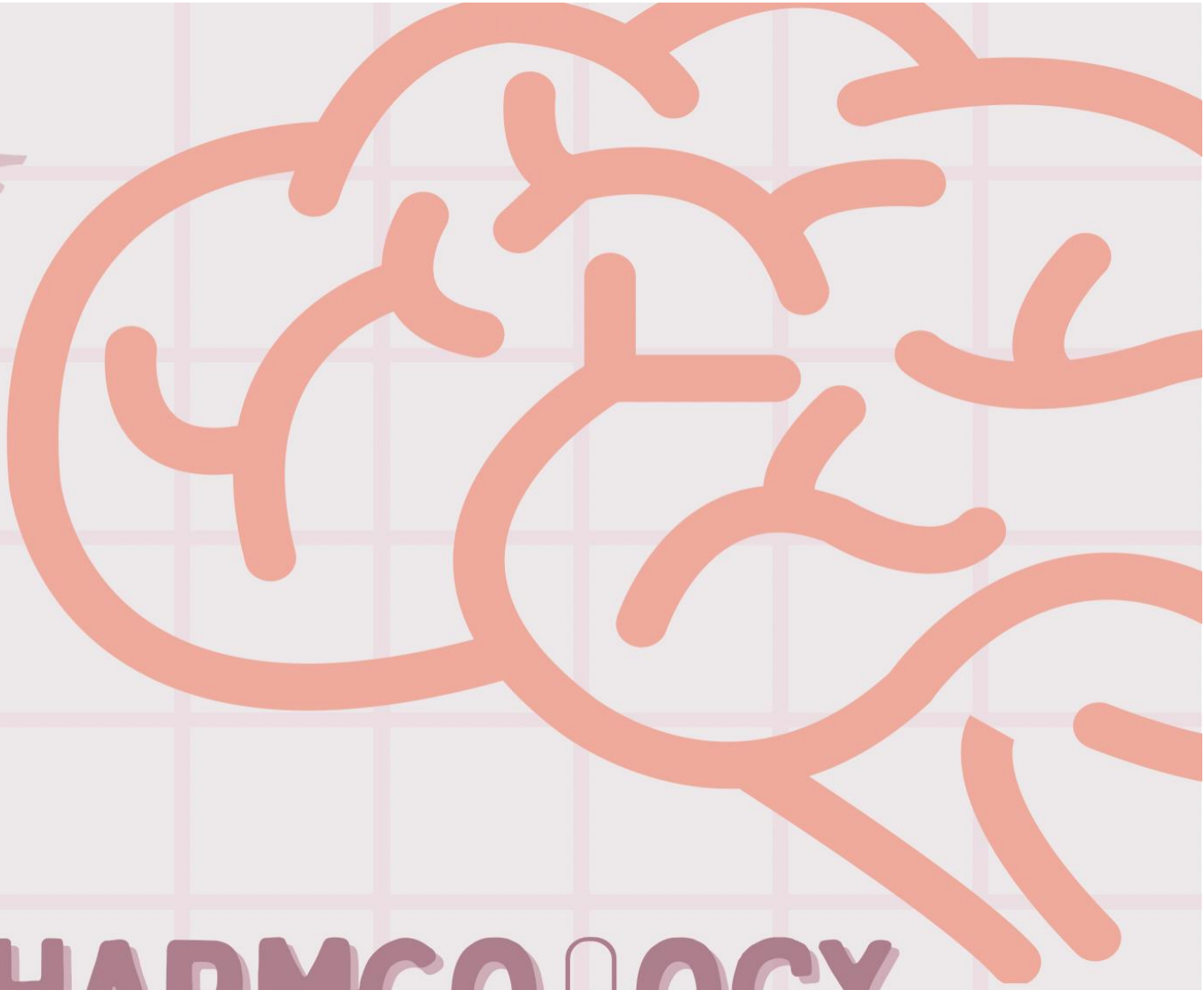


PHARMCOLOGY

SHEET NO. 13 (last lecture)

WRITER : Ola Alahdab

CORRECTOR :

DOCTOR : Yaqoub Irshaid

بسم الله.. توكلنا على الله.. المحاضرة الأخيرة ♡

*كالعادة.. كلام الدكتور بالبنفسجي الفاتح

Drugs of Abuse:

• Drugs are abused when they are **used in ways that are not medically approved**.
• Usually because they produce a strong feeling of **euphoria**, or alter perception.
• Repetitive exposure induces widespread adaptive changes in the brain.
• As a consequence drug use **may become compulsive** إجباري (**the hallmark of addiction**).
• Once the abused drug is no longer available, **signs of withdrawal** become apparent, which defines **dependence**. signs of withdrawal + abstinence = dependence.
• Dependence is **not always a correlate of drug abuse**.
• It can also occur with many classes of nonpsychoactive drugs such as vasoconstrictors, bronchodilators, and organic nitrates.
• As a general rule, all addictive drugs **activate the mesolimbic dopamine** system ➡️ **increase in dopamine** (not 100% true, cause not all details are known).
• **Mesolimbic dopamine codes for the difference between expected & actual reward,** & thus, constitutes a **strong learning signal**.

