Understanding of 'Addiction' at Cellular Level in Relation to Behavioural Epigenetics

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Abstract

Drug addiction (or substance dependence) is a condition where people compulsively use psychoactive drugs, to the point where the user has no effective choices other than to continue. As per National survey an estimated 7.5 crore Indians are drug addicts and the number is going up significantly. So to make our country out of that we have to better understand both the physical dependency and psychological dependency of Drug Addiction at the cellular level and to treat the pathological pursuit of rewards by epigenetic modulations.

Keywords: Addiction; Tolerance; Dependence; Epigenetic mechanisms.

1. Introduction

Addiction', the word is a substantial burden to the societies worldwide when it comes with alcohol, tobacco, and illegal drugs. It results in enormous direct medical costs, premature mortality and disability that result to crime, negative impacts on families, derailed lives, and personal sufferings. In a broader aspect 'Addiction' damages to our social health which is also very important for a Republic country. Addictive drugs are both rewarding (i.e., interpreted by the brain as intrinsically positive) and reinforcing (i.e., behaviors associated with drugs use tend to be repeated).With the repeated use, however, addictive drugs can produce such molecular changes that leads to tolerance and dependence to the drug that itself promote continued drug taking behavior in a manner that becomes increasingly difficult to control. Tolerance refers to the diminishing effect of a drug after the repeated administration at the same dose, or to the need for an increase in dose to produce the same effect. On the other hand, dependence represents an adaptive state that develops as a homeostatic response to repeated drug administration. So, understanding the molecular and cellular actions of addictive drugs is obligatory if we are to better understand the pathophysiology and develop potent pharmacotherapies to treat the addiction and drive it out from the society.

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2. Indian Scenario

As per National survey on extent, pattern and trends of drug abuse in India conducted by the centre in collaboration with United Nations office on Drugs and Crime, the current prevalence rates within the age group of 12-18 years was alcohol (21.4%), cannabis (3%), opiates (0.7%) and any illicit drug (3.6%)[1] .

3. Category of Drugs and Their Functions

It is difficult to group the drugs as virtually all acts by very different mechanisms. All addictive drugs, including the psychostimulants, can produce an emotional–motivational component of dependence, manifested by symptoms such as dysphoria, anhedonia, and drug craving.

Name of the categorized drug	Function
Psychostimulants	Most widely abused psychostimulants are cocaine and the amphetamines. Both result in increases of extracellular dopamine and other monoamines and produce similar effects on behavior.
Ethanol	Ethanol is a central nervous system depressant that produces behavioral euphoria, reduced anxiety, decreased motor coordination, and sedation.
Opiates	The opiates and their synthetic analogues are the most effective analgesic agents known, and at the same time can produce tolerance, dependence (including somatic dependence), and addiction.
Cannabinoids	Δ-9-Tetrahydrocannabinol (THC) is the major psychoactive compound contained in marijuana which effects in humans that range from mild relaxation, euphoria, analgesia, and hunger to panic attacks.
Nicotine	Nicotine is the main psychoactive ingredient of tobacco and is responsible for the stimulant effects, reinforcement, and dependence that result from tobacco use. Cigarette smoking rapidly delivers nicotine into the bloodstream.

4. Molecular Targets of Addictive Drugs

The overall effect of each of the addictive drugs depends on the particular neurons and circuits that express their molecular targets, and the nature of those targets. But, in a broader way, addictive drugs share the ability to activate mesocorticolimbic dopamine projections that are critical substrates for both rewarding and reinforcing effects of natural stimuli. Mesocorticolimbic dopamine projections originate in the VTA (Ventral Tegmental Area) of the ventral midbrain and project to structures that include the NAc (Nucleus Accumbens) (a complex structure within the ventral striatum that is the best-established substrate for reinforcement), and the prefrontal cerebral cortex.

