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Pharmacogenetics – A Treatment Strategy for Alcoholism

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1. Introduction

Alcoholism is a complex relapsing disorder of heterogeneous etiology, affecting people internationally. Alcohol dependence is a cumulative response of inability to stop drinking, craving and developing the symptoms of physical dependence and tolerance. In past two decades, mounting evidence has suggested that alcoholism or alcohol addiction is a host of major psychological, social, financial and health problems (Poznyak et al., 2005). According to World Health Organization, alcoholism is responsible for 4% of global disease burden and is the third major preventable risk factor for premature death and disability in developed nations (World Health Organization, 2002). Although, the exclusive biological mechanisms underlying the development of alcoholism are still uncertain, the major risk factors contributing towards the development of alcoholism are age (adolescents are at higher risk of developing alcoholism), gender (men are more prone to develop alcoholism as compared to women due to depression), personality (experience seeking), and psychiatric or behavioral disorders. The prevalence, age of onset, clinical symptoms and outcome of alcoholism differs from individual to individual and varies according to ethnicity (Kenneth et al., 2011). In addition to this, lower social status and low education have also been found to be associated with alcoholism in cross sectional and longitudinal studies (Fukuda et al., 2005; Poznyak et al., 2005; Subramanian et al., 2005; Wray et al., 2005).

According to World Health Organization report on global alcohol status, it has been found that approximately 2 billion people consume alcoholic beverages and there are about 76.3 million people with diagnosable alcohol disorder (World Health Organization, 2004). In India the prevalence of alcoholism has been found to be 21.4% as recoded by epidemiological surveys (Benegal, 2005).The deleterious effects of alcohol on central nervous system can be observed in the form of changes in mood and personality, anxiety and depression. Although, it affects all the organs in the body, brain neurotransmitters are the main target sites of alcohol (Wertheimer et al., 2003). The specific physiological effects of alcohol depend on dose, concentration in blood, absorption, distribution, metabolism, excretory conditions, prior drinking experience, concurrent use of other drugs, and

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comorbid conditions. The body adapts metabolically and neurally to repeated exposure of alcohol so as to develop tolerance (Zaleski et al., 2004).

Recent advances in the field of neurobiology have improved our understanding about associated risk factors and neurochemical mechanisms responsible for the development of alcoholism. Evidences suggest that there is large inter-individual variation in terms of development of alcohol dependence and treatment of alcoholism. People consume alcohol and respond to its effects in a number of ways e.g. some develop no side effects even in moderate to higher levels and some may develop problems even when consumed in smaller doses. This variation is the result of individual's genetic makeup directly influencing the metabolism of alcohol (Strat et al., 2008).

Genetic factors have been found to play a critical role in the etiology of alcoholism (Heath et al., 2001; Sloan et al., 2008; Kenneth et al., 2011). Researchers have suggested that 50-60% of alcohol dependence is determined by genetics (Goldman and Bergen 1998; McGue et al., 1999). Based on results of adoption, twin, and family studies it is now clear that the vulnerability to alcoholism is determined by genetic factors as well as by environmental factors (Moussas et al., 2009). However, it is difficult to determine the individual determinant of alcoholism (Flensborg-Madsen et al., 2007). The candidate gene approach has revealed a number of biomarkers, which are responsible for alcoholism. Certain variants of alcohol dehydrogenase and aldehyde dehydrogenase genes (genes encoding for alcohol metabolizing enzymes) have been found to alter the metabolism of alcohol in a dramatic way (Nurnberger et al., 2004). In addition to this, polymorphisms in neurotransmitter genes (target receptor genes) such as gamma amino butyric acid and opioid receptor genes have also been reported to be associated with marked risk of alcohol dependence (Strat et al., 2008). Current treatment approaches to alcoholism are moderately effective with perhaps as many as half of the patients receiving treatment due to abstinent or significantly reducing episodes of binge drinking (Group, 1997). Pharmacotherapy and behavioral therapy including psychosocial support are two main types of treatment in alcoholism. The pharmacological agents approved by FDA prescribed in the treatment of alcoholism are disulfiran (antabuse), naltrexone (revia), acamprosate (campral) and Vivitrol (Krishnan-Sarin & O'Malley et al., 2008).

The major drawback of ineffectiveness of pharmacotherapy of alcoholism is inter-individual variation in response to medication (Radel and Goldman, 2001). There are individuals, showing lesser/no therapeutic efficacy of a drug prescribed, known as non-responders. Another group of individuals showing high therapeutic efficacy towards the same drug are known as responders (McLeod et al., 2000).

Recent advances in the area of molecular biology have increased our knowledge of understanding the influence of genetic variants on pharmacokinetic and pharmacodynamic profile of alcohol and neurobiology of alcoholism (Ray et al., 2010a). The unavoidable alcohol withdrawl symptoms, depression, unpredicted death, medical complications, socioeconomic repercussions of alcoholism suggest that the treatment strategies should be improved with new and targeted approach of pharmacogenetics.

Pharmacogenetics is a measure of predicting individual's genetic profile responsible for variable drug responses. The genetic analysis along with consideration of other factors of alcoholic patients can lead to the identification of clinical subtypes of patients with specific

treatments. This will improve the treatment of alcoholism. Alcohol pharmacogenetics has great potential in improving treatment strategies for alcoholism (Radel and Goldman, 2001; Quickfall and el-Guebaly, 2006). The treatment strategy of combining clinician's views based on genotypic information would individualize and optimize the treatment for alcoholism with best possible outcome of individual's good health free of alcohol dependence. Pharmacogenetics is expected to add new dimensions and would tailor the therapeutic treatment of alcoholism.

The chapter provides an overview of the molecular, pharmacological and neurological aspects of alcoholism with main emphasis on pharmacogenetics of alcoholism treatment.

