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Critical Review of Alcohol, Alcoholism and the Withdrawal Symptoms I. Mechanisms of Addiction and Withdrawal Syndrome

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Abstract

Alcoholic beverages are socially accepted around the world, consumed mostly to socialize, celebrate, and relax. The pleasant effects of alcohol are attributed to (i) an increase in $GABA_{ergic}$ (inhibitory signals), OP_{ergic} and $5HT_{ergic}$ (euphoric effects) neuronal activities and (ii) a decrease in DA_{ergic} ('want' signal or craving), Glu_{ergic} (excitatory signals),NE_{ergic} (stress signals) neuronal, and the HPA axis (stress hormones) activities. If alcohol drinking continues, the receptors are sensitized, resulting in development of tolerance when alcohol drinking must be increased to achieve desired effects. In *genetically/Environmentally predisposed* subjects, chronic alcohol drinking results in the development of addiction, characterized by a condition when alcohol caseation results in rapid onset of withdrawal symptoms including, but not limited to, alcohol craving and moderate to severe discomfort. Because pharmacotherapy alone or in combination with behavioral approaches is only modestly effective in treating alcoholism symptoms, there is an urgent need to development effective and safe therapies. At present, a lack of clear understanding of the mechanisms underlying addiction hinders possible development of new treatment strategies. Therefore, the aim of this article is to discuss the mechanisms underlying (i) the euphoric, relaxing and adverse effects of alcohol drinking and (ii) addiction and the withdrawal symptoms.

Keywords

Acetaldehyde, Alcoholism, Addiction, Epigenetic, Ethanol, Genomics, Herbal therapy, Pharmacogenomics, Pharmacotherapy, Tolerance, Withdrawal

Introduction

Alcoholic beverages are socially accepted drinks, expected to bring pleasure, satisfaction, and relief from stress [1]. In general, most people drink alcohol responsibly, but, continued drinking may serves as a prelude to alcohol abuse and an escape route for social, personal or career pressures [2]. In the presence of a genetic predisposition and environmental cues, persistent drinking may result in the development of tolerance and addition or alcoholism (defined as a cluster of behavioral, cognitive, and physiological abnormalities developing after repeated alcohol use and resulting in a physical withdrawal state upon abstinence) that may interfere with a person's ability to function normally and impairing his/her daily life [3]. Abnormal alcohol drinking may also be an important risk factor for a number of diseases such as infection, cancer, atrial fibrillation, hypertension, etc [4-17]. In the United States alone, about 17 million people of different age suffer from alcoholism [18]. Thus, alcoholism may exert tremendous economic consequences not only for the drinking individuals, but also for the society at large [19-21]. The journey from responsible alcohol drinking to alcoholism involves four stages listed in Table 1.

The transition from the responsible use of alcohol to an excessive, uncontrolled alcohol consumption (alcohol addiction) results from a complex neuro adaptations involving various excitatory and inhibitory pathways in different brain regions. In alcohol-naïve subjects, the adaptation pathways such as aversive hangover response may keep the social intake of alcohol in check, while, in subject practicing abnormal alcohol drinking, the neuro adaptations in the brain may cause behavioral transitions, resulting in uncontrolled alcohol drinking [22]. Although, there are compelling evidence in support of causal relationship between the

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Table 1: The journey from responsible alcohol drinking to alcoholism-stages and possible mechanisms [22,195,196].

Stages of alcohol addiction	Possible mechanisms discussed in the review
Acute phase positive reinforcement	Rising BAC, dopamine, opioid, GABA and serotonin receptors
Negative reinforcement	Falling BAC, glutamate, NMDA and GABA receptors, and receptor/voltage gated Na^+ channels.
Hangover/Tolerance craving	Alcohol metabolism, acetaldehyde accumulation, excitatory neurotransmitters, inflammatory signaling, serotonin receptors
Alcohol addiction	Adenosine, dopamine, serotonin, GABA and glutamate receptors.
Withdrawal symptoms	NMDA/Glutamate receptors, GABA, hyper-excitation, seizures.

Table 2: Inclusion and exclusion criteria for literature search.

Inclusion criteria	Exclusion criteria
Years searched: 1990 to present. Back volumes were searched if cited in the manuscript.	Review articles (listed for information only), case reports.
English language articles.	Non-English language articles.
Human populations diagnosed as addicted-imaging and blood-chemistry studies.	Therapeutic studies in humans or animals.
Animal studies-BAC toxicokinetics, acute and chronic alcohol drinking, alcohol consumption as primary outcome, behavioral abnormalities.	Studies with insufficient number of animals or animals exposed to non-alcohol drugs (opioid addiction may be included in limited cases).
Animal brain studies-whole animal imaging, stimulatory and inhibitory signaling, genomics, proteomics, metabolomics, epigenetics and alcohol metabolism at different stages (acute euphoric effects, tolerance, and addiction and withdrawal) of alcohol abnormalities.	Secondary analyses of randomized control trials in which the major outcome of interest was not alcohol consumption.
In vitro studies using animal tissue (neural and non-neural) or cell line samples exposed to ethanol for characterization of cell-signaling, gene expression, epigenetics and alcohol metabolism.	*In vitro* studies using animal tissue (neural and non-neural) or cell line samples exposed to non-alcohol drugs.

adaptive changes occurring in the brain (genomic changes, epigenetic modifications and changes and gene-environment interactions) and the development of alcohol's rewarding, aversive, addiction, and other alcohol-related effects, an integrated and unified mechanisms for these alcohol-related abnormalities are lacking. This gap may be hindering development of effective and safe medications to treat alcoholism and other alcohol-related disorders. Therefore, the aim of this review article is to critically evaluate the research papers published in the area of alcohol's euphoric effects and addiction, and then propose possible mechanisms underlying each stages of alcohol drinking disorders discussed above.

Literature Search Methodology

Overall literature search approach described by Meline [23] was used. Initial searches were performed on the following literature database: MEDLINE, Google Scholar and Web of Science using search words either alone or tagged with qualifying words. Some examples are listed below:

i. *Alcohol drinking* tagged with statistics, social, abnormal, gender, age, tolerance, addiction, blood alcohol concentrations (BAC), etc.

ii. *Alcohol dehydrogenases or ADH* tagged with genetic polymorphism, alcoholism, tolerance, demographic (Asians, Indians, Caucasians, Africans, etc.), acetaldehyde, acetaldehyde dehydrogenase-ALDH, blood alcohol concentration-BAC, etc.

iii. *Alcoholism or alcohol addiction* tagged with uncontrolled drinking, statistics, demographics, tolerance, brain pathways (dopamine, opiates, GABA, glutamate, NMDA, serotonin, adenosine), brain regions, abstinence, withdrawal syndrome, etc.

Other search words were tolerance, dependence, craving, genomics, epigenetics, hangover, etc. The initial results were subjected to certain inclusion and exclusion criterion listed in Table 2 and an example is shown in Table 3.

Acute Alcohol Intake, Blood Ethanol Concentrations and Alcohol's Positive/Negative Reinforcements

This section describes the possible mechanisms for the pleasant and aversive effects of acute alcohol drinking in people practicing responsible drinking. Acute alcohol drinking results in a rapid increase, followed by a gradual decrease (Figure 1) in the blood alcohol concentrations (BAC). The euphoric/pleasant effects correlated with the rising phase of BAC, while the falling phase of BAC correlated with a transition from rewarding effects to unpleasant and depressing effects [24,25]. During the ascending BAC phase, the brain's reward pathways are activated, while during the desending phase, the brain's aversive and pain patheays are activiated (Figure 2).

Mechanisms of alcohol's euphoric effects during rising BAC

Table 3: Literature search strategy.

