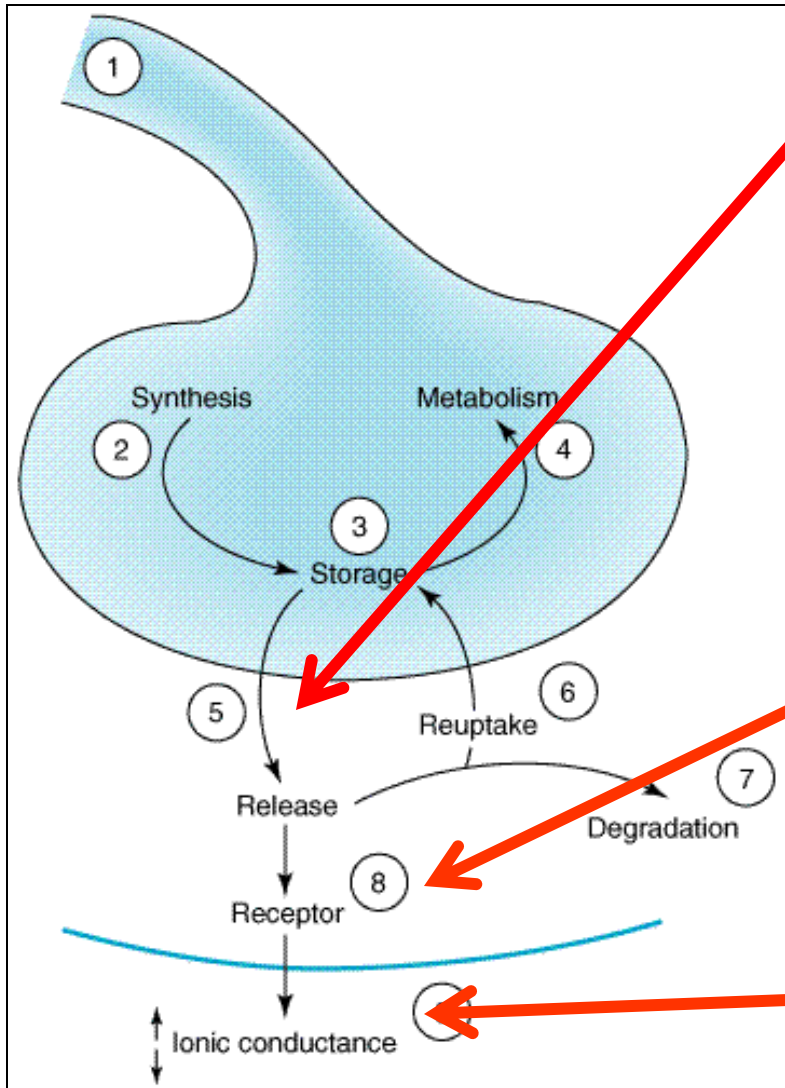
Filled points: $p < 0.05$
 $n = 6$

Chronic



Filled points: $p < 0.05$
 $n = 5$

Excitatory Neurons



1) Enhance Neurotransmitter release:

- Amphetamine

2) Inhibit Neurotransmitter Uptake:

- Cocaine

3) Activate postsynaptic receptors

- Nicotine

4) Interfere with 2nd messenger

- Caffeine