2. Metabolism of alcohol

Alcohol is generally taken orally, absorbed unchanged through the whole length of digestive tract. Almost 20% absorption takes place rapidly through stomach and 80% through small gut (Caballeria, 2003). The rate of absorption depends on volume, concentration, nature of alcoholic drink, presence and absence of food in stomach, permeability of gastric and intestinal tissues and genetic variation. After absorption into the blood-stream, alcohol is distributed quickly throughout the total body fluid (Pawan, 1972). The distribution of alcohol is accelerated by vascularization and blood flow e.g. organs rich in blood supply such as brain and lungs achieve the higher initial concentrations of alcohol.

Liver is the main site of alcohol metabolism. In hepatocytes three systems are involved in alcohol metabolism located in three different cellular compartments. These are alcohol dehydrogenase (*ADH*) located in cytosol, microsomal ethanol oxidizing system (*MEOS*) situated in endoplasmic reticulum and catalase in peroxisomes (Caballeria, 2003). These are involved in conversion of alcohol to acetaldehyde (Figure 1).

The metabolic pathway involves conversion of alcohol (ethanol) to acetaldehyde via oxidation catalyzed by *ADH* in cytoplasm of hepatocytes, a rate limiting step. The second reaction is catalyzed by aldehyde dehydrogenases (*ALDH*), acetaldehyde is converted to acetic acid and finally to carbon dioxide and water through citric acid cycle into circulation. Acetaldehyde plays central role in the toxicity produced by alcohol consumption as in liver it reaches to saturation point and escapes into blood circulation. Further it impairs mitochondrial functions and reactions leading to damage of hepatocytes. The rate of metabolism of alcohol differs from person to person because it is influenced by genetic variants of metabolizing enzymes mentioned above (Quertemont, 2004).

2.1 Alcohol dehydrogenase system

Alcohol dehydrogenase (ADH) occurs in multiple forms and is encoded by 7 different genes. These are ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6 and ADH7. These genes are aligned along a small region of chromosome 4. ADH enzymes encoded by ADH gene function as dimers i.e. the active forms are composed of two subunits. On the basis of their similar amino acid sequences and kinetic properties, these seven ADH types have been divided into five classes. The class I genes ADH1A, ADH1B and ADH1C are closely related. These encode for α, β and γ subunits respectively, which form homodimers or heterodimers and account for most of the alcohol oxidizing capacity in liver (Hurley et al., 2002; Lee et al.,

2006). Further, ADH1A, ADH1B and ADH1C are mainly present in liver and linings of stomach. ADH4 encodes π-ADH which has been reported to contribute significantly to ethanol oxidation at higher concentration. The ADH5 gene encodes for χ-ADH, a ubiquitously expressed formaldehyde dehydrogenase, which has low affinity for ethanol. ADH6 mRNA is found in fetal and adult liver. Since the enzyme has not been isolated from tissues so far, therefore little is known about it. ADH7 encodes for σ-ADH, which oxidizes both ethanol and retinol (Edenberg, 2007).

2.2 Aldehyde dehydrogenase

These enzymes rapidly convert acetaldehyde to acetate using cofactor NAD^+ via oxidation. ALDH is divided into nine major categories. Some of these are significantly involved in acetaldehyde metabolism, and others metabolize a variety of substrates. Two main ALDH enzymes reported to be involved in metabolization of acetaldehyde during the oxidation of ethanol are ALDH1 and ALDH2. ALDH1 encoded by ALDH1A1 gene is found in fluid filling cells (the cytosol) while ALDH2 is found in mitochondria and is encoded by the ALDH2 gene. The two genes are 52 kb and 43 kb in length and are present on chromosome 9 and chromosome 12 respectively. Both genes have a similar structure with 13 exons and the protein encoded by both the genes is 70% similar in sequence and structure (Hurley et al., 2002). ALDH1A1, ALDH1B1 and ALDH2 are mainly involved in acetaldehyde oxidation.

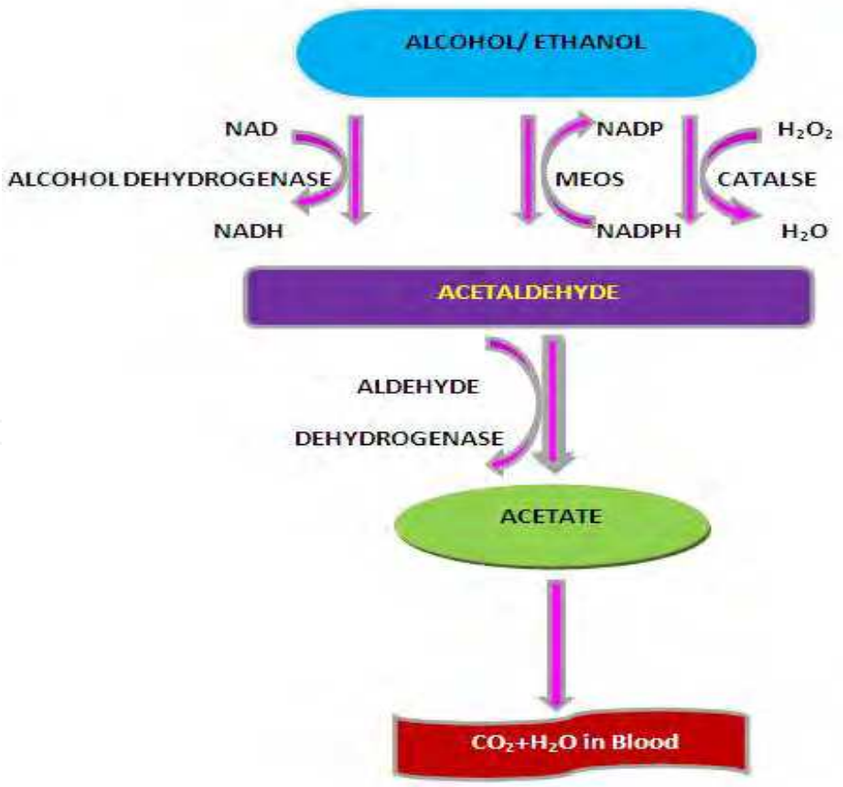

Fig. 1. Metabolism of alcohol in liver hepatocytes using 3 systems, (i) Alcohol dehydrogenase, (ii) Microsomal ethanol oxidizing enzyme (iii) Catalase and finally Aldehyde dehydrogenase converts acetaldehyde into acetate