Addiction:

• Is a **disease of maladaptive learning**.
• Characterized by a **high motivation** to obtain & use a drug **despite** negative consequences.
• With time, drug use becomes **compulsive** "**wanting without liking**".
• Addicted individuals are at high risk of **relapsing**.
- **Relapse is typically triggered by one of the following 3 conditions:**
A. **Re-exposure** to the drug of abuse.
B. **Stress**.
C. A context that **recalls** prior drug use. for ex, if his friends رفقاء السوء or a certain place was related to taking these drugs, once the pt sees that place or those friends, he remebers taking the drug, and he develop symptoms!
• **Large individual differences** exist in vulnerability to addiction.
• Whereas one person may become “addict" after a few doses, others may be able to use a drug occasionally during their entire lives without ever having difficulty in stopping.
• Even when dependence is induced with chronic exposure, only a fraction of dependent users will go on to become addicted.

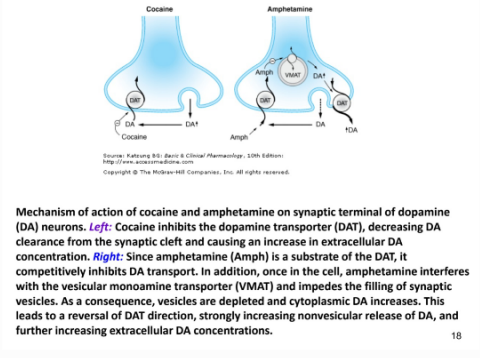
Cocaine:

• The prevalence of cocaine abuse is high & is a major public health problem worldwide.
• Cocaine is **highly addictive**, and its use is associated with a number of **complications**.
• It can be used by injection or inhalation.
• In the *peripheral nervous system*, cocaine **inhibits voltage-gated Na channels**, thus blocking initiation & conduction of action potentials (but this is not the cause its of addictive effects).
• This action is **NOT** responsible for the acute rewarding or the addictive effects.
• In the *central nervous system*, cocaine **blocks the uptake of dopamine, norepinephrine, & serotonin** through their respective transporters.
• The block of the dopamine transporter (DAT), & increasing dopamine concentrations in the

nucleus accumbens, has been implicated in the rewarding effects of cocaine. (So the cause of its addiction is the effect on dopamine transporter).
• Block of the norepinephrine transporter (NET) leads to an **acute increase in arterial pressure, tachycardia, and often, ventricular arrhythmias**.
• Cocaine exposure **increases the risk for intracranial hemorrhage, ischemic stroke, myocardial infarction, & generalized or partial seizures**.
• Subjects typically **loose appetite, are hyperactive, & sleep little**.
• Cocaine overdose may lead to **hyperthermia, coma, & death**.
• Susceptible individuals may become dependent & addicted after only a few exposures to cocaine.
• Although a withdrawal syndrome is reported, it is not as strong. The opposite to opioids and sedative-hepnotics drugs, remember? NO? it's okay :")
• **Tolerance may develop**, but in some users **a reverse tolerance is observed**; that is, **they become sensitized to small doses of cocaine**.
• This behavioral sensitization is, in part, context-dependent. لما يشم ريحة الدوا أو يشوف رفاق السوء بصير عنده الأعراض
• **Cravings are very strong & underline the very high addiction liability of cocaine**.
• To date, no specific antagonist is available.

Amphetamines:

• Amphetamines are a group of synthetic, indirect-acting sympathomimetic drugs that **cause the release of endogenous biogenic amines, such as dopamine, serotonin and norepinephrine**.
• **Amphetamine, methamphetamine** (methyl amphetamine), and their derivatives **reverse the action** of biogenic amine **transporters** at the plasma membrane.



