

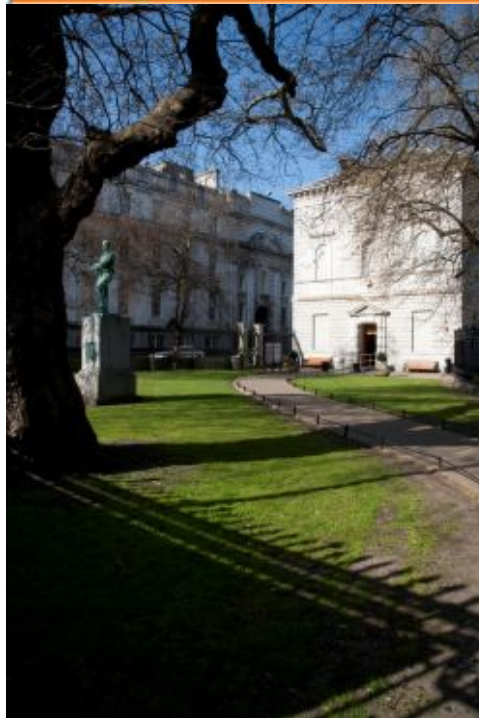
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Neurobiological aspects of addiction.

Brian E. Leonard, PhD,DSc,MRIA.
Emeritus Professor of Pharmacology,
National University of Ireland, Galway.

Overview of lecture.

- 1. Some definitions
- 2. Theories of addiction.
- 3. The addiction cycle: neurophysiological basis.
- 4. Why are some drugs “addictive”?
- 5. Brain changes in addiction.
- 6. Are there reliable markers of addiction?
- 7. Treatment possibilities.

Definitions-1.

- Drug abuse:
- Use of any drug in a manner which is at variance with the approved use in that culture.
- For example, khat (from *Catha edulis* leaves) is acceptable in Yemen but alcohol is forbidden. The converse is the case in Western Europe.

Definitions-2.

- Drug tolerance:-
- Metabolic tolerance-following chronic use the drug is more rapidly metabolised. Thus it must be given in a higher dose to obtain the same pharmacological effect (eg.sedatives).
- Tissue tolerance- the drug desensitises the receptors responsible for its pharmacological activity (eg.opiates).
- Psychological tolerance-reduction in the desired effect with time of chronic administration.

Definitions-3.