2.3 Microsomal ethanol oxidizing enzymes

Apart from ADH which accounts for greater part of ethanol oxidation, a quantitatively small portion of alcohol is catalyzed by microsomal ethanol oxidizing system involving CYP2E1 (Edenberg, 2007). Studies have shown that CYP2E1 is induced by high ethanol concentration and by chronic intake of alcohol or ethanol (up to 10 fold) (Quertemont, 2004). It has been found that after chronic ethanol consumption CYP2E1 increases the rate of ethanol clearance and this may result in development of ethanol tolerance (Lieber et al., 1968; 1988; Takahashi et al., 1993; Tsutsumi et al., 1989). CYP2E1 induction may further lead to higher concentrations of acetaldehyde leading to injuries in hepatocytes.

2.4 Catalase

Catalase oxidizes alcohol to acetaldehyde within the peroxisomes (Oshino et al., 1973). This reaction is hydrogen peroxide (H_2O_2) dependent. Under normal conditions catalase plays a minor role in ethanol oxidation. However, the functional activity of catalase is accelerated in the presence of reactive oxygen species and H_2O_2 (Quertemont, 2004). Zimatkin et al. (1997) have suggested that catalase may be one of alternative metabolic pathways for ethanol oxidation in brain where CYP2E1 and ADH appear to be of minor importance. However, the precise role of catalase in brain ethanol oxidation is still not clear.

2.5 Nonoxidative ethanol metabolism

Apart from oxidative metabolism of alcohol, nonoxidative metabolism also takes place in organs lacking oxidative metabolism such as heart (Beckemeier et al., 1998). A minor extent of alcohol is metabolized by nonoxidative pathway using enzyme fatty acid ethyl synthases resulting in the formation of fatty acid ethyl esters (Caballeria 2003). Further, these esters have been found to be involved in alcohol-induced organ injuries (Beckemeier et al., 1998).

3. Genetic variants affecting alcohol metabolism

Genes encoding for alcohol metabolizing enzymes are supposed to have major influence on development of alcoholism. There are multiple ADH and ALDH enzymes encoded by different genes. Some of these genes have been reported to occur in several variants or alleles. The enzymes encoded by different alleles can differ in the rate at which they metabolize ethanol (Edenburg, 2007).

3.1 Genetic variants of alcohol dehydrogenase

Researchers have studied the genetic variants of ADH1B and ADH1C genes that result in the production of enzymes with different kinetic properties and have been implicated in the susceptibility to develop alcoholism. These genetic variants or SNPs and their effects have been widely studied in different populations and three different alleles have been reported which alter the amino acid sequence of the encoded beta subunit. ADH1B*1 allele, (reference allele) encodes for β1 subunit that has arginine at positions 48 and 370. ADH1B*1 is the predominant allele in most populations. ADH1B*2 encodes for β2 subunit with histidine at position 48 and is commonly found in Asians. ADH1B*3 encodes for β3 subunit that has cysteine at position 370 and is prevalent in people of African descent. In β2 and β3 subunits,

amino acid substitutions occur at an amino acid which contacts with coenzyme nicotineamide dinucleotide (required for ethanol oxidation) (Hurley et al., 2002). The substitution results in enzymes, which have 70- to 80- fold higher turnover rate than the β1 subunit. This is because the coenzyme is released more rapidly at the end of reaction.

For ADH1C gene, there are 3 alleles ADH1C*1 encoding γ1 subunit with arginine at position 272 and isoleucine at position at position 350. ADH1C*2 encodes the γ2 subunit which has glutamine (Gln) at position 272 and a valine (Val) at position 350. These two SNPs occur together (i.e., are in very high linkage disequilibrium). It has been found that the ADH with two γ1 subunits (i.e., the γ1γ1 homodimeric enzyme) has a turnover rate that is about 70 percent higher than that of the γ2γ2 enzyme (Edenberg, 2007). ADH1C*Thr352 encodes for a subunit with threonine at position 352 and has been found in Native Americans (Osier et al., 2002). However, the studies on this protein are still lacking. Researchers have identified the differences in the rate of metabolism of ethanol in liver on the basis of difference in amino acid sequence resulting in difference in kinetic properties of encoded enzyme. If a person carries two copies of reference allele i.e. ADH1B*1 and ADH1C*1 alleles (homozygous for ADH1B*1and ADH1C*1) the enzyme (together α, β, γ subunits) together accounts for liver's 70% ethanol oxidizing capacity, additionally π ADH accounts for 30% (Hurley et al., 2002). ADH1B*1 allele has been reported to reduce the occurrence of alcohol abuse and alcoholism in Asians, in Whites and in Jewish populations where this allele has a relatively high prevalence (Carr et al., 2002; Neumark et al., 1998). ADH1B*2 has been found to occur in a higher frequency in nonalcoholics and in moderate drinkers relative to heavy drinkers. As far as ADH1B*2 is concerned, this allele has been found to be associated with lower rates of heavy drinking and alcohol dependence in Native Americans (Quertemont, 2007).

A meta-analysis conducted by Whitfield has concluded that ADH1B*1 allele is associated with a threefold increase in risk of alcoholism in comparison with ADH1B*2 allele.ADH1B*2 allele encodes for an enzyme with a faster ethanol oxidation rate (Whitfield, 1997). It has been assumed that this allele protects against alcoholism and alcohol abuse because of the unpleasant effects associated with acetaldehyde accumulation (Yin, 1994). The frequency of ADH1C*1 allele has been reported to about 50% in European population and up to 90% in some Asian and African populations (Goedde et al., 1992; Osier et al., 2002). This allele has also been shown to provide a protection against alcohol abuse and alcoholism since a higher frequency of this allele has been found in nonalcoholics especially from Asian population.

Gene-gene interactions have also been found to play an intricate role in development of alcoholism. Oseir et al. (2004) found that there is potential epistatic interaction between ADH1B and ADH7 which leads to protective effect against alcoholism among Han Chinese population (Oseir et al., 2004).