Selection steps • Search topic: Alcohol dehydrogenase • Database: PubMed • Years: 1990-2014	Search result	
ADH	7017	
ADH + genetic polymorphism (GP)	721	
ADH + GP + alcoholism (ALC)	187	
ADH + GP + ALC + Asian population	23	
+ African American	7	
+ Japanese	28	
Applying inclusion criteria for ADH + GP result n = 721		
Reductions	*Criteria not met (n)*	*Remaining (n)*
Inclusion criteria not met	310	411
Design, statistics language issues	210	201
Comparison groups/outcome not clear	97	104
Full article not available	14	90
Demographic distribution	*%*	
Total remaining n = 90		
Asian population (- Japanese and Indian)	28	
Japanese population	32	
Indian population	11	
African American	9	
American Indians	8	
Caucasians	12	

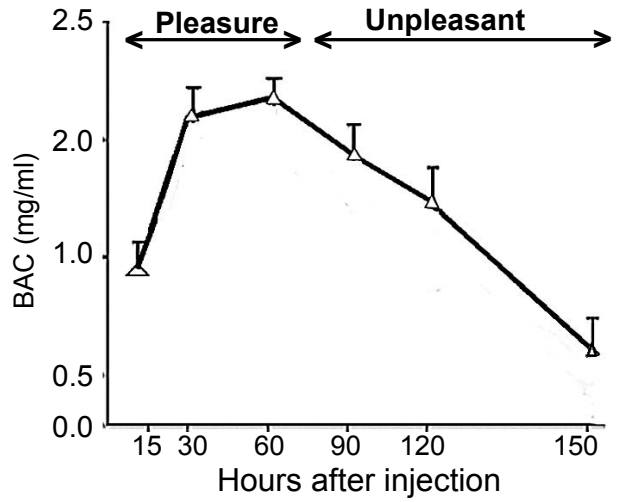

Figure 1: Blood alcohol concentrations (BACs) in alcohol injected P rats (2.5g/kg dose of ethanol): The ascending phase is associated with the pleasure effects, while the descending phase is associated with the unpleasant effects of alcohol intake (unpublished data from author's laboratory).

The rising BAC activates the rewarding pathways that further (i) activates the synthesis and release of of β-endorphin, (ii) inhibits $GABA_{ergic}$ neurons and (iii) activates orbitofrontal (OFC) cortex [26,27]. A decrease in $GABA_{ergic}$ signaling disinhibits DA_{ergic} neurons, while an increase in β-endorphine activated DA_{ergic} neurons, resulting in releases DA. β-Endorphin and DA activate the Hedonic hot spotes and ensuing sensory pleasures. DA also induces serotonin (5-HT) levels that induces enkephalin release. DA and enkephalin together may further inhibit $GABA_{ergic}$ neurons and initiate alcohol 'craving'. Activagtion of the Hedonic hot spotes and OFC may develop a conditioned response. The 'stimulatent' effects of alcohol may be mediated via release of norepinephrine (NE) from adrenergic neurons and corticosteroids via the HPA axis [28-31]. As shown in Figure 3, $GABA_{ergic}$, $ACh_{ergic,}$ Glu_{ergic}, $5\text{-}HT_{ergic}$ and NA_{ergic} activities, directly or indirectly, are dynamically regulated via the NMDA receptors present on $GABA_{ergic}$, $5\text{-}HT_{ergic}$ and NA_{ergic} neurons [30,31]. Glu may regulate DA, opioid peptides, GABA, glutamate and 5-HT concentrations that mediates alcohol reinforcement by differentially modulating the $GABA_{ergic}$ neurons. During the rising phase of BAC, the rewarding effects of alcohol drinking may also be associated with an inhibition of NMDA and DA receptors and HPA axis [30,31].

Mechanisms of alcohol's aversive effects during declining BAC

The descending phase of BAC, as shown in Figures 2,

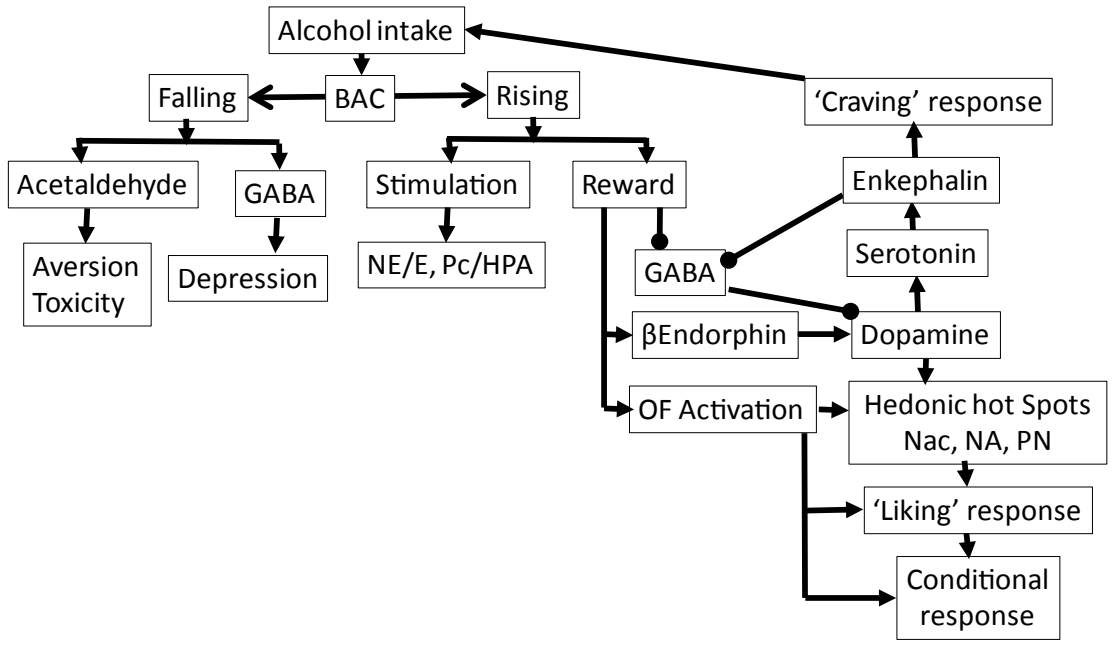

Figure 2: Schematic illustration of possible mechanisms underlying the biphasic effects of BACs: During the rising phase of BAC, the brain's reward (PFC, VTA and ANc) and the stimulatory (Pc, HPA) sites are activated, resulting in release of β-endorphin, inhibition of $GABA_{ergic}$ neurons and activation of orbitofrontal (OFC) cortex. A decrease in $GABA_{ergic}$ signaling disinhibits DA_{ergic} neurons, while an increase in β-endorphine activates DA_{ergic} neurons that release DA. β-Endorphin and DA activate the Hedonic hot spots and induce sensory pleasures. DA also induces serotonin levels that induce enkephalin release. DA and enkephalin together may further inhibit $GABA_{ergic}$ neurons and initiate alcohol 'craving'. Activation of the Hedonic hot spots and OFC may develop a conditioned response. The 'stimulant' effects of alcohol may be mediated via release of norepinephrine (NE) from adrenergic neurons and corticosteroids via the HPA axis. The 'falling' phase of BAC is characterized with the aversive and depressive effects mediated by an increase in acetaldehyde concentration or an increase in $GABA_{ergic}$ activity, respectively. These pathways are discussed in detail later in the article.

is characterized by an increase in acetaldehyde that (1) deactivates the NMDA receptors, resulting in an attenuation of $GABA_{ergic}$-mediated neuroinhibition and (2) react with DA and synthesized salsolinol that is shown to depolarize and disinhibit DA_{ergic} neurons, decrease $GABA_{ergic}$ activity and enhance nitric oxide production [32,33]. Thus, acetaldehyde and salsolinol together may participate in development of alcohol-related negative reinforcement. In addition, the aversive response of the declining phase of BAC may block the rewarding effects as described below [34].