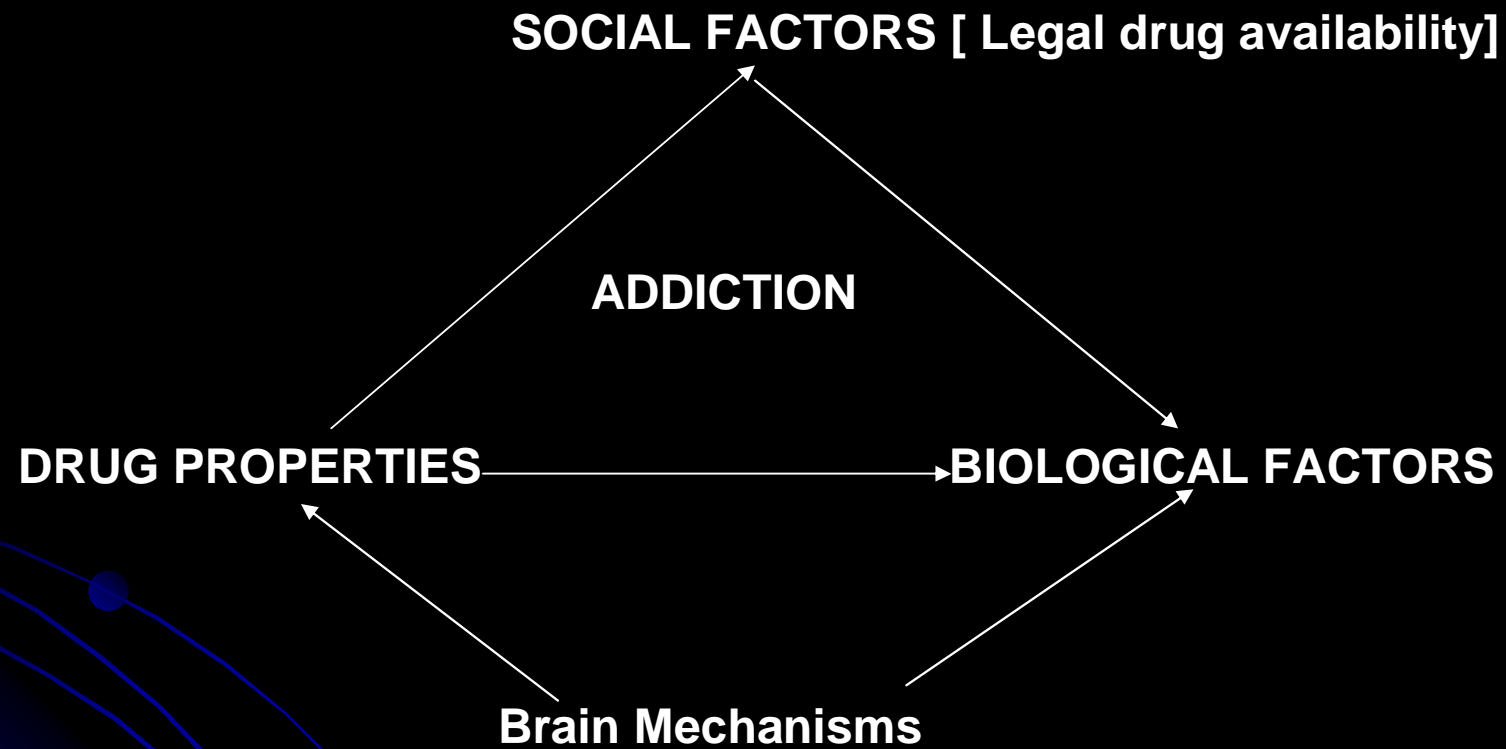
- Stimulants cause a psychological tolerance. Psychological tolerance may occur independently of tissue or metabolic tolerance.
- Physical dependence:-abnormal behavioural and autonomic symptoms occurring when the drug is abruptly withdrawn.
- The symptoms depend on the pharmacological properties of the drug (eg.stimulants associated with fatigue,hyperphagia,depression; opiates with shivering,tremor,nausea,joint pain,intestinal cramps etc.)



Definitions-4.

- Psychological dependence:-Usually associated with dysphoria and intense craving for the drug.
- Cross dependence:-One drug suppresses the withdrawal symptoms of another drug that has a similar mode of action (eg. Benzodiazepines and alcohol).
- Withdrawal syndrome:-occurs due to abrupt withdrawal of the drug from receptors, ion channels etc. Often associated with hyperarousal due to receptor adaptation following drug removal

THE ADDICTION TRIANGLE.



Theories of addiction.

- 1] Self medication to regulate mood or performance.
- 2] As an escape from adverse effects of drug withdrawal.
- 3] Sensitization effects of repeated drug exposure leading to addiction.
- 4] Pathological habit similar to OCD
- 5] Learning theory: choice of small, immediate rewards over a larger but delayed reward.
- ADDICTION=a chronic, relapsing brain disorder!

The addiction cycle.

- Stage 1: Binge/Intoxication.
- Stage 2: Withdrawal/ Negative affect.
- Stage 3: Preoccupation/Anticipation
[Craving].
- Stage 4: Addiction.
- See: “Brain science, addiction and drugs” edited
Gabriel Horn, Academy Medical Science,
London, 2008.

Neurophysiological basis of addiction cycle-1.

- Binge: Intoxication- the reinforcing effects of the drug activate the “reward” neurotransmitters dopamine and opioids associated with the nucleus accumbens followed by the stimulus –response pathways associated with the dorsal striatum

Neurophysiological basis-2.

- Withdrawal/Negative affect: Pathways involve the extended amygdala region in the basal forebrain with projections to the hypothalamus and brain stem.
- Main neurotransmitters involved are noradrenaline, corticotrophin releasing factor and dynorphin, transmitters that are involved in stress response, anxiety and negative reinforcement.

Neurophysiological substrates-3.

- Preoccupation/Anticipation: involves conditioned reinforcement in forebrain [Basolateral nucleus] and contextual information by hippocampus. Cortex (prefrontal, orbital and cingulate) and amygdala also involved.
- Neurotransmitters involved: dopamine and glutamate.