3.2 Genetic variants of aldehyde dehydrogenase (ALDH)

The best known variation of alcohol metabolizing enzymes has been associated with ALDH2 gene. A variant of this gene known as ALDH2*2 allele leads to the substitution of lysine to glutamine at 504 position (Chou et al., 1999). This substitution results in the production of a nearly inactive ALDH2 enzyme which no longer oxidizes acetaldehyde to acetate. Studies have demonstrated that this variant is dominant because people who are heterozygous (ALDH2*1 and ALDH2*2) have almost no detectable activity of ALDH2

enzyme in the liver. People with an ALDH2*2 allele show an alcohol flush reaction even when they consume alcohol in relatively small amounts (Harada et al., 1981). The presence of even a single ALDH2*2 allele has been shown to be strongly protective against alcohol dependence. The protective effect of ALDH2*2 is the most widely reproduced association of a specific gene with alcoholism (Chen et al., 1999; Hurley et al., 2002; Luczak et al., 2006; Thomasson et al., 1991).

3.3 Genetic variants of microsomal ethanol oxidizing system

Another enzyme, microsomal ethanol oxidizing enzyme involved in alcohol metabolism is encoded by CYP2E1 gene. CYP2E1 is induced (increase in activity up to 10 fold) by chronic alcohol drinking and may contribute to development of metabolic tolerance in alcoholics. Studies have revealed that polymorphism in CYP2E1 (CYP2E1*1D) has been found to be significantly associated with alcohol dependence in Canadian native Indians (Howard et al., 2003; Itoga et al., 1999). Another rare mutant named as c2 allele (CYP2E1*5B) in CYP2E1 gene has been found to be associated with higher transcriptional activity leading to elevated level of the enzyme as compared to wild type c1 allele i.e. CYP2E1*5A (Hayashi et al., 1991).

3.4 Genetic variants of catalase

Studies have revealed that subjects with positive family history of alcoholism have a higher mean activity of catalase as compared to control subjects (Koechling and Amit et al., 1992). A significant positive correlation was observed in brain and blood catalase activity in rats (Amit and Aragon., 1988). Koechling and Amit (1992) have reported a significant coorelation between blood catalase activity with alcohol consumption. However, there are no studies on the association of genetic polymorphism of catalase with alcoholism.

4. Neuropharmacological aspects of chronic alcoholism

The neuropharmacological actions of alcohol such as cognitive impairment and other behavioral changes are mediated via their interaction with brain neurotransmitters. Neurotransmitters are the chemicals involved in communication of neurons in brain and may be inhibitory or excitatory depending upon their mechanism of action. Although alcohol does not have any specific target neurotransmitter, it acts on multiple neurotransmitter systems (Deitrich and Erwin, 1996; Tabakoff and Hoffman, 1992).

Chronic alcohol consumption may cause cognitive impairment, tolerance and physical dependence due to changes in neurotransmitter system in brain. The neuropharmacological changes caused by chronic alcoholism involve monoamine oxidase, neurotransmitter amino acids and calcium ion channels and some other pathways leading to neuroadaptations and development of tolerance (Zaleski et al., 2004). The complex mechanism of action involving neurochemical changes explains why even moderate doses of alcohol may lead the subject to develop psychiatric complications and alcohol dependence. The addictive and alcohol seeking behavior can be explained by understanding the neurotransmitter involved in the processes (Vengeliene et al., 2006).

Few of the neurotransmitters involved in alcohol dependence are as follows:

4.1 Alcohol and monoamines

Ethanol affects the release of the main neurotransmitters present in central nervous system, such as dopamine, gamma amino butyric acid (GABA), serotonin, noradrenaline and opioid peptides (Kianmaa &Tabakoff, 1983; Tabakoff, 1977, 1983). Alcohol activates the firing of dopaminergic neurons in the ventral tegmental area and nucleus accumbens structures which together are a part of mesolimbic pathway and play an important role for the rewarding effect of ethanol (Diana et al., 1992). Studies have demonstrated that the stimulation of dopaminergic neurons may indirectly activate serotonergic pathways. The low levels of serotonin have been reported to be a risk factor for development of alcoholism (Lovinger, 1991).

4.2 Alcohol and neurotransmitter amino acids

Several studies have demonstrated the actions of ethanol on neurotransmitter amino acids which consist of glutamate-main excitatory neurotransmitter in the central nervous system. It has N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA), and kainate receptors. The NMDA receptors are controlled by several regulatory sites. To open the channel of NMDA receptor, presence of glycine is required. Glycine is an amino acid which has its own site, acting as a coagonist. Alcohol has been reported to act on glycine binding site therefore, inhibiting the function of NMDA receptor (Woodword, 1994). The receptor has been found to play an important role in learning and memory and in development of alcohol tolerance (Longo et al., 2002). Glutamate, a neurotransmitter has been found to play a significant role in the pathogenesis of alcohol dependence by mediating excitatory pathways (Sander et al., 2000). Chronic alcohol use has been found to be associated with upregulation of NMDA receptors. Alcohol shows lower affinity for AMPA and kainate glutamate receptors (Ferreira & Morato, 1997). In case of acute ethanol withdrawal, NMDA receptor releases increased amount of glutamate which is associated with tremors, anxiety, ataxia, and convulsions.

Alcohol produces sedative-hypnotic effects mediated via GABA, an inhibitory neurotransmitter. There are three types of GABA receptors, GABA A, GABA B, and GABA C in brain. GABA A receptors are responsible for the intoxicating effects of alcohol such as motor incoordination, anxiolysis and sedation. The neurobehavioral effects of ethanol mediated via neurotransmitter GABA are directly dose-dependent. The effects of alcohol at GABA A receptors vary across brain regions. This might be due to the differential expression of GABA A receptor subunits (Loh et al., 1999).