Hangover and Tolerance

Hangover (a feeling of general misery comprising of drowsiness, concentration problems, dry mouth, dizziness, gastro-intestinal complaints, sweating, nausea, hyper-excitability, and anxiety) is always associated to acute alcohol intoxication and/or heavy episodic drinking [35-37]. In addition to unpleasant feeling, hangover also has several social and clinical negative consequences such as work and academic absenteeism and neurocognitive impairments [38-40]. Tolerance is defined as a person's diminished euphoric response to alcohol when used repeatedly over time. As tolerance develops, person may need relatively higher quantity of alcohol to achieve the same level of response achieved initially. While hangover keeps a check on alcohol drinking, tolerance motivates people to drink more for desired effects. The following sections discuss the mechanisms underlying hangover and tolerance.

Hangover

Although possible mechanisms underlying development of hangover are not fully understood, earlier studies have proposed possible roles of dehydration [41-44], hypoglycemia [45], acetaldehyde accumulation [46-52], pro-inflammatory cytokines [53] and neuro-stimulation [54] in the development of hangover (Figure 4).

Tolerance

Three basic types of tolerance have been described in literature [55].

- *Cellular tolerance* occurs at the level of a neuron or a network of many neuronal and supportive cells including astrocytes and glial cells,
- *Molecular tolerance* involves adaptation processes developed by individual molecules (e.g., ion channels) during exposure to ethanol and,
- *Behavioral* tolerance that involves the level of the activity of an entire animal.

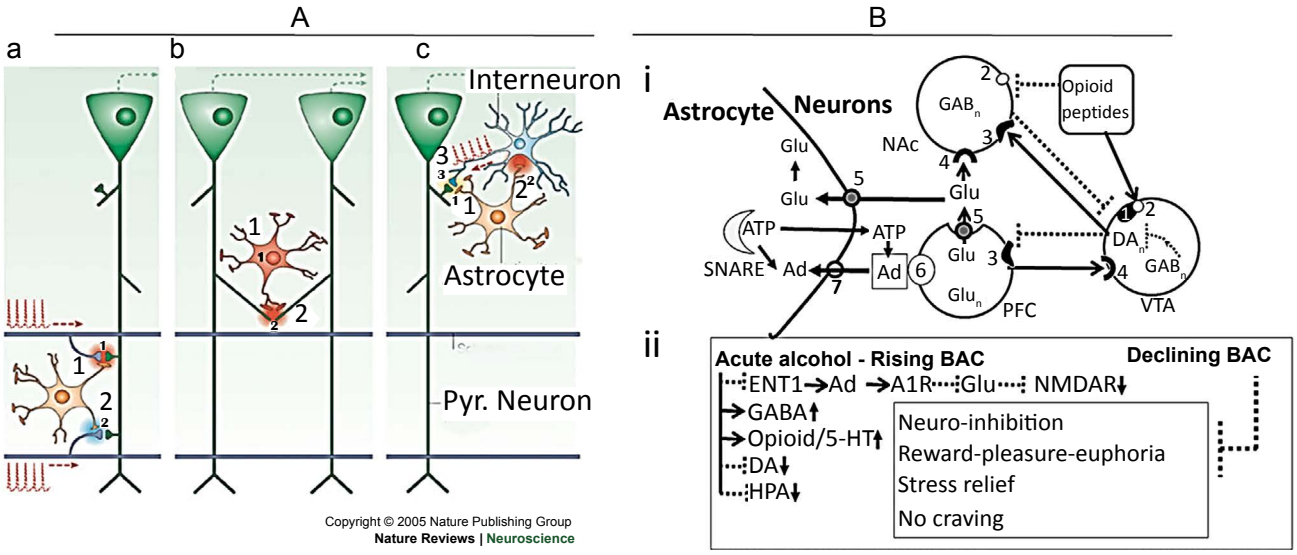

Figure 3: Schematic illustration of interaction between astrocyte and neuronal circuits associated with ethanol's rewarding effects.

A: Although neurons and synapses play a key role in the brain's physiology and pathology, astrocytes can generate various regulatory signals and bridge neuronal, vascular system and networks that are otherwise disconnected from each other **(a)** Glu (1: red spot) released from stimulated neurons stimulates an interposed astrocyte which releases ATP that is hydrolyzed into adenosine (2: blue spot), which suppresses a different SC (Schaffer collaterals) - PN (pyramidal neurons) connection through the activation of a presynaptic A_1 adenosine receptor; **(b)** Bridging non-directly connected neuronal circuits. Spontaneous oscillations in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in an astrocyte (1) trigger glutamate release (2: red spot), which is sensed simultaneously by two contiguous PNs. This leads to the generation of synchronous NMDAR-dependent excitatory currents; **(c)** Feedback synaptic modulation. GABA that is released (1: yellow spot) by repetitive firing at GI (GABA interneurons)-PN synapses activates $GABA_B$ (GABA type B) receptors on a neighboring astrocyte, which responds by releasing Glu (2: red spot) onto the GI. This causes feedback potentiation of the GI's inhibitory drive (3) on the PN. [Volterra and Meldolesi, 2005, with permission].

Bi: Astrocyte-neuron signaling associated with blood alcohol concentrations (BAC)**.** Adenosine (Ad), released by astrocytes directly or via ATP hydrolysis, binds to the Ad receptors (B6) on PFC's Glu_{ergic} neurons and induce Glu release. Glu binds to and modulate the NMDA receptors (B4) on GABAergic (in NAc and VTA) and DA_{ergic} (in VTA) neurons. Glu is also transported into the astrocytes via Glu transporter (B5). Opioid peptides induce DA_{ergic}, but inhibit $GABA_{ergic}$ neurons. Solid line: direction and/or positive effects, broken lines: negative effects.

Bii: Alcohol, during the rising phase (i) activates binding of Ad (either from ATP or transported via ENT1) to AdR that inhibits the NMDAR activity; (ii) upregulates $GABA_{ergic}$, OP_{ergic} and $5\text{-}HT_{ergic}$ neurons, and (iii) inhibits DA_{ergic} neurons and the HPA axis. This results in overall neuro-inhibition, reward effects and stress relief. As the BAC begin to decline, the neuronal state shifts from inhibition to excitation and stress relief to anxiety, resulting in alcohol craving.

Abbreviations*:* NAc: nucleus acumbens; PFC: prefrontal cortex; VTA: the ventral tegmental area; A(−): alcohol's negative effects; A(+): alcohol's positive effects; A(±): positive and negative effects; GAB_n: $GABA_{ergic}$neurons; DA_n: $dopamin_{ergic}$ neurons; Glu_n: $Glutamine_{ergic}$neurons;

1. GABA receptors; 2. μ or κ opioid receptors; 3. dopamine (DA) receptors; 4. Glu receptor (AMPA, NMDA or mGluR); 5. Glu transporter; 6. adenosine receptors; 7. Equilibrative Nucleoside Transporter 1 (ENT1).

Alcohol tolerance can also be classified as acute, rapid, and chronic, based on how long after exposure to alcohol tolerance develops. Possible molecular mechanisms proposed to explain the development of different types of tolerance are shown in Figure 5.

Development of Alcohol Addiction or Alcoholism

Many scientific studies have shown that children of alcoholics are about four times more likely than the general population to develop alcoholism, suggesting an important role of genetic factors in development of alcoholism [56-59]. However, studies have also shown that genetic factors are not the sole determinant of the development of alcoholism, the environmental (social, parental and peer) factors may also be involved (Figure 6) [60-62]. This is because the environmental factors they may either increase susceptibility for developing an alcohol use disorder or attenuate possible genetic risk by producing a level of protection for vulnerable individuals (Figure 6 inset) [63].

In this section, participation of genetic and environmental factors in development of alcoholism will be discussed in detail.