Compulsivity

Loss of control

Loss of control [executive function]

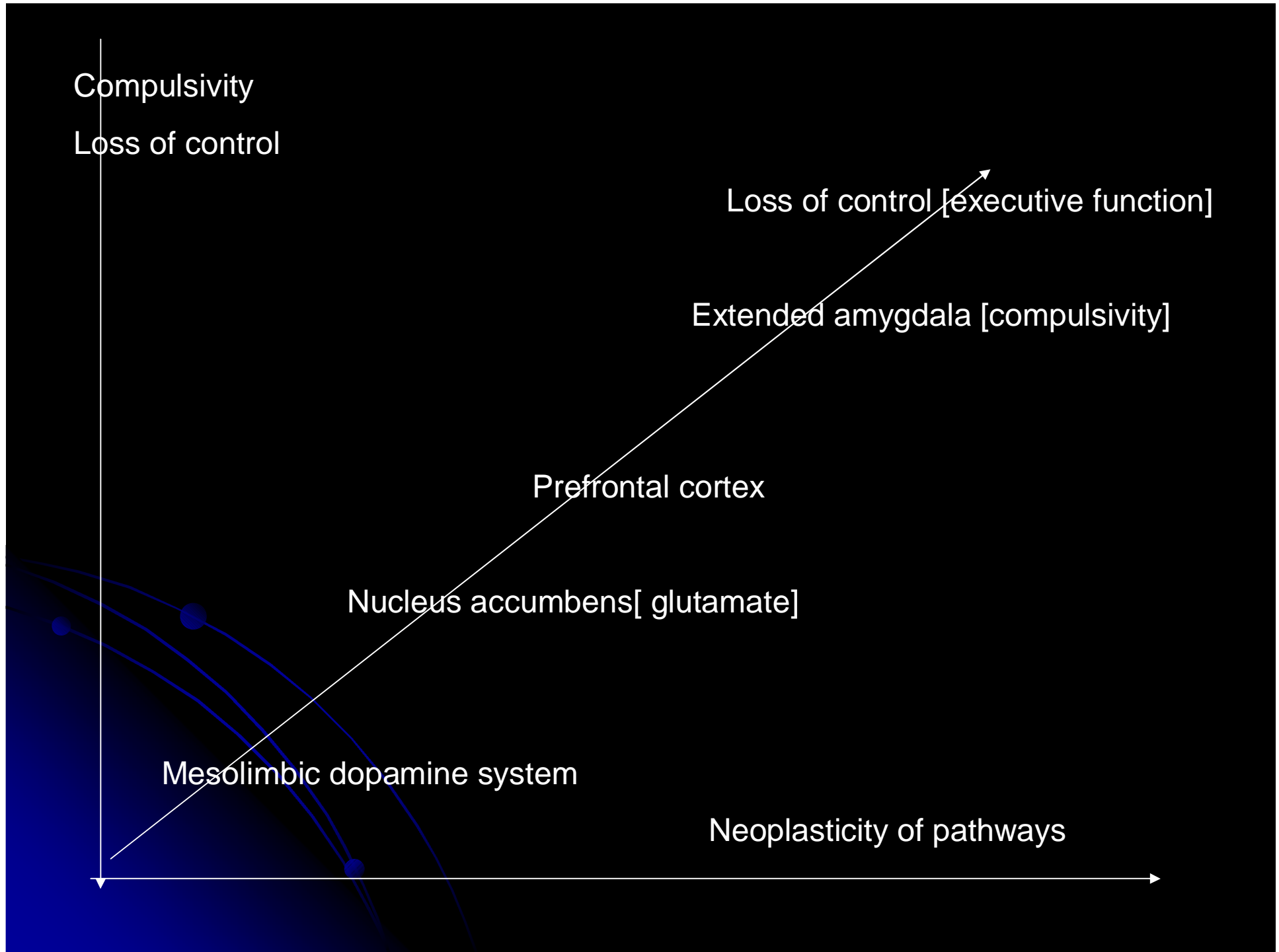
Extended amygdala [compulsivity]

Prefrontal cortex

Nucleus accumbens[glutamate]