Another neurotransmitter, Neuropeptide Y (NPY) is an amino acid peptide which has been associated with reward, appetite and anxiety. The association of NPY has also been reported with alcohol dependence in animal models. NPY-deficient mice have been reported to show higher alcohol consumption as compared with wild type mice (Thiele et al., 1998).

4.3 Alcohol and calcium ion channels

Voltage sensitive calcium channels (VSCCs) play a major role in gating synaptic calcium influx and thereby modulating a range of calcium dependent intracellular processes, membrane potential, and neurotransmitter release (Kennedy & Liu, 2003). The types of

VSCC are of L-type (dihydropyridine-sensitive), N-type (neuronal), P-type (Purkinje), R-type (Resistant), and T type (transient) channels. It has been found that alcohol (ethanol) blocks L-type channels. The L-type VSCC antagonists show some ethanol, like effects in rats. Evidence suggested that chronic administration of alcohol in mice up-regulates the number and function of N-type calcium channels. Ethanol actions at VSCCs may modulate its behavioral effects in humans (Zaleski et al., 2004). It has been reported that there is an increase in the inflow of Calcium ions through these channels, contributing to the development of withdrawal symptoms such as seizures and craving.

4.4 Alcohol and other mechanisms of actions

Studies assessing cognitive functions have associated the chronic ingestion of ethanol with the reduction in concentration of acetylcholine in humans as well as mice, caused by the degeneration of brain tissues which seems to be related to the development of tolerance of alcohol. Chronic consumption of alcohol may affect opioid receptor system thus exerting neurobehavioral effects such as reinforcement. The three major classes of opioid system are μ, δ and κ. Alcohol may stimulate the release of certain opioid peptides such as endorphins and enkephalins, which in turn, could interact with the centers (mesolimbic dopamine pathway) of the brain, associated with reward and positive reinforcement and may lead to further alcohol consumption (Vengeliene et al., 2008). Human and animal studies have suggested that μ opioid receptor is mainly involved in initial sensitivity and response to alcohol. The increased activity of brain opioid peptide systems, in response to ethanol exposure, may be important for initiating and maintaining high alcohol consumption and for mediating the positive reinforcing effects of alcohol (Gianoulakis et al., 1996).

5. Genetic variants of neurotransmitters

Alcohol exerts its effects such as reward and reinforcement by acting on a number of neurotransmitter in the brain. Studies have revealed that polymorphisms in genes encoding for neurotransmitter may increase the risk of developing alcoholism (Radel & Goldman, 2001; Foley et al., 2006). The knowledge of gene variants affecting neurotransmitters is very important as it serves the basis for developing novel and targeted therapeutic agents in treatment of alcoholism. A few of the genetic variants of neurotransmitters associated with alcohol dependence are as:

5.1 Glutamate

Candidate gene studies have shown that individuals bearing G603A polymorphism of glial glutamate transporter gene (EAAT2) are at increased risk of alcoholism (Sander et al., 2000). The individuals with genetic variants of NMDA (subunit NR2A) and glutamate receptor metabotropic gene (mGLUR5) have been studied in a hospital based study in Germany (Schumann et al., 2008). It was found that carriers of the NR2A risk genotypes for rs2072450 CC and rs9924016 Del/Del had higher risk of developing alcohol dependence as compared to the individuals with protective genotypes rs2072450 AC and rs9924016 Del/Ins (Schuman et al., 2008). In the case of mGLUR5 gene, individuals of the risk genotypes rs3824927 C/C and rs 3462 G/G have been found to be at higher risk of developing alcohol dependence when compared with individuals bearing the protective genotypes rs3824927 CA and rs3462 GA.

5.2 Gamma amino butyric acid

Association of genetic variants of GABARA1 and GABAR6 with alcoholism has been reported in Korean population (Park et al., 2006).The GG genotype of GABAA1 receptor has been found to be significantly associated with early onset and severity of alcoholism in Korean population (Park et al., 2006). It has been also been reported that Pro385Ser substitution in GABA A6 is associated with alcohol dependence and with antisocial alcoholism (Sander et al., 1999).

5.3 Norepinephrine

Studies have suggested that alcohol produces biphasic effects on norepinephrine turnover in the brain, with low doses increasing turnover and higher doses depressing turnover. The sensitivity of noradrenergic systems to ethanol effects varies among brain regions. A few studies have been attempted to see the effect of genetic variants of norepinephrine on alcoholism. Huang et al. (2008) reported that norepinephrine transporter polymorphisms T-182C and G1287A are not associated with alcohol dependence and its clinical subgroups in Han Chinese population.

5.4 Dopamine

Research studies have revealed that there is a positive association between polymorphism in Dopamine receptor gene (DRD) with alcoholism. Ponce et al. (2008) reported that the two SNPs (-141C Ins/Del) and TaqI A, present on DRD2 gene locus were associated with alcoholism in North Indian population. Studies from South Indian population have reported no association between TaqI A polymorphism and alcoholism.

The -141 Ins/Del polymorphism in DRD2 gene has been found to be associated with alcoholism in several studies across different populations, but with inconsistent results. This promoter polymorphism plays a significant role in D2 receptor expression via altering the transcriptional activity. Johann et al. (2005) studied the association of -141I Del variant (-141C) SNP in German alcoholics. It was found that -141 Del C variant of DRD2 gene might be a protective factor against development of alcoholism. On the other hand the -141 Ins allele has been found to be a genetic risk factor for alcoholism in Mexican-Americans. This can be correlated with decreased DRD2 receptor density in alcoholic patients which in turn stimulates craving-reward pathway- thereby promoting alcoholism.

Another polymorphism in DRD2 gene Taq I A in Ankyrin repeat and Kinase Domain containing (ANKK1)(rs 1800497) is one of the most frequently studied mutations. The DRD2 gene is actually not located on DRD2 but rather within the protein coding region exon 8 of the adjacent ANKK1gene (Neville et al., 2004). TaqI A SNP causes an amino acid substitution within the 11th ankyrin repeat of the putative protein and has been found to affect the substrate binding specificity (Ponce et al., 2008). In a meta-analysis, the single nucleotide variant TaqIA (rs 1800497) of the DRD2 gene has been found as a vulnerability gene for alcoholism in more than 40 studies, but with conflicting results.