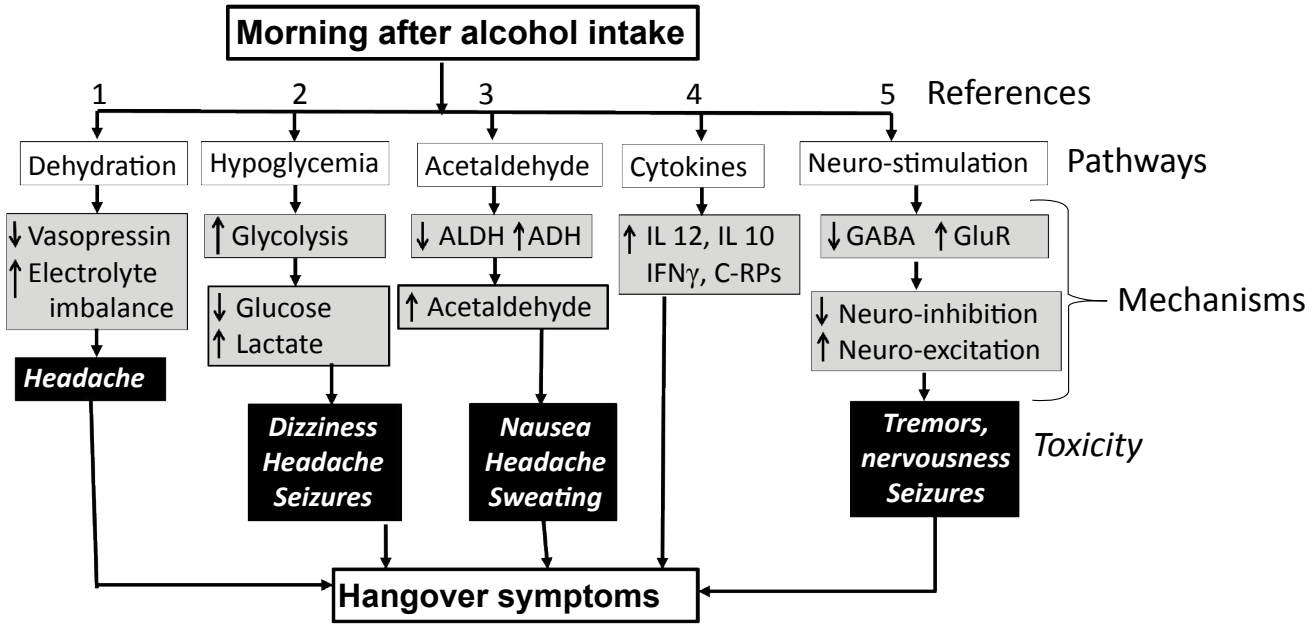

Figure 4: Possible mechanisms underlying alcohol related hangover [41-54].

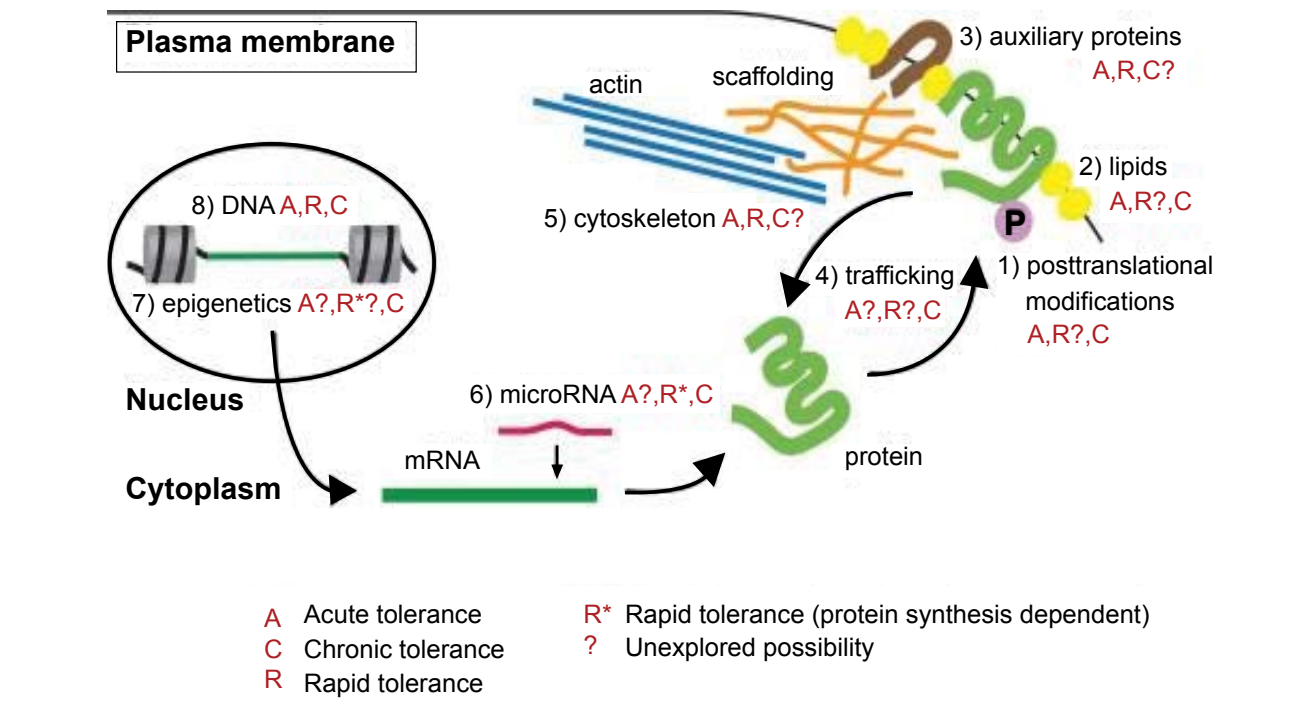

Figure 5: Mechanisms for development of alcohol tolerance.1) Posttranslational modifications of existing channels (mainly phosphorylation), 2) Interactions with the lipid microenvironment, 3) Interactions with auxiliary proteins (e.g., regulatory subunits) of channels, 4) Trafficking of channels to and from the cell surface, 5) Cytoskeleton reorganization, 6) Epigenetic cytoplasmic mechanisms (e.g., microRNA regulation) of channel message stability and 7) Epigenetic nuclear mechanisms (e.g., chromatin remodeling) and 8) genetic factors [55].

Genetic/Epigenetic predisposition to alcoholism

The evidence for genetic predisposition arises from studies involving the 'twins' of alcoholic parents that are more susceptible to develop alcoholism than children of normal parents, even when they were adopted and brought up in different environment (one adaptive parent abused alcohol while the other did not) [61-64]. Several important polymorphs associated with alcoholism predisposition have been identified (Table 4). The μ-opioid receptor A 118 G (OPRM1) having Asn40Asp SNP has been studied extensively, however, the results have been controversial. Some studies support an association between A 118 G (OPRM1) and addiction [65-68], while other studies do not [69-72]. Ray, et al. [73] showed that Asp40 carriers in adolescents

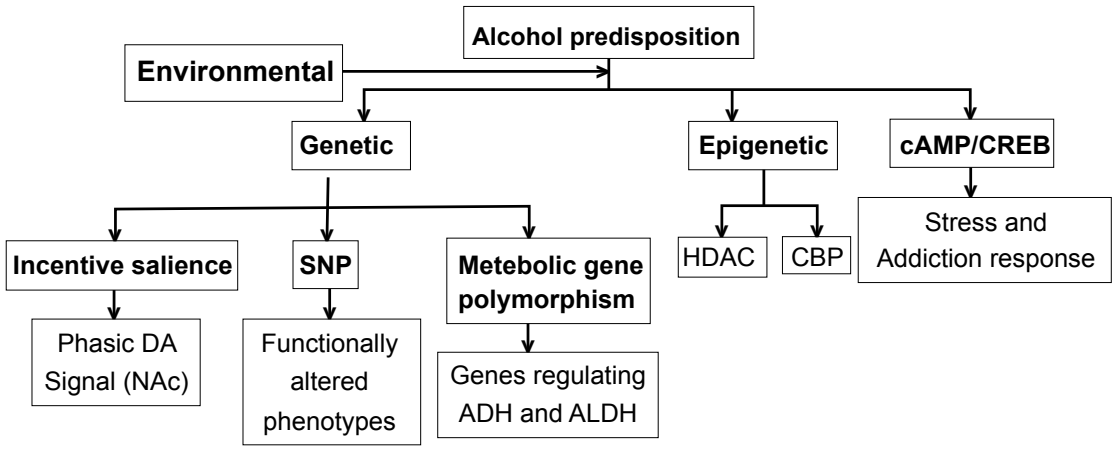

Figure 6: Genetic and epigenetic predisposition to alcoholism. The predisposed people initiate unique genetic, epigenetic and cAMP/CREB mediated responses, resulting in development of addiction.