Mechanism of Tolerance and Dependence in Brain Stress System

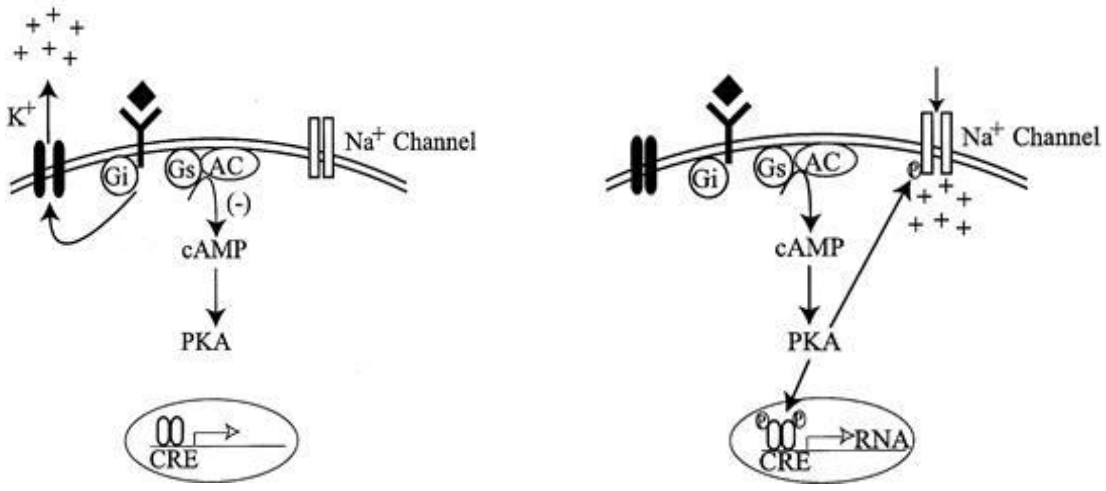

Fig.1.Mechanism of opiate tolerance and dependence in the locus ceruleus: Acute administration of opiates increases outward K^+ current, thereby hyperpolarizing locus ceruleus cells (LEFT). With chronic opiate use the cAMP signaling system is up-regulated, leading to PKA-dependent phosphorylation of the Na^+ channel. In this state, the channel is more active, allowing Na^+ ions to flow into the cell, increasingly the intrinsic excitability of the cell. Up-regulation of the cAMP system also increases CREB Ser^{133} phosphorylation and CRE-dependent gene transcription. Alterations in CRE-driven genes may contribute to the increased LC neuron excitability as well. (Adapted from Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci 1992; 12:483-488)

Hypothetical Scheme to Explain Increased Neuronial Excitibility with Drug Withdrawal