5.5 Serotonin

The genetic variants of serotonin receptor gene for example rs1042173 may influence alcohol dependence (Jhonsan et al., 2011). The presence of genetic variation may lead to

manipulation of serotonergic transmission therefore affecting the rate of development of tolerance and alcohol dependence (Yoshimoto et al., 1996).

5.6 Cholinergic and nicotinic receptor gene

Evidence from genetic studies suggested that alcohol dependence as well as cigarette smoking in families share the genetic vulnerability. Research studies have identified a missense mutation (rs16969968) in exon 5 of the nicotinic receptor (CHRNA5) gene and a variant in the 3′-UTR of the CHRNA3 gene in association with alcoholism and nicotine dependence (Wang et al., 2009). Cholinergic muscarinic 2 receptor (CHRM2) SNP (rs1824024) has been significantly associated with the pathogenesis of depression and alcohol dependence disorders (Jung et al., 2011; Luo et al., 2005).

5.7 Opioids

Bart et al. (2005) have identified positive association between A118G polymorphism and increased risk of alcohol dependence in individuals from Sweden. The single nucleotide polymorphism A118G in exon 1 of opioid receptor gene (OPRM1) results in increase in 3 fold binding capacity of beta endorphin. However, the results of a number of research studies are contradictory. Few studies have failed to find the association between the A118 G allele and alcoholism (Bergen et al., 1997; Franke et al., 2001; Gelernter et al., 1999; Kim et al., 2004; Kranzler et al., 1998; Schinka et al., 2002), while few others have found positive association between the A118 allele and alcoholism (Town et al., 1999). The explanations for these conflicting reports may be small sample size of the populations under study and the ethnic variation.

5.8 Other neurotransmitters (Neuropeptide Y)

In Humans, Leu7Pro polymorphism in NPY gene has been established to affect the release of mature NPY. Individuals with Pro7/Leu7 allele have 42% higher plasma concentration of NPY as compared with Leu7/Leu7 variant. Kauhanen et al. (2000) reported that Pro7allele is associated with more (34% higher) alcohol consumption in a cohort of Finnish middle aged men. Lappalainnen and others have reported that NPYPro7 allele significantly contributes towards the heritability of alcohol dependence in European American population (Lappalainnen et al., 2002).

6. Pharmacotherapy of alcoholism

The first step in the treatment of alcoholism is detoxification assisted by medical treatment (Wertheimer and Chaney 2003). Detoxification is required to manage the clinical and psychological symptoms of alcoholism. After detoxification there is need for counseling or psychotherapy and rehabilitation (Williams, 2001). The pharmacological agents or medicines in use for alcoholism treatment act on specific neurotransmitter systems. The treatment is aimed at normalizing the alcohol specific neuroadaptations (Krishnan-Sarin et al., 2008). The selection criteria for treatment of alcoholism is based on the length of illness and additional amount of alcohol related problems (Wertheimer &Chaney, 2003).

6.1 FDA approved drugs for treatment of alcoholism

Some of the drugs approved by FDA for treatment of alcoholism are as follows (Krishnan-Sarin et al., 2008).

6.1.1 Disulfiram

Disulfiram has been in use to treat alcoholism since 1940. Disulfiram produces an aversive effect by disrupting alcohol metabolism. The proposed mechanism of action of disulfiram on alcohol use has been found to be primarily related to the inhibition of liver aldehyde dehydrogenase (metabolizing enzyme of alcohol) and secondarily related to central nervous system actions, via modulation of catecholamine neurotransmission. It blocks ALDH activity by forming intermolecular disulfide bridges resulting in acetaldehyde accumulation. Excessive buildup of acetaldehyde results in many unpleasant effects including lowered blood pressure, palpitation, nausea, vomiting, headache and difficulty in breathing.

In clinical doses, disulfiram inhibits the enzyme dopamine–β–hydroxylase, which converts dopamine to norepinephrine, leading to increase in dopamine levels in brain (Goldstein & Nakajima, 1967; Goldstein et al., 1964). It has been found in clinical trials of disulfiram that there are lower rates of relapse to drinking in those who are compliant with the medication (Fuller et al., 1986). However, due to aversive nature of this drug, noncompliance is one of the biggest problems encountered with its use. The use of disulfiram is supervised in many clinical settings.

6.1.2 Naltrexone

Naltrexone is a drug used mainly for the treatment of alcohol dependence, and is available as oral medication and in injectable form. The drug is well tolerated with primary gastrointestinal side effects (O'Malley et al., 1992; Volpicelli et al., 1992). The efficacy of naltrexone in reducing alcohol drinking is mediated via interactions between the endogenous opioid system and dopamine systems, specifically through antagonism of the μ−opioid receptors. The studies on animal models suggested that alcohol increases release of β−endorphins in certain portions of the brain known to be involved in alcohol reward (Marinelli et al., 2003; Zalewska-Kaszubska et al., 2006). Nalotrexane blocks the release of these endorphins. Naltrexone has also been shown to reduce drinking in animal models (Froehlich et al. 2003; Swift, 2000).

A number of clinical trials indicate that alcoholics receiving naltrexone treatment in combination with behavioral intervention have lower levels of relapse and reduced levels of alcohol craving (O'Malley et al., 1992). Recent reports (Bouza et al., 2004; Srisurapanont & Jarusuraisin, 2002) suggest that naltrexone has modest efficacy in preventing relapse to drinking. Although, naltrexone is well tolerated, the potential risk of toxicity of liver at high doses is the major cause of concern in patients with liver disease.

6.1.3 Acamprosate

Acamprosate is available in an oral, delayed release formula, Camprel. The mechanism of action is through antagonizing of the N-methyl D-aspartate (NMDA) glutamate receptor site or via modulation of glutamate neurotransmission (DeWitte et al., 2005; Harris et al., 2002).

