Drug addiction, abuse and adverse drug reactions

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Drug addiction

- Drug addiction is a chronic disease which causes long lasting permanent neurobiological changes.
- Vulnerable changes are found even after years of abstinence.
- Long term drug use can cause physiological as well as behavioural changes.

Drug tolerance: Need for increasing dose of a drug to achieve the same effect.

Sensitization: Enhancement of drug response by repeated drug exposure.

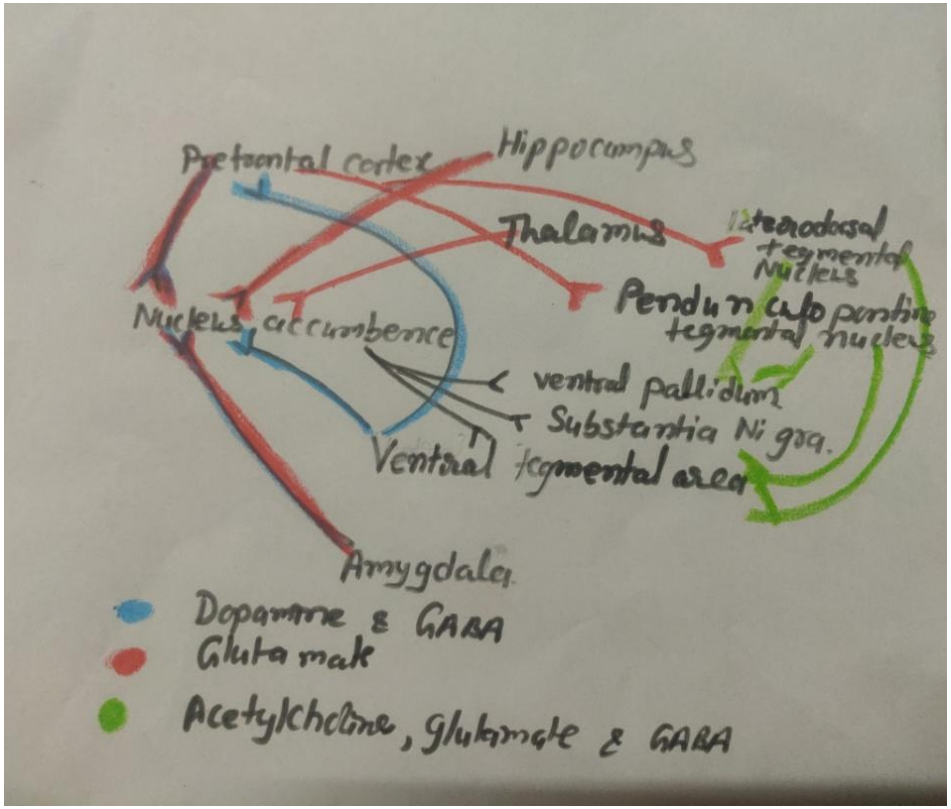
Dependence: It is an adapted physiological state that develops to compensate for excessive stimulation by a drug. When drug intake stops, withdrawal syndrome appeared. During withdrawal negative emotional state of anxiety and irritability motivate the drug seeking behaviour.

- Drug addiction leads to poor decision making and impulsivity.

Neuronal circuitry of drug addiction

Mesocorticolimbic dopamine system

Drugs cause reinforcing effect and reinforcing action of most addictive drugs appear in the mesocorticolimbic dopamine system.



- The ventral tegmental area (VTA) innervates nucleace accumbence (NA) and prefrontal cortex (PFC)
- Nucleus accumbens receives inputs from PFC, amygdala, hippocampus and thalamus
- NA integrates information and transmit it to ventral pallidum, VTA and substentia nigra (SN).
- The PFC sends glutamate projections to NA, VTA, SN, pedunculopontine tegmental nucleus (PPT) and laterodorsal tegmental nucleus (LTD).
- The PPT and LDT send cholinergic, glutamate and GABA projections to VTA and SN.

Other neuronal circuit involvement in drug addiction

- **Drug craving**: Three types of stimuli involved in drug craving:

(1) Cues associated with prior drug use, eg. syringe, empty bottles of alcohol
(2) Re exposure of a mild dose of drug
(3) Exposure to stress

Basolateral amygdala is involved in first stimuli and stress induced reinforcement involves nor epinephrine system and corticotropin releasing factor (released by paraventricular nucleus of hypothalamus).

- In habituation, dorsal striatum and orbito-frontal cortex are involved.