Mesolimbic dopamine system

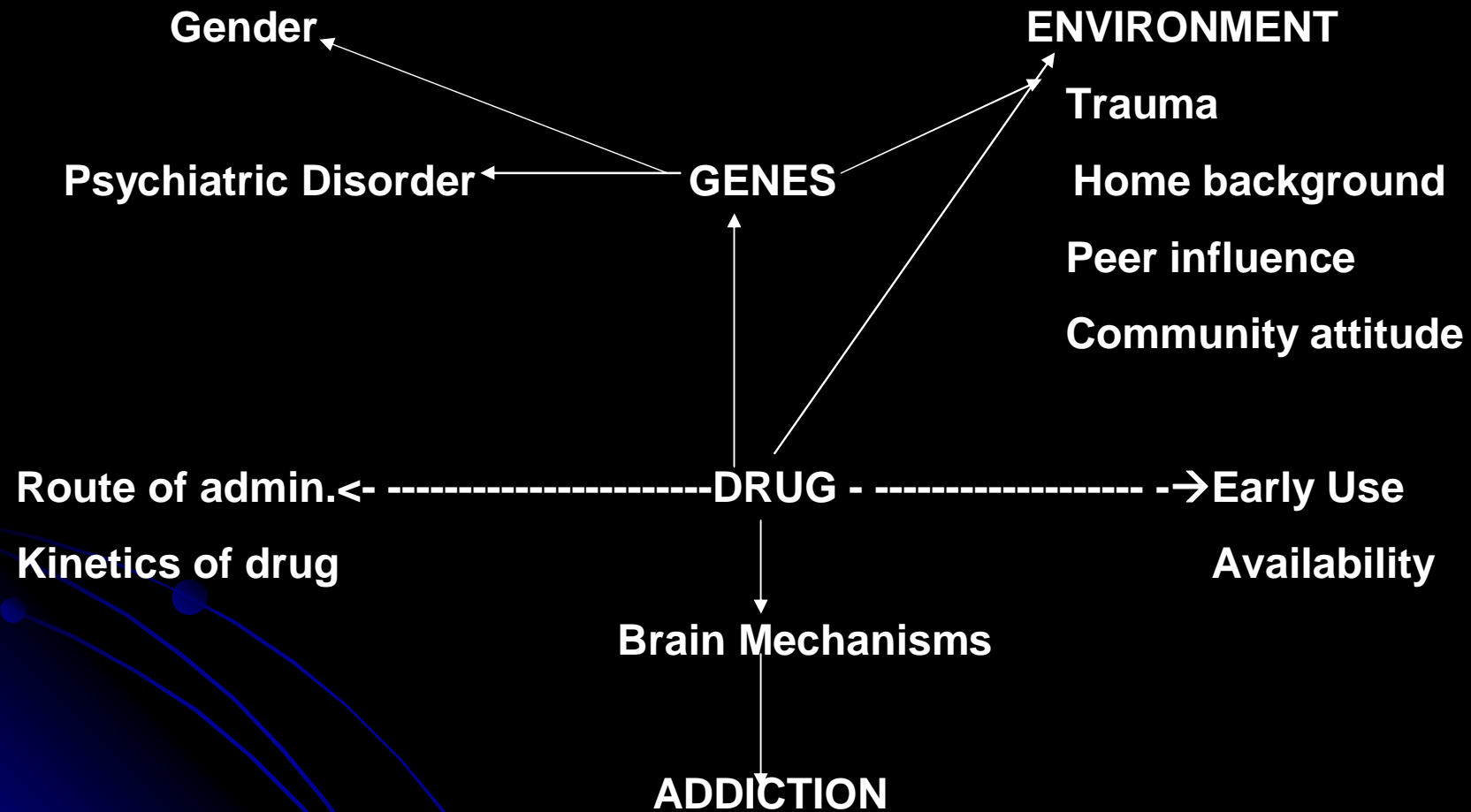
Neoplasticity of pathways



What determines whether drug causes dependence?

- RAPID ENTRY INTO THE BRAIN AT OPTIMAL PHARMACOLOGICALLY ACTIVE CONCENTRATION.
- Opioids
- Sedatives
- Stimulants
- Cannabis, Khat.
- Why are most psychotropic drugs used in psychiatry NOT addictive?