Mechanism of action of cocaine and amphetamine on synaptic terminal of dopamine (DA) neurons. *Left:* Cocaine inhibits the dopamine transporter (DAT), decreasing DA clearance from the synaptic cleft and causing an increase in extracellular DA concentration. *Right:* Since amphetamine (Amph) is a substrate of the DAT, it competitively inhibits DA transport. In addition, once in the cell, amphetamine interferes with the vesicular monoamine transporter (VMAT) and impedes the filling of synaptic vesicles. As a consequence, vesicles are depleted and cytoplasmic DA increases. This leads to a reversal of DAT direction, strongly increasing nonvesicular release of DA, and further increasing extracellular DA concentrations.
18

*Look at the figure, the normal action of transporters is the reuptake of the NTs into the cytoplasm of the original neuron, so then it is reuptaken (entering) into the vesicle, in case of amphetamines, reversing its effects means that no reuptaking into the vesicles, so NTs (including dopamine) remain in the cytoplasm of the neuron, & exist through non-vesicular way, increasing dopamine extracllularly.
• Amphetamines are substrates of these transporters and are taken up into the cell.
• Once in the cell, amphetamines interfere with the vesicular monoamine transporter (VMAT), **depleting synaptic vesicles of their neurotransmitter content**.
• As a consequence, levels of dopamine (or other transmitter amine) in the cytoplasm increase & quickly become sufficient to cause release into the synapse **by reversal of the plasma membrane DAT**.
• Normal vesicular release of dopamine consequently decreases, while nonvesicular release increases.
• In general, amphetamines lead to elevated catecholamine levels that **increase arousal & reduce sleep**, while the effects on the dopamine system **mediate euphoria** but may also cause **abnormal movements** & precipitate **psychotic episodes**.
• Effects on serotonin transmission may play a role in the **hallucinogenic & anorexigenic**

functions as well as in the hyperthermia often caused by amphetamines.

• Unlike many other abused drugs, amphetamines are neurotoxic. The exact mechanism is not known, but neurotoxicity depends on the NMDA receptors & affects mainly serotonin & dopamine neurons.

• Can be taken by abusers orally or smooked, & ultimately by intravenous administration.

• Within hours after oral ingestion, they increase alertness, & cause euphoria, agitation, & confusion.

• Bruxism (tooth grinding بطحن بأسنانه) & skin flushing may occur.

• With increasing dosage these agents often lead to tachycardia & dysrhythmias.

• Hypertensive crisis & vasoconstriction may lead to stroke.

• Spread of HIV & viral hepatitis infection has been associated with needle sharing by IV users of methamphetamine (this is applied to all drugs of abuse).

• With chronic use, tolerance may develop, leading to dose escalation تصعيد.

• Withdrawal consists of dysphoria, drowsiness, insomnia, & general irritability.

Ecstasy (MDMA): (a group of drugs)

• Ecstasy is the name of a class of drugs that includes a large variety of derivatives of the amphetamine-related compound methylenedioxymethamphetamine (MDMA).

• The main effect of ecstasy appears to be fostering تعزيز feelings of intimacy ألفة & empathy تعاطف without impairing intellectual capacities.

• MDMA causes release of biogenic amines by reversing the action of their transporters.

• It has a preferential affinity for the serotonin transporter (SERT), & therefore, increases the extracellular concentration of serotonin.

• This release is so profound that there is a marked intracellular depletion for 24 hours after a single dose.

• With repetitive administration, serotonin depletion may become permanent.

• Several studies report long-term cognitive impairment in heavy users of MDMA.

• MDMA has several acute toxic effects, in particular hyperthermia, which along with dehydration, may be fatal.

• Other complications include serotonin syndrome (mental status change, autonomic hyperactivity, & neuromuscular abnormalities, & seizures).

• Following warnings about the dangers of MDMA, some users have attempted to compensate for hyperthermia by drinking excessive amounts of water, causing water intoxication involving severe hyponatremia, seizures, & even death.

• Withdrawal is marked by a mood "offset" characterized by depression lasting up to several weeks.

• There have also been reports of increased aggression عدوانية during periods of abstinence in chronic MDMA users.

• The evidence for irreversible damage to the brain, implies that even occasional recreational use of MDMA cannot be considered safe.

Cannabinoids: القنّب أو الحشيش أو الماريوانا

1- *Endogenous cannabinoids* that act as neurotransmitters: **2-arachidonyl glycerol (2-AG) & anandamide**, both of which bind to **CB1** receptors.

• These **very lipid-soluble** compounds are **released at the postsynaptic somatodendritic membrane** (they are not released from the cell they affect).

• **Then they diffuse through the extracellular space** to **bind at presynaptic CB1 receptors**, where they **inhibit the release of either glutamate or GABA**.