Abbreviations: ADH: alcohol dehydrogenase; ALDH: acetaldehyde dehydrogenase; CREB: cAMP response element-binding protein; CBP: CREB-binding protein; DA: dopamine; NAc: nucleus accumbens; HDAC: histone deacetylase; SNP: single nucleotide polymorphism.

Table 4: Genetic polymorphs associated with alcohol predisposition. [74] NIH open access.

Receptor transporter	Allele	Reference
COMT	Val 158 Met	[194]
GABA R3	-181 allele/1519 T > C GABAR - Aα	[195]
5-HTR	5-HTR 2A-1438 A, -T 102 C	[197]
DAR1	Halotypesrs 686 T and rs4532 G	[198]
DAR2	Taq A1 allele A1/A1 and A1/A2	[199]
DAR3	1-C-G-A2/1-C-A-A2	[200]
DAR4	-521/C > T polymorph, 7R VNTR	[201,202]
DAT1	7R > 9R/10R	[203]
MAO	MAO-A uVNTR	[204,205]
μ Opioid	A 118 G (OPRM1)/C 17 &	[71]

may mediated the association between *OPRM1/Asp40* genotype and alcoholism and that a significantly higher frequency (51.9%) of the Asp40 allele occurred among youth with alcohol-related disorder (ARD), as compared to non-ARD controls (16.3%). In addition to genetics, earlier studies have also provided strong evidence for epigenetic predisposition to addiction in people who have higher probably to develop addiction upon chronic alcohol drinking [74-79].

Li, et al. [80] analyzed data using a linkage association in chromosome regions of addiction and identified 1,500 addiction-related genes and five molecular pathways (neuro-active ligand-receptor interaction, long-term potentiation, GnRH signaling pathway, MAPK signaling pathway and gap-junction pathways) that were significantly enriched for alcoholism. They connected the common pathways into a hypothetical common molecular network for addiction. As shown in Figure 7, fast and slow positive feedback loops were interlinked through CAMKII, which may provide clues to explain some of the irreversible features of addiction. Activation of CAMKII may play a central role in the development and maintenance of addiction states. The fast and slow positive feedback loops interlinking through CAMKII may be essential for the development and consolidation of addiction.

Pandey and collogues [81-90] have provided compelling evidence that innate anxiety levels are important in initiating craving for ethanol consumption [91]. Predisposition to anxiety might alter the acquisition or expression of incentive salience for alcohol via the following pathways:

i. Dopamine receptor (DR) pathways for phasic (short term) and tonic (long term mediated by catechol-O-methyl transferase, Val 158 Met polymorph) DA release in NAc and PFC, respectively [91], and

ii. Cannabinoid receptor 1 (*CNR1*), *C* allele of rs2023239 in the PFC [92].

According to the incentive salience theory of addiction [92], repeated exposure to addictive drugs including alcohol can, in susceptible individuals and under particular circumstances, persistently change brain cells and circuits, a psychological process involved in motivated behavior (Figure 8). Individuals with the DR Val158Met

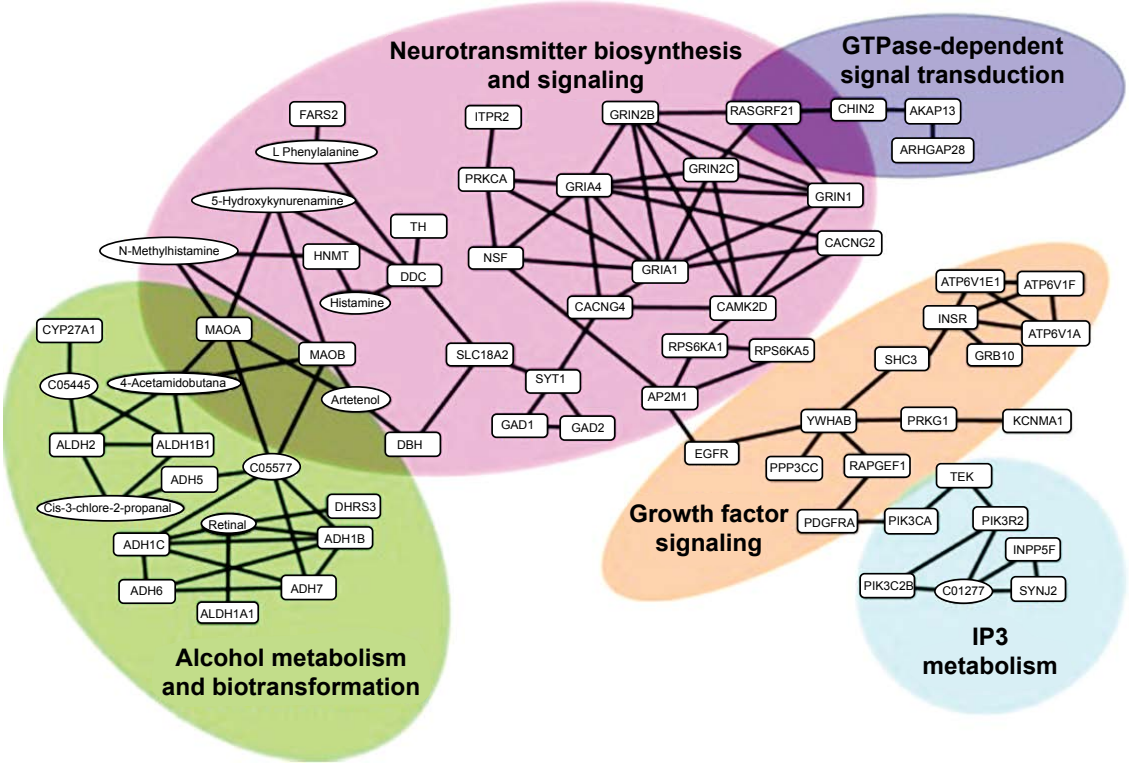

Figure 7: Interactive network of candidate genes in networks that were significantly enriched ($P < 0.005$) for alcohol metabolism and biotransformation, inositol triphosphate metabolism, neurotransmitter biosynthesis and signaling, growth factor signaling and GTPase-dependent signal transduction. For abbreviation: KEGG http://www.genome.jp/kegg/pathway.html.

polymorph and CNR1-C allele of rs2023239 may carry a genetic vulnerability that affects respective receptor-mediated signaling in the mesocorticolimbic structures, resulting in incentive salience to alcohol cues.

Gene-Environment (GxE) interaction

Although genetic predisposition (G) is associated with development of alcoholism, the GxE interaction potentiates (Figure 9) the effects of genetic factors. The joint effects of GxE are significantly greater than would be predicted from the sum of the separate effects [93]. The genetic influences on alcohol drinking behavior is commonly studied among sibling pairs reared in the same family and environmental influence, while the GxE is studied among sibling pair reared in different families and environmental influence [93].

Some of the studies reporting GxE interaction in development of alcoholism are described below.