RISK FACTORS FOR DRUG ABUSE.



Factors governing the addictive properties of drugs 1.

- 1. Lipophilicity of the drug and its speed of transport into the brain.
- Heroin (diacetyl-morphine) rapidly transported into brain and converted to morphine.
- Codeine, low lipophilicity and low addiction potential.
- Cocaine, as free base or hydrochloride, rapid transport particularly when smoked.
- Nicotine, in alkaline smoke for optimal effect.

Factors governing addictive properties of drugs 2.

- 2. Potency at site of action in the brain.
- 3. Speed of exit of drug from brain.
- Faster the exit, more rapid the relapse.
- Thus drugs with shorter $T_{1/2}$ more problematic than those with long $T_{1/2}$.
- For example, triazolam verses diazepam, lorazepam vs. diazepam [<15 vs >60 hours].
- Speed of exit usually linked to liver cyt.P450 in liver.

BRAIN CIRCUITS INVOLVED IN BIOLOGY OF ADDICTION.

1. REWARD AND PLEASURE: VENTRAL STRIATUM,
NUCLEUS ACCUMBENS.
2. COGNITIVE CONTROL : PREFRONTAL CORTEX.
3. MOTIVATION, DRIVE AND IMPORTANCE OF THE EVENT (saliency).
ORBITOFRONTAL CORTEX.
4. MEMORY: HIPPOCAMPUS AND AMYGDALA.

Volkow et al. 1997,2010.



RELEVANCE OF BRAIN CIRCUITS TO DRUG ADDICTION.

REWARD CIRCUITS DETECT PLEASURE OF THE DRUG.

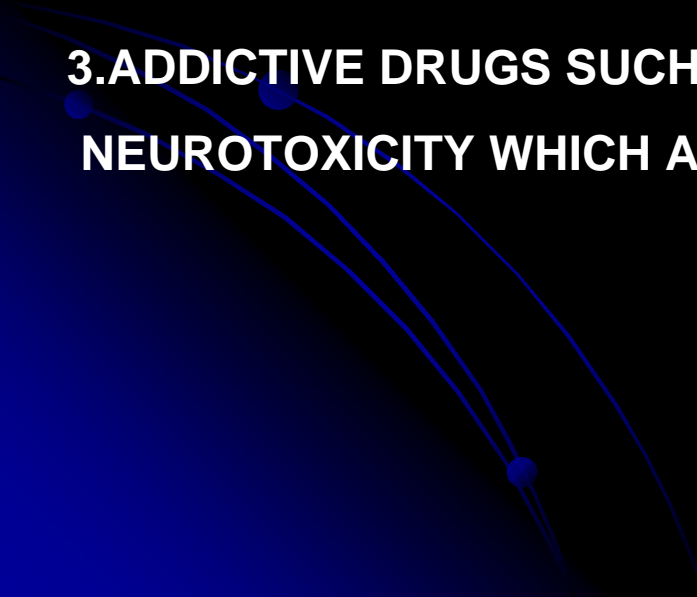
EMOTIONAL MEMORY OF EVENT ENCODED IN THE AMYGDALA.

DECLARATIVE MEMORY [where the event happened and with whom] IS ENCODED IN THE HIPPOCAMPUS.