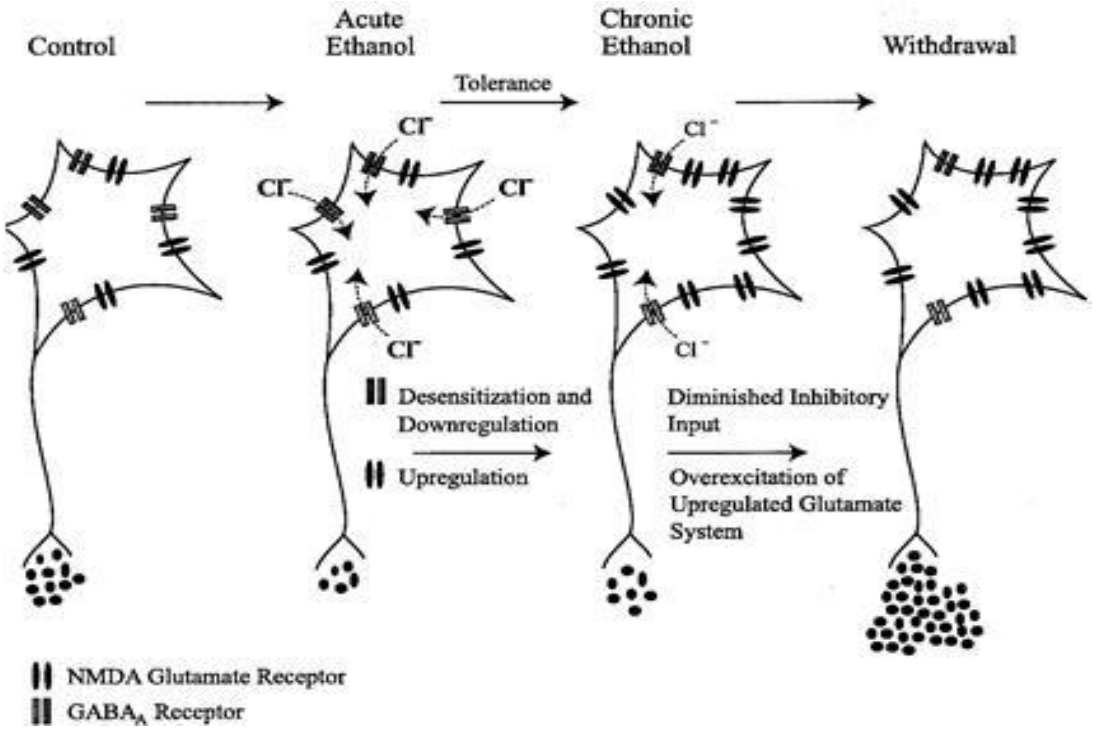

Fig.2.Hypothetical scheme to explain increased neuronal excitability with ethanol with- drawal: Acute ethanol exposure increases chloride conductance via the $GABA_A$ receptor and inhibits NMDA glutamate receptors, thereby reducing neuronal excitability and glutamate release. With chronic ethanol exposure, there is putative down-regulation of $GABA_A$ receptor subunits and possibly up-regulation of NMDA receptors. On ethanol withdrawal, inhibitory input from ethanol is removed; therefore, excitatory influences are relatively unopposed. The neurons release increased quantities of glutamate, which may act on up-regulated receptors. The unopposed cellular hyperexcitability can promote seizure activity as groups of neurons become overexcited. (Adapted from Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci 1992; 12:483-488).

5. Epigenetic Mechanism and The Role of Chromatin Modifying Enzyme

The word ‘epigenetic’ historically refers to a heritable phenotype not coded by DNA itself but by a cellular process ‘above the genome’. Cellular differentiation is a classic example where epigenetic phenomena have a critical role [2,3] .Because all cells in an organism contain the same genetic information, the ability to form clonal populations of distinct cell types with unique functions (e.g. neurons versus hepatocytes) is achieved by transmitting the correct transcriptional programs from parent to daughter cell. This epigenetic process is in large part

coordinated through control of chromatin structure. Increasing evidence indicates that changes in chromatin structure not only mediate these heritable epigenetic phenomena[4] but also that the same types of changes in chromatin occur in mature, post-mitotic neurons [5,6].

Chromatin modifications, or 'marks', such as histone acetylation and methylation are dynamic processes, controlled by enzymes that either add or remove the specific mark. Histone acetyl transferases (HATs) catalyze the addition of acetyl groups onto lysine residues of histone proteins [7-9].