Major drug classes and their receptors

1. Opiates

   Morphine; Target: μ opioid receptor

2. Psycostimulants

   Cocaine; Target: monoamine transporter

3. Cannabinoids (Marijauna)

   Δ^9Tetra hydro canabinol; Target: Cannabinoid CB1 receptor

4. Nicotine; Target: Nicotinic acetylcholine receptor

5. Alcohol

   Ethanol; Target: ligand gated and voltage gated ion channels

6. Hallucinogens

   Lysergic acid diethylamine; Target: Serotonin receptor

7. Dissociative drugs

   Phenylcyclidine; Target: NMDA receptor

Opiates

- Opium, extracted from poppy plants.
- Morphine is derived from opium and heroin is synthesised from morphine.
- Heroine was developed to treat cough in late 1800s.
- Naturally occurring endogenous opioid peptides are also present in body, which are enkephalins, endorphins, dynorphins and endomorphins.
- In VTA, opiates stimulate μ opioid receptor (MOP-Rs) on GABA neurons, that synapse on dopamine neurons and inhibits the GABA neurons. This enhanced dopamine release in nucleus accumbens.

Psychomotor stimulants

- Cocaine and amphetamine are psychomotor stimulants.
- Effect of psychomotor stimulants causes euphoria, talkativeness, increased activity and decreases the feeling of fatigue and hunger.
- High doses can produce stereotyped behaviour, convulsions, coma and even death.
- Transporters for dopamine (DAT), serotonin (SERT), and norepinephrine (NET) are the targets for psychomotor drugs.
- By interacting with DAT, SERT and NET, psychomotor drugs increase the level of extracellular monoamine neurotransmitters (dopamine, serotonin and epinephrine).

Cannabinoids

- Marijauna and hashish are extracted from Canabis sativa (hemp) Plant.
- Cannabinoids relax the mood by causing euphoric effect. Higher dose can cause anxiety, paranoia, increased appetite, declined problem solving ability, impaired learning and memory.
- Cannabinoid effects are mediated by cannabinoid receptor 1 (CB1), which are highly expressed in limbic system, cerebellum, basal ganglia and neocortex.
- By activation, CB1 receptors inhibit the release of glutamate and GABA neurotransmitters by inhibiting Ca ions.
- Cannabinoids increase the firing rate of VTA dopamine neurons and increase dopamine release in nucleus accumbens.
- Stimulation of CB1 receptors on GABA terminals at VTA, decrease the release of GABA and disinhibition of dopamine neurons and ultimately, cause the reinforcing effect of drug.

Nicotine

- Nicotine is extracted from the tobacco plant.
- Nicotine causes temporary feeling of relaxation as well as reducing stress, anxiety and pain.
- Most of the people, who want to quit smoking will relapse within a year due to its withdrawal syndrome.
- Withdrawal syndrome of nicotine includes craving for nicotine, anxiety, restlessness, irritation and increased appetite. Withdrawal syndrome can be treated by nicotine gum and patches, varenicline and bupropion.
- VTA is the targeted site for nicotine. Nicotine causes activation of dopamine transmission.
- Pedunculopontine tegmental nucleus and laterodorsal tegmental nucleus send cholinergic projections to VTA and play an important role in action of nicotine.

Ethanol

- At the beginning of alcohol consumption the dopamine release increases which creates a pleasurable sensation (euphoria) with minor impairment of reasoning and memory. High dose of alcohol cause depression, loss of consciousness, poor decision making, blurred vision, slurred speech and impaired motor responses, memory and self- control.
- Consuming large amount of alcohol in a short time period can cause acute alcohol poisoning which may results in severe respiratory depression and even death.
- Alcohol withdrawal syndrome causes sweating, tremor, hypertension, agitation, anxiety and seizures.
- Alcohol interacts with GABA, NMDA, glycine, nACh, 5-HT receptors and Ca ion and GIRKs channels.
- Alcohol abuse increases the firing rate of dopamine neurons of VTA. Endocannabinoid transmission also plays a key role in alcohol craving.
- After dependence of alcohol, its anxiolytic effects force to continue alcohol consumption and provide relief from negative emotional state due to alcohol withdrawal.

Hallucinogens

- Hallucinogenic compounds are being used from ancient times as a part of religious ritual as Psilocybe mushroom by Maya and peyote cactus by Aztec.
- In 1938 Hofmann chemically synthesized the lysergic acid diethylamide (LSD). After 5 years accidently some of LSD consumed by Hofmann. On the basis of his report on the effects of LSD, psychiatrists began to use this drug to treat mentally disturbed patients.
- LSD produces hallucinogenic effects, including dreamlike state, heightened awareness of sensory stimuli, mixing of perception as sound can evoke images and images can evoke smells.
- Due to the resemblance of LSD with serotonin, it acts on the serotonergic system.
- LSD causes activation of 5-HT 2 receptor signaling pathways.
- Frontal cortex and thalamus are potential targets for LSD. Modulation of glutamate in these regions may be responsible for impaired perception and cognition. In addition, LSD also affects the locus ceruleus which may contribute to enhancement of sensory experience.

Dissociative drugs

- Dissociative drug like phencyclidine (PCB) distorts perception and produces feeling of dissociation from reality.
- PCB causes social withdrawal, delusions, paranoia, hallucinations (mimics schizophrenia) and problems in thinking, memory and mood.
- By blocking NMDA type glutamate receptor, PCB can activate dopamine neurones.

References

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