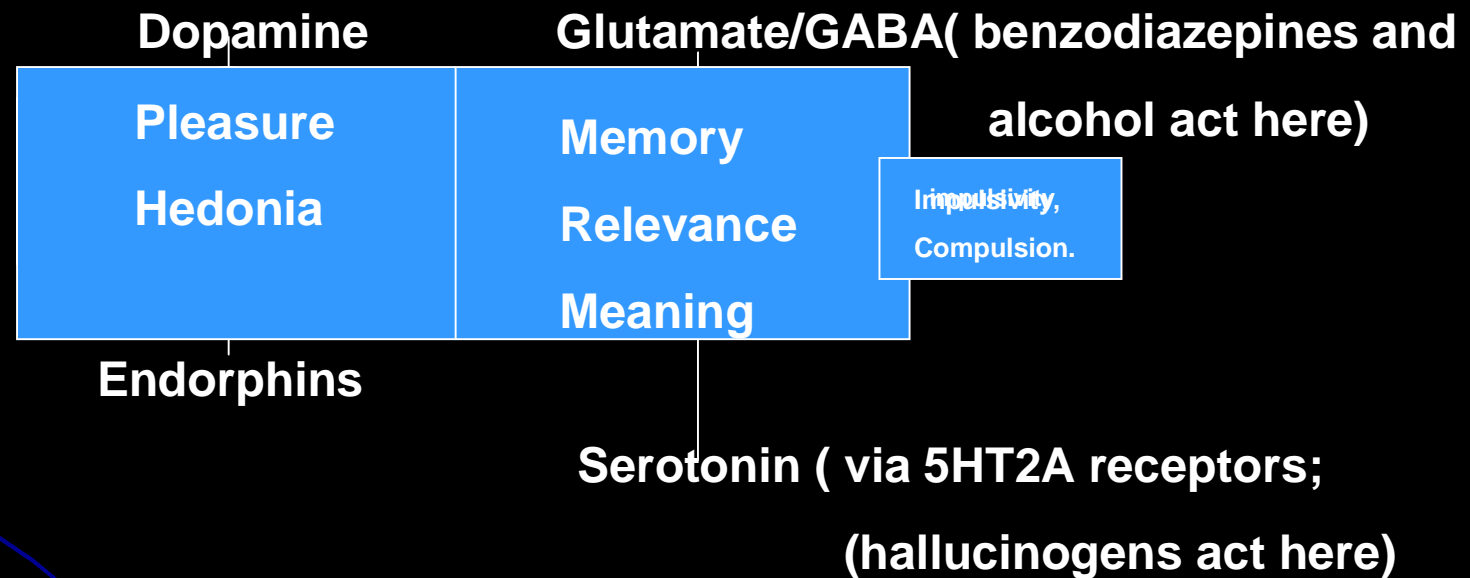
THE DRIVE TO TAKE THE DRUG IS ENCODED IN THE FRONTAL CORTEX [this reflects curiosity, peer pressure or clues regarding the drug].

[Volkow et al..1997;2010]

FUNCTIONAL BRAIN CHANGES INDUCED BY DRUGS OF ADDICTION.

- 1. IN THE NORMAL BRAIN ,THE PREFRONTAL CORTEX EXERTS AN INHIBITORY CONTROL OVER THE SUBCORTICAL EMOTIONAL CENTRES.**
 - 2. IN ADDICTION,THE REWARDING CENTRES [N.ACCUMBENS etc.] PREDOMINATE USUALLY DUE TO THE DRUG INDUCED SENSITIZATION OF THE DOPAMINERGIC SYSTEM.**
 - 3.ADDICTIVE DRUGS SUCH AS ALCOHOL CAUSE BRAIN DAMAGE DUE TO NEUROTOXICITY WHICH ACCELERATE THE PROCESS OF ADDICTION.**
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BRAIN SUBSTRATES OF ADDICTION.



Opiates, endorphins, enkephalins- mu receptors.
Nicotine-Acetylcholine nicotinic receptors
Cannabis-cannabinoid 1 receptors
Cocaine-dopamine receptors.

Are there any reliable vulnerability markers?

- No!
- Possible markers: Reduced D2 receptors in striatum.
- Genetic studies: linkage studies in family pedigrees; association studies of specific alleles occurring more frequently in addicts; gene expression analysis.
- Drugs of abuse alter hundreds of genes!.
- Epigenetic changes-5HT transporter gene [s-allele] and increased alcohol consumption; COMT gene and increased effect of amphetamines.

Treatment possibilities for drugs of addiction -1..

- 1. Use antagonist, for example rimonabant blocks cannabinoid-1 receptors.
- 2. Use partial agonists, for example buprenorphine for opiate withdrawal and varenicline for nicotine withdrawal.
- These drugs induce some receptor stimulation but block the effects of the full agonist.
- 3. Block the pleasurable effects of the drug, for example nalmefene or naltrexone in alcohol and amphetamine dependence.
- 4. Use safer forms of the drug, for example methadone for opiate addiction and baclofen or oxybate for alcohol dependence.
- 5. Increase inhibitory input of the prefrontal cortex with modafinil (?)

THANK YOU !

QUESTIONS AND COMMENTS PLEASE!