ADH/ALDH x environment: Earlier studies [94-96] have shown that liver may contain active and inactive alleles of liver mitochondrial aldehyde dehydrogenases ($ALDH_{2s}$). The active forms are encoded by the gene ALDH ($2^*1/2^*1$), while the inactive form is encoded by the genes ALDH ($2^*1/2^*2$) or ALDH ($2^*2/2^*2$). The inactive ALDH form provides a genetic deterrent of heavy drinking and alcoholism among Asians. As shown in Figure 10, the normal active enzyme ($ALDH2^*1/2^*1$) decreased, while the partially inactive enzyme ($ALDH2^*1/2^*2$) increased between 1979 and 1992 in Japanese population. ALDH2 genetic polymorphisms have been shown to develop hypertension in a prospective cohort and that alcohol intake significantly modified the conferred risk [97]. These data strengthen GxE interaction in Asian populations.

5-HT transporter gene x environment: Nilsson, et al. [98] have shown that adolescents (aged 16 to 19) who had the heterozygous *5-HTTLPR l/s* genotype and came from families with neutral or poor relationships had over 10-fold increased risk for high intoxication frequency, compared with heterozygous adolescents who had a good relationship with their families. Preadolescents or early adolescents having the heterozygous *5-HTTLPR l/s* genotype and were maltreated exhibited a 40% greater risk for alcoholism then those who were not abused. Covault, et al. [99] reported that the *5-HTTLPR s*-allele also may be linked with increased use of alcohol and other drugs among college students who have had multiple negative life events. Thus, an interaction between stress and *5-HTTLPR* s/l or s/s alleles may predispose a person to abuse alcohol with increased risk of alcoholism.

GABRA x environment: A review of literature has provided substantial evidence for a key role the GABA receptors play in development of alcohol addiction [100-104]. An interaction between α_1 (A > G SNP) and α_6 (C > T SNP) subunits of $GABRA_1$ and $GABRA_2$ and the environment

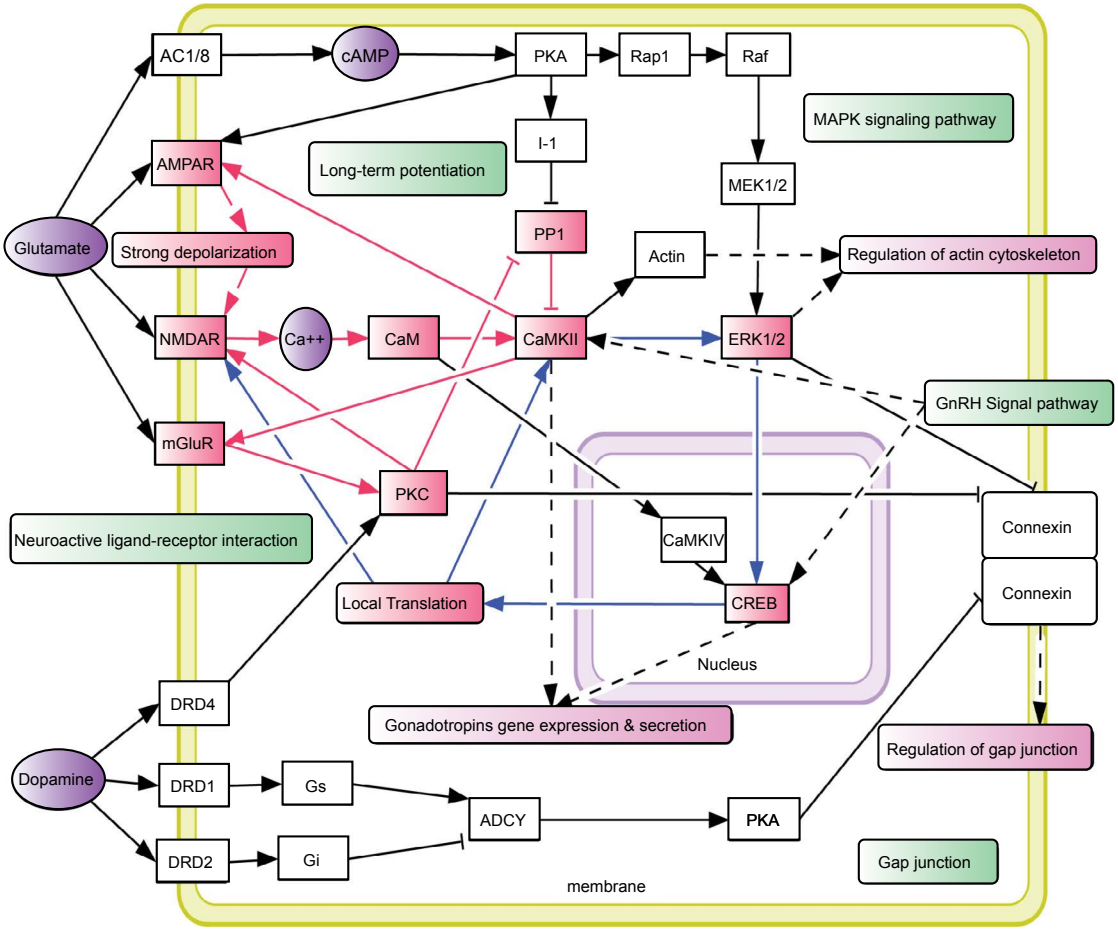

Figure 8: Candidate genes (white boxed) and alcohol addiction network. Neurotransmitters and secondary massagers are highlighted (purple oval) and common pathways (green boxed). Activation of CAMKII may play a central role in the development and maintenance of addiction states. The fast and slow positive feedback loops interlinking through CAMKII may be essential for the development and consolidation of addiction. Carmine boxes represent four functional modules: regulation of cytoskeleton, regulation of cell cycle, regulation of gap junction, and gene expression and secretion of gonadotropins. Fast positive feedback loops (involving signal transduction) are highlighted in red lines and slow ones (transcription and translation) are highlighted in blue lines.

Abbreviations: AC/ADCY: adenylate cyclase; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CaM: calmodulin; CaMKII: calmodulin kinase II; cAMP: cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; DRD1-3: dopamine receptor D1-D3; Gs: stimulatory GTP binding proteins; Gi: inhibitory GTP binding proteins; mGluR: metabotropic glutamate receptor; NMDAR: N-methyl-D-aspartate receptor; PKA: protein kinase A; PKC: protein kinase C; PP1: protein phosphatase 1; Raf and Rap1: part of Ras-Raf-MEK (mitogen activated protein kinase) - ERK (extracellular regulated protein kinase) pathway [92].

has been implicated in the development of alcoholism [105-107]. In family-based studies, *GABRA*$_2$ has been associated with alcohol dependence exhibiting 13-28 Hz β electroencephalographic frequency in children of alcoholic parents, not in children of control parents [106,108-110]. People with the high-risk allele of *GABRA*$_2$ and unhappy marriage had higher likelihood of developing alcoholism than people with the allele or marriage alone [106].

Dopamine transporter 1 gene × environment: There is some but not compelling evidence for involvement of dopamine transporter genes in development of alcoholism. Laucht, et al. [111] have shown that in adolescents who were homozygous for either of the *DAT1* gene variants and grew up in psychosocially adverse familial conditions exhibited higher risk factors for alcoholism (impulsivity, hyperactivity, and inattention) than did adolescents with other genotypes or those with the same genotypes who grew up in less adverse family conditions. However, Vandenbergh, et al. [112] failed to show any correlation between DAT1 alleles and risk to alcoholism. More research is needed to clarify the role of DAT in alcohol predisposition. Taken together; these observations indicate that the gene-environmental interaction may play a key role in development of alcoholism phenotypes.