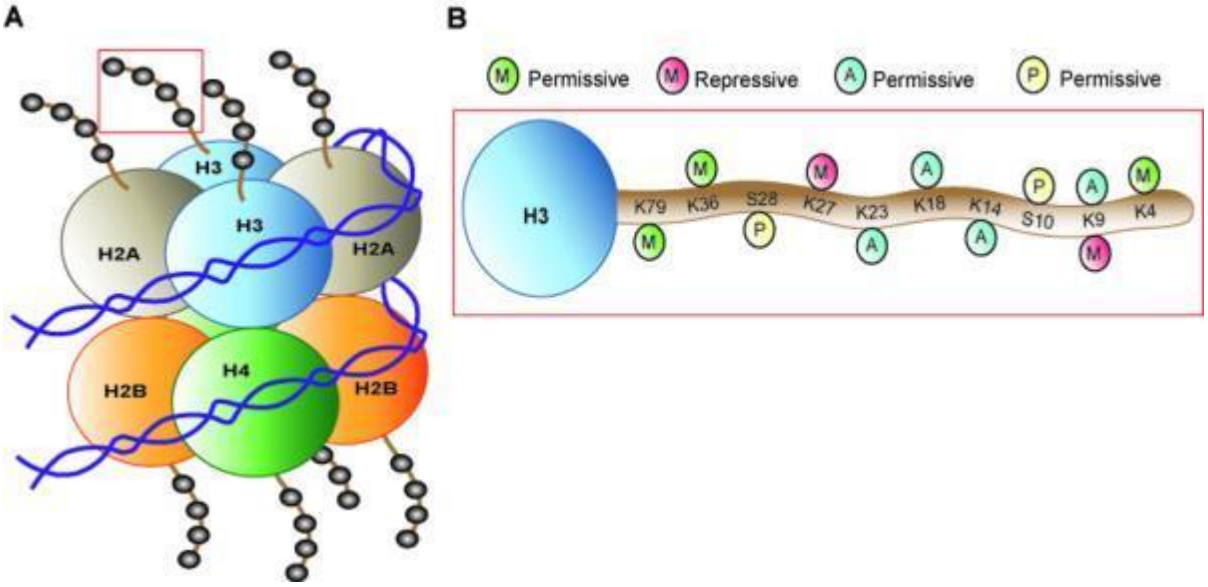

Fig.3.Post-translational modifications of histones regulate gene expression. Shown in panel **(A)** is the nucleosome core particle, representing the functional repeating unit of chromatin, composed of 147 bp of DNA wrapped around a core octamer of histone proteins (two copies each of H2A, H2B, H3 and H4). **(B)**Combinations of acetylation, phosphorylation, methylation, etc. on histone tails (here, H3 is depicted) alter chromatin compaction promoting altered levels of gene expression in cells. Histone modifications that weaken the interaction between histones and DNA (e.g., histone acetylation at K23, K18, K14, and K9, as well as methylation at K79, K36, and K4 or phosphorylation at S28 and S10) correlate with permissive gene expression. Histone deacetylation or histone methylation on H3K27 or H3K9, which strengthen histone:DNA contacts, promote a state of transcriptional repression. (Adapted from Maze I. & Russo, S.J. 2010. Transcriptional mechanisms underlying addiction-related structural plasticity. Molecular Interventions*)*.

6. Drug-Induced Changes in Chromatin Structure

Histone Acetylation: Acetylation of histone lysine residues reduces the electrostatic interaction between histone proteins and DNA, which is thought to relax chromatin structure and make DNA more accessible to transcriptional regulators[10]. Genome-wide studies have shown that hyperacetylation in promoter regions is strongly associated with gene activation, whereas hypoacetylation is correlated with reduced gene expression [11,12]

Histone Phosphorylation: Histone phosphorylation is generally associated with transcriptional activation; it can be observed on the promoters of immediate early genes such as c-fos when they are induced after cAMP induction or glutamate treatment in cultured striatal neurons [13,14].

Histone Methylation: Histone methylation is particularly complex and can exist in mono-, di- (me2) or tri-methylated (me3) states, enabling each state to recruit unique coregulators and exert distinct effects on transcriptional activity [10].

7. Genome-Wide Analysis of Chromatin Regulation in Animal Models of Addiction

Using genome-wide techniques involving hybridizing immunoprecipitated chromatin to of new information can been uncovered about epigenetic regulation in specific brain regions, as well as novel gene targets that control behavioral responses to drugs of abuse. Such analyses are just now getting underway for drug addiction models.

8. Interplay Between Transcription Factors and Epigenetic Mechanisms

In order for environmental stimuli to regulate chromatin structure on the correct set of genes, mechanisms exist to guide the proper chromatin-remodeling enzymes and transcriptional regulators to the right gene locus.

The transcription factor CREB, which plays an essential role in behavioral responses to cocaine [15], was one of the first transcription factors known to direct a chromatin-modifying enzyme to gene promoters. When CREB is phosphorylated, it interacts with CBP, a HAT that helps facilitate target gene activation by acetylating neighboring histones [16].

Interplay between transcription factors and chromatin-remodeling enzymes suggest that developing small molecules that stabilize or disrupt these complexes could provide a new avenue for addiction treatment.

9. Conclusion

All of the initial molecular targets of drugs of abuse have been characterized and cloned. However, the molecular biology of processes relevant to tolerance, dependence, sensitization, and most important, compulsive drug use, and late relapse, are in their relatively early stages. Drug-induced alterations in chromatin structure have now been implicated in both the pathogenesis and maintenance of the addicted state. An important area for future research is to translate these findings from simple behavioral models. Another area for future research is to dissect the many types of potential changes in chromatin structure beyond histone acetylation that also occur after drug exposure. Perhaps

a place to start is to explore those marks known to be regulated in brain in other behavioral models. However, regardless of the epigenetic mechanism studied, we must ultimately understand what is happening to the underlying expression of specific gene targets

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