• Because of such **backward signaling**, endocannabinoids are called **retrograde messengers**.

2- *Exogenous cannabinoids* (**in marijuana or cannabis** الحشيش), comprise several pharmacologically active substances including: **Δ9-tetrahydrocannabinol** (THC), **a powerful psychoactive substance**.

• THC **causes disinhibition of dopamine neurons**, mainly **by presynaptic inhibition of GABA neurons in the ventral tegmental area** (VTA).

*GABA normally inhibits the release of dopamine, when these drugs inhibit GABA, they activate dopamine release.

• The half-life of THC is about 4 hours.

• The onset of effects of THC after **smoking marijuana** occurs within minutes and reaches a maximum after 1–2 hours.

• The most prominent effects are **euphoria & relaxation**.

• Users also report feelings of **well-being, grandiosity, & altered perception of passage of time**. ما بيهتموا بالوقت

• **Dose-dependent perceptual changes (visual distortions), drowsiness, diminished coordination, and memory impairment** may occur.

• Cannabinoids can also create a **dysphoric state** & in rare cases, following the use of very high doses, may result in **visual hallucinations, depersonalization** (a state in which one no longer **perceives** the reality of one's **self** or one's **environment** بطلع من جسده), & **frank psychotic episodes**.

• Additional effects of THC include (the therapeutic uses of cannabinoids): **increased appetite, attenuation of nausea, decreased intraocular pressure, and relief of chronic pain, have led to the use of cannabinoids in medical therapeutics**.

• Chronic exposure to marijuana leads to **dependence**.

• **withdrawal syndrome (distinctive, but mild and short-lived): Restlessness, irritability, mild agitation, insomnia, nausea, and cramping**.

• Synthetic agents include Δ9-THC analogs **dronabinol & nabilone**. [Used in therapeutics].

Nonaddictive Drugs of Abuse:

• Some drugs of abuse do not lead to addiction.
• This occurs with substances that **alter perception without causing sensations of reward and euphoria**, such as the **hallucinogens & the dissociative anesthetics** (like ketamine).
• These agents **primarily target cortical & thalamic circuits**, unlike addictive drugs which **primarily target the mesolimbic dopamine system**.

LSD, Mescaline, & Psilocybin:

• They are commonly called **hallucinogens** because of their ability to **alter perceptions** such that the individual **senses things that are not present**.
• They induce perceptual symptoms, including **shape & color distortion.**
• Subjects have **impaired ability to make rational judgments** & **understand common dangers** مثلا يقطع الشارع بغض النظر عن وجود سيارات, which puts them at risk of accidents & personal injury.
• Psychosis-like manifestations (depersonalization, hallucinations, distorted time perception) have led some to classify these drugs as **psychotomimetics**.
• They also produce somatic symptoms (dizziness, nausea, paresthesias, & blurred vision).
• Some users have reported intense re-experiencing of perceptual effects (**flashbacks**) وجود أعراض التعاطي بدون تعاطي في فترة معينة كل سنة مثلا up to several years after the last drug exposure.
• They induce **neither dependence nor addiction**.
• However repetitive exposure still leads to rapid tolerance.
• These drugs also **fail to stimulate dopamine release**, further supporting the idea that only drugs that activate the mesolimbic dopamine system are addictive.
• Instead, **hallucinogens increase glutamate release** in the cortex.
• The molecular target of hallucinogens is the **5-HT2A** receptor.

Phencyclidine (PCP) & Ketamine:

• Ketamine & PCP were developed as general anesthetics.
• They produce **use-dependent, noncompetitive antagonism of NMDA glutamate receptor**.
• Sold as a liquids, capsules, or pills, which can be snorted, ingested, injected, or smoked.
• Psychedelic effects last for about 1 hour and also include **increased blood pressure, impaired memory function, & visual alterations**.
• At high doses **unpleasant out-of-body & near-death experiences** have been reported.
• Although ketamine and phencyclidine do not cause dependence and addiction, chronic exposure, particularly to PCP, may lead to **longl-asting psychosis** closely resembling schizophrenia, which may persist beyond drug exposure.

"إذا أدارَ الله سفينتك لليمين فتأذيتَ وتألمت، فاعلم أنَّ اليسارَ كان موتكَ المُحتّم.. ثق بتدبير الله دائماً"
- محمد متولي الشعراوي

وآخرُ دعوانا أنِ الحمدُ لله ربِّ العالمين ♡..
١٦ رمضان ١٤٤٣ هـ