Anatomical Changes in Alcohol-Addicted Brain

Alcohol addiction is characterized by compulsion to seek and take alcohol, loss of control in limiting intake, and emergence of withdrawal syndrome when access to the drug is prevented [113]. As discussed earlier, the positive

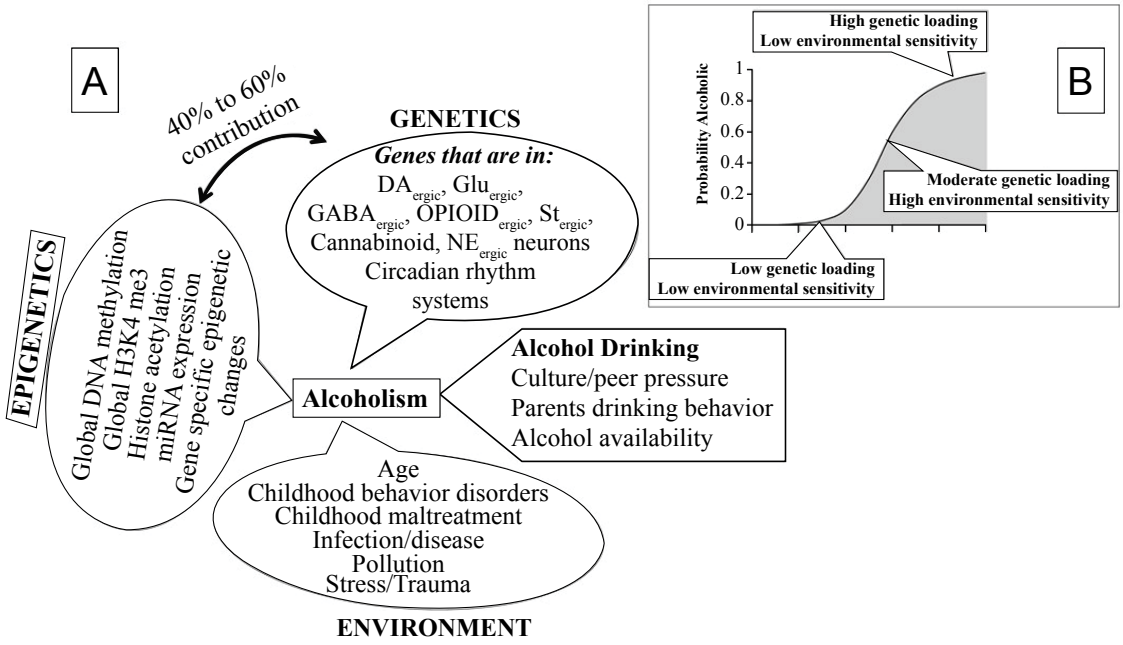

Figure 9: Possible roles of genetic, epigenetic and environment interactions in development of addiction **(A)** The candidate genes and environmental/social factors and; **(B)** Relationship between genetic loading in environmental sensitivity. The gene-environment interaction may contribute either to an increased susceptibility for developing an alcohol use disorder or attenuate possible genetic risk by producing a level of protection for vulnerable individuals. Factors related to a family environment, social relationships, and parenting styles may be involved.

Abbreviations: DA$_{ergic}$: dopaminergic neurons; Glu$_{ergic}$: glutamate neurons; GABA$_{ergic}$: inhibitory GABA neurons; Opioid$_{ergic}$: opioid neurons; St$_{ergic}$: serotonin neurons, neurons possessing cannabinoid receptors; NE$_{ergic}$: central noradrenergic neurons.

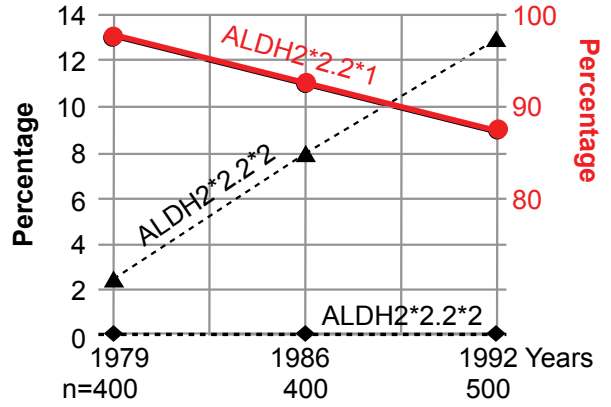

Figure 10: ALDH2 genotype (ALDH2*1/2*1 (active), ALDH2*2/2*2 (inactive) and ALDH2*1/2*2 (partially inactive, social influence)) patterns among Japanese alcoholics in three different years. Values are % of total cases [98].

reinforcing effects (euphoria and reward) of acute alcohol ingestion is mediate through the cortico-mesolimbic DA$_{ergic}$ pathways, extending from the ventral VTA to the NAc, AMY, HIP, PFC, SN, CP and related structures. The opposing effects (anxiety and stress), mediated through the HIP, muscarinic cholinergic neurons, NE$_{ergic}$ neurons and HPA axis, remain inhibited during this phase [113,114]. The brain of alcoholic patients exhibited abnormalities in many of the brain regions associated with the rewarding and opposing effects of alcohol drinking [115,116]. In general, the addiction related pathology can be classified as 'complicated' and 'uncomplicated' disorders.

In complicated neuropathy, the addicted subjects, in addition to the cognitive deficits, also suffer from liver damage and vitamin B1 deficiency, a condition known as Wernicke-Korsakoff syndrome-WKS, [117-119] consisting of two separate syndromes, a short-lived and severe condition called Wernicke's encephalopathy and a long-lasting and debilitating condition known as Korsakoff's psychosis. Wernicke's encephalopathy [120] includes mental confusion, oculomotor disturbances, and difficulty with muscle coordination. Korsakoff's psychosis is a chronic and debilitating syndrome characterized by persistent learning and memory problems [121]. Patients with Korsakoff's psychosis are forgetful and quickly frustrated, have difficulty with walking and coordination and exhibit anterograde amnesia [122-124]. Abstinent WKS patients show significant impairment in neuropsychological tests compared to controls [125]. This suggests that the neurological effects of alcohol with thiamine deficiency may be more severe and permanent.

Uncomplicated (non-WKS) alcoholic patients display mostly neuropsychological and behavioral disorders that exhibit significant recovery of functions upon long alcohol abstentions, although some components of these functional

Table 5: Areas of grey and white matter, CSF and total internal cranium. Values are mean ± SD. Data from Shear, et al. [157].

	Alcohol addiction	Control	p values
Gray matter	569.4 ± 63.5 ml	631.9 ± 62.75 ml	0.002*
White matter	435.5 ± 61.2 ml	470.1 ± 68.9 ml	0.085
Cerebrospinal fluid	712.7 ± 137.7 ml	565.7 ± 93.20 ml	0.001*
Total cranial	1717.6 ± 205.6 ml	1667 ± 202.2 ml	0.423

*p< 0.05, significant when compared with control.

domains recover faster or more fully than others [126-136]. Kopera, et al. [137] have shown only partial recovery in brain function of alcoholic patients abstinent for more than a year. Thus there may be some processes in the brain that do not easily recover over time.

The proceeding sections describe some of the permanent, reversible and dementia-like abnormalities associated with alcoholic brains.

Permanent brain damage

Chronic alcohol use may initiate neuronal loss in different brain regions (larger neurons (greater than 90 μm) are more sensitive than smaller neurons) and reduce the white matter volume in cortex and cerebellum. This may compromise the cerebellum-cerebral cortex loop (complicated >> uncomplicated) [138-141]. Neuronal loss in cortex, hypothalamus and cerebellum may result in lasting impairment in behavior such as decision-making activities [142,143]. Loss of GFAP in neurons (complicated >> uncomplicated) occurred without gross changes in brain pathology or brain weight and was not restricted to pathologically susceptible brain regions [144]. Alcoholic patients having vitamin B1 deficiency exhibits symptoms of alcoholism-related poly neuropathy (ALPN), a potentially debilitating disease associated with sensory, motor, and autonomic nerve dysfunctions [145,146]. Although B1 deficiency is believed to be the prime cause of ALPN, many studies have shown that ALPN was not significantly abated or reversed by thiamine repletion [147-149]. ALPN progresses slowly with burning pain and superficial loss of sensation due to irregular segmental [150], whereas thiamine deficiency result in acutely progressive deficits in superficial and deep sensation, due to degeneration of large fiber axons and sub-perineurial edema [151].