It has been found that acamprosate reduces neuronal hyperexcitability during alcohol withdrawal, due to reductions in glutamate levels, so as to normalize the balance between excitatory and inhibitory neurotransmitters produced in chronic alcohol consumption (Spanagel et al., 1996; Dahchour et al., 1998; Littleton & Zieglgansberger, 2003).

6.2 Other promising medicines

In addition to the drugs approved by FDA for treating alcoholism there are other medications which are in use because of some clinical evidence of efficacy.

6.2.1 Ondansetron

Ondansetron is a 5HT3 receptor antagonist used mainly as antinausea medicine after postoperative nausea and as anticraving medicine in alcoholism. Human laboratory studies have demonstrated that ondansetron decreases alcohol preference and desire to drink (Johnson et al., 1993). The efficacy of ondansetron in reducing drinking behavior has also been reported in Clinical trials, especially in drinkers with early onset alcoholism (Kranzler et al., 2003).

6.2.2 Baclofen

Baclofen, a GABA B receptor antagonist is used clinically for the treatment of muscle spasticity. The preclinical trials have shown the effectiveness of baclofen in reducing chronic alcoholism (Colombo et al., 2004). In a recent clinical trial, it was found that the drug is well tolerated in alcohol dependent patients with liver cirrhosis and has some efficacy in improving abstinence rates. However, more clinical research is needed to establish its efficacy and tolerability in alcoholic patients.

6.2.3 Topiramate

Topiramate is an antiseizure medication which has been shown to be effective in reducing alcohol use in recent clinical trials. Its action is mediated via antagonizing α amino-3-hydroxy 5-methylisoxazole 4-propionic acid (AMPA) and kainate glutamate receptors as well as inhibition of GABA A receptors, L type calcium channels, and voltage dependent sodium channels (SCN). Topiramate has been shown to reduce alcohol use in animal models (Farook et al., 2007). It also helps in reducing alcohol withdrawl induced convulsions. It has some side effects such as numbness, anorexia, cognitive difficulty, and taste distortion, as well as some rare incidents of visual side effects including myopia, glaucoma, and increased intraocular pressure. The clinical trials used a slow titration over several weeks to the desired dose to reduce the incidence of side effects.

6.2.4 Selective serotonin reuptake inhibitors (SSRI)

Selective serotonin reuptake inhibitors such as fluoxetine, citalopram, and sertraline are used in the treatment of alcoholism because existing evidence has shown that lowering brain serotonin levels decrease preference for alcohol and SSRI. SSRI's are basically used in the treatment of depression, therefore the effectiveness has been found in depressed alcoholics in some clinical trials.

7. Pharmacogenetics of alcoholism

The sequencing of the human genome has become the foundation for one of the most significant scientific contribution, the idea that although all human individuals are genetically similar, each retains a unique genetic identity. The publication of the human blueprint has triggered an explosion in pharmaceutical research to utilize this knowledge in the prescription of drugs for various ailments including alcoholism to be tailored according to the genetic makeup of susceptible individuals or in other words personalized medicine.

Just before half a century ago the Human Genome Project, scientists had realized that inheritance was an important factor which accounts for individual variation in drug response (Kalow, 1962; Venter et al., 2001). This led to the birth of the term Pharmacogenetics. Pharmacogenetics is the study of the role of inter-individual genetic variation in drug response. Although human beings are 99.9% similar in their genetic makeup, 0.1% variability in terms of single-nucleotide polymorphisms is significantly accountable for an individual's susceptibility to diseases and inter- and intra-individual variation of drug response (Brooks, 1999).

On the basis of our current understanding of neurobiology numerous candidate genes have been implicated in the etiology and response to treatments for different addictions including alcoholism. The focus is on functional genetic variants of proteins involved in the neural response to alcohol including alcohol sensitivity, reward and tolerance and variants of the enzyme involved in metabolism of alcohol.

8. Genetic predictors of medication response

The inter-individual variation in drug response results in categorization of alcoholic patients into responders and nonresponders. The responders experience therapeutic efficacy with a particular drug given in therapeutic range without any toxicity or adverse effects. The nonresponders do not show any therapeutic effect, even when the administered drug reaches to peak level in blood, leading to ineffective treatment, known as poor as poor metabolizers. Therefore the traditional approach of one dose fits for all is no longer helpful in predicting the therapeutic efficacy of a drug. The pharmacogenetics focuses on identifying genetic factors that is with are responsible responsible for variability in pharmacotherapeutic effect both in terms of pharmacodynamics and efficacy (Evans &Johnson, 2001). The field has greatly benefitted from advances in molecular genetic tools, developments in bioinformatics and functional genomics for identifying genetic variants.

Genetic factors can account for interindividual differences in drug toxicity and efficacy in many ways e.g. the variability in genes may lead to differences in drug metabolism and disposition through functional differences in activity of enzymes or drug transporters (Ray et al., 2010a). Alternatively genetic variation may impact a drug's target such as particular receptor. Genetic variants that may modulate the effects of naltrexane have been identified in the gene coding for μ OPRM1, which is the primary target of naltrexaone (Oslin et al., 2003). One of the most widely studied SNPs in OPRM1 is +118A/G (rs 1799971) located in the +118 position of exon1 one which encodes for Asn40Asp substitution (Bond et al., 1998). This A/G substitution has been reported to affect the receptor affinity for endogenous ligands, β-endorphin leading to gain in function such that the G variant was thought to bind β-endorphin with greater affinity than A allele. However, some recent studies have shown

that G allele has a loss of function rather than a gain. Further, the results of the study testing the relationship between this SNP of the OPRM1 gene and alcoholism have shown inconsistent results, some support the association of this SNP and alcohol dependence while others have failed to replicate this association (Schinka et al., 2002; Kranzler et al., 1998; Town et al., 1999). Further, this SNP of OPRM1 gene has also been associated with a differential response in clinical trials of naltrexone. Oslin et al. (2003) has reported that this SNP is associated with clinical response to naltrexaone among alcohol dependent patients such that individuals with at least one copy of the G allele, coding for more potent OPRM1 receptor reported lower relapse rates and longer time to return to heavy drinking after treatment with naltrexone, in comparison with individuals who were homozygous for the A allele.

It has been reported that persons of Asian descent possess an ALDH2*2 genetic variant (Quertemont et al., 2004). ALDH2*2 genetic variant of the ALDH enzyme metabolizes slowly and leads to accumulation of acetaldehyde (Edenberg, 2007). When the individuals bearing this variant drink alcohol they develop high acetaldehyde blood concentration and experience of flushing reaction similar to that seen in combination of ethanol and disulfiram. ALDH2*2 variation is the best characterized genetic factor protecting against the development of alcohol dependence. Pharmacogenomic studies suggest that it is highly unlikely that disulfiram will be helpful in treating the patients who have genetically compromised ALDH.

In addition disulfiram chelates copper and thus inhibits copper containing enzyme dopamine beta hydroxylase which further inhibits norepinephrine and dopamine in brain (Haile et al., 2009). The individuals harboring TT allele of dopamine beta hydroxylase (DβH) gene with C1021T polymorphism respond better to disulfiram treatment and need less dose whereas carriers (CT) would need intermediate dose and those with CC allele need maximum concentration to reach the efficacy level.

Acamprosate, is a drug used for abstinence and maintenance as it reduces craving in alcoholic patients who have undergone detoxification (De Witte et al., 2005). The effective acamprosate response in alcohol dependent subjects may be influenced by genetically controlled variation of NMDA receptor and the type of glutaminergic mGLU5 receptor. Confirmation of this hypothesis could lead to development of effective individualized treatment and recommendation for alcohol dependent patients based on pharmacogenetically relevant genetic variant.

Ondansetron, an antagonist of serotonin is important in the treatment of alcoholism. Serotonin transporter gene is an important regulator of neuronal 5-HT's function. The genetic difference in this gene may modulate the severity of alcohol consumption and predict the therapeutic response to 5-HT3 receptor antagonist ondansetron. A variable tandem repeat polymorphism (5-HTT LPR) is common in the promoter region of 5-HTT gene which alters the transcriptional activity. Two important variants are long (insertion LL) and short (SS) version. It has been reported in a randomized clinical trial that individuals with LL genotype (Homozygous for the long version) of 5-HTT gene showed significant results in improvements of alcoholism with treatment of ondansetron as compared to LS and SS genotype (Johnson et al., 2011).

Another functional T/G polymorphism (rs1042173) as in the 3/ untranslated region of the 5-HTT gene may alter the therapeutic response in alcoholism treatment with ondansetron in

alcohol addiction treatment (Jhonsan et al., 2011). The effect of ondensateron will be higher in individuals possessing the combination of LL genotype and TT genotype of 5-HTT gene.

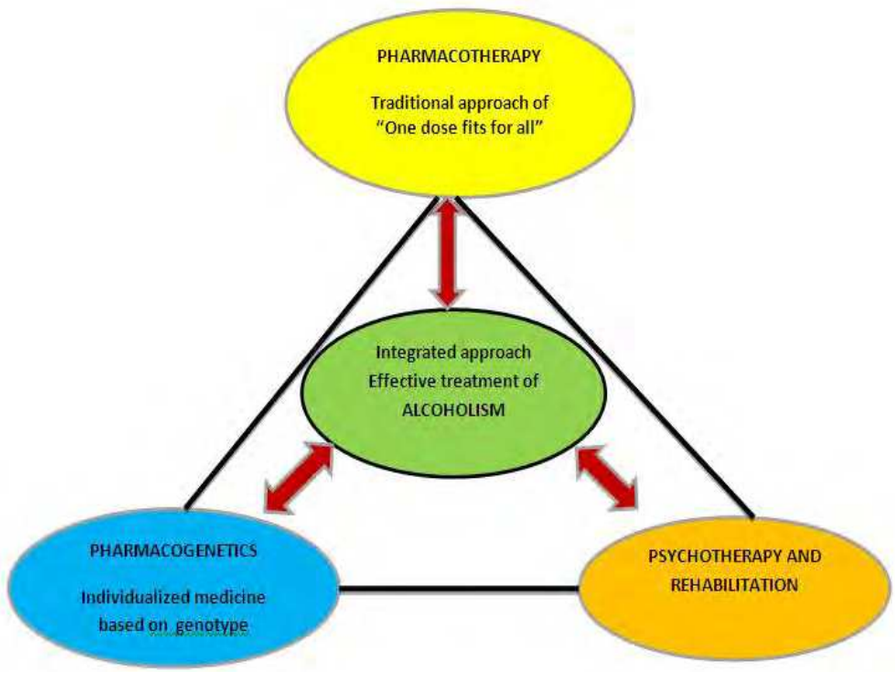

Fig. 2. Alcoholism Treatment: A Treatment approach to use a trio of Pharmacotherapy using pharmacological agents, where a traditional approach of "One dose for all" is used and Psychotherapy – an important part of treatment in alcoholism and Pharmacogenetics based on Genetic makeup of the Individual for better and effective treatment in alcoholism

9. Conclusion

Lot of work still needs work still needs to be done in order to improve our understanding of the genetic and environmental factors underlying alcohol dependence and also utilizing the genetic information in prescribing the drugs as per the genetic architecture of the individuals. The integrated approach of incorporating a trio of pharmacogenetic, pharmacotherapy and psychotherapy would be more promising in treatment of alcoholism (Fig 2). As the genetic testing becomes more common in the practice of medicine variety of ethical and practical challenges unique to alcohol addiction, will also need to be addressed.

10. References

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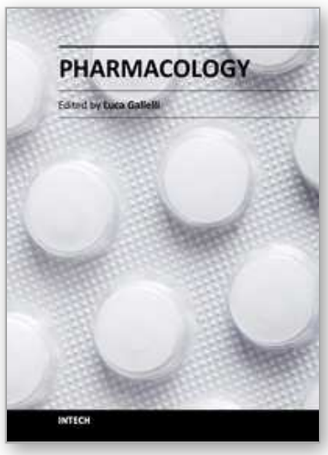

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The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

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