Transient brain damage

Substantial evidence associate alcoholism with global cerebral atrophy and ensuing cognitive dysfunction with age being a critical modulating factor [152-154]. Beck, et al. [155] have shown that alcohol addiction is associated with altered density of gray matter and white matter of specific brain regions, thus supporting the assumption that alcohol dependence is associated with both local gray matter dysfunction and altered brain connectivity (Table 5). The volumetric changes in the brain and certain cognitive impairments can be reversed with abstinence [156,157].

Earlier studies [158-160] have shown age related recovery of alcoholics, younger alcoholics improving to the level of the control groups in the area of visual-spatial functions (which are among those most sensitive to the effects of chronic alcohol abuse), whereas the older alcoholics continued to show deficits. Sclafani, et al. [161] have shown a positive relationship between age and ventricular volume (as % of total brain volume). Studies have shown relatively greater CSF filled spaces in frontal cortices and cerebellum of alcoholics, especially those with thiamine deficiency (Table 5). Shrinkage of Superior Cerebellar Vermis associated with Purkanje cells loss (complicated > uncomplicated) after chronic alcohol intake have been frequently reported [162]. They reported a 21%-40% reduction of Purkinje cell density in the cerebellar vermis with shrinkage of the molecular and granular layers.

Alcohol Withdrawal Syndrome

Earlier studies have shown that many of the alcohol-induced neurological abnormalities listed above (section 8.2.) were partially reversed with maintained abstinence [142,163]. However, in alcohol addicted subjects, abstinence (alcohol withdrawal) results in severe physical and emotional distress (paleness, excessive perspiration, nausea, stomach discomfort, heart palpitations, headaches, appetite loss, shakiness, seizures, nervousness, and, in extreme cases, death) that may increase alcohol craving [145]. Alcohol drinking rapidly reverses the withdrawal symptoms [164]. The aim of this section is to discuss the mechanisms underlying the development of the withdrawal symptoms in response to alcohol withdrawal.

In general, a state of neural hyper-excitability, lasting for at least 24 h to 72 h following withdrawal may be central to the development of the withdrawal symptoms [165]. Geisler, et al. [148] have shown that neural hyper-excitability to primary electrical stimulation may exist for at least 72 h and then subsiding at 1 week after alcohol withdrawal in alcoholics. A secondary stimulation given a week after the first stimulation resulted in a state of hypo-excitability (Figure 11). This shows long-term effects of alcohol withdrawal in rats.

Earlier studies have suggested that chronic ethanol exposure induces a net excitation state in Dorsal Raphe (DR) neurons that contributes to enhanced anxiety and excitation during ethanol withdrawal [166-168]. The neurotransmit-

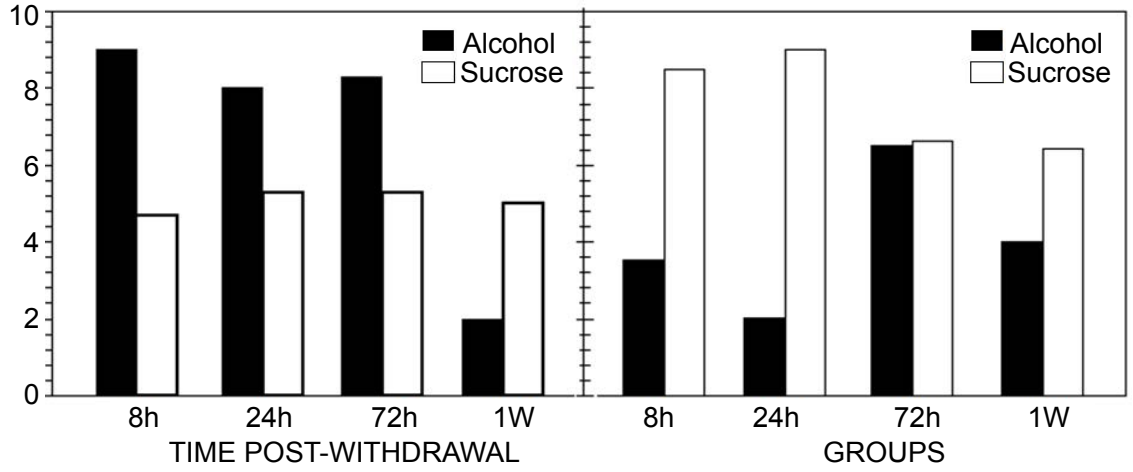

Figure 11: Alterations in neural excitability (latency to convulsion during direct electrical stimulation of hippocampus) at different times post-withdrawal in ethanol-dependent and sucrose-control groups. *Left panel*: median difference in latency to convulsion assessed before treatment and during first post-withdrawal stimulation (primary latency). Bars: separate group of rats. *Right panel*: median difference in latency to convulsion assessed before treatment and during second post-withdrawal stimulation (secondary latency) [148].

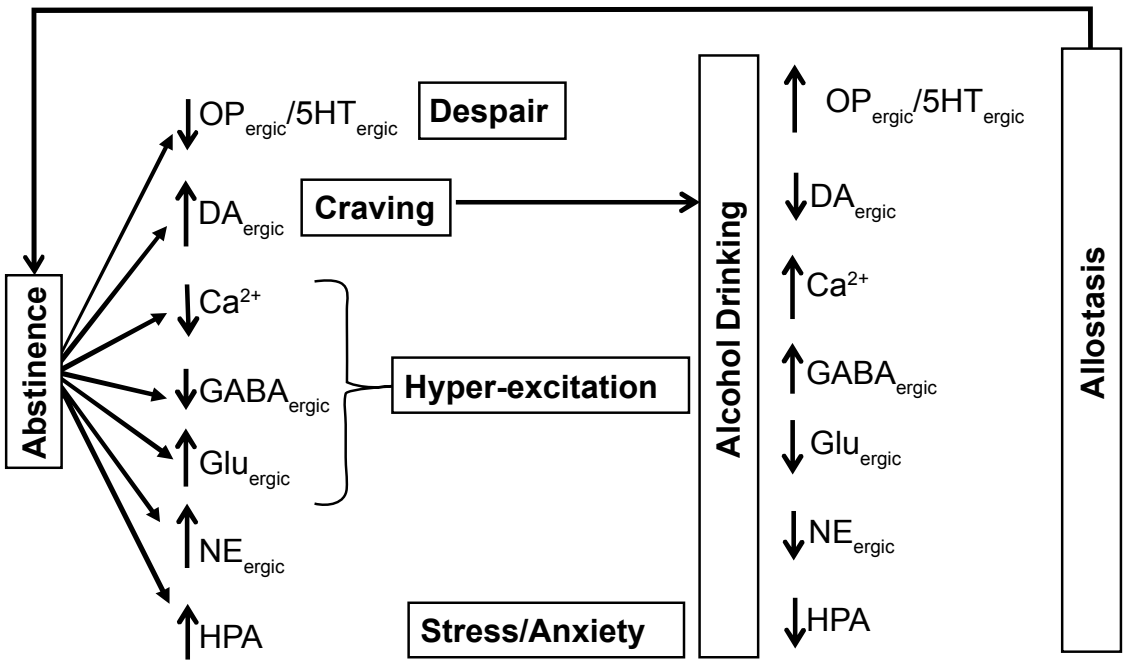

Figure 12: Possible mechanisms underlying development of the withdrawal symptoms following abstinences in alcoholics.

ter changes occurring in the brain of alcoholics that may be associated with the withdrawal symptoms are shown in Figure 12. $GABA_{ergic}$ neurons in NAc, inter neurons in VTA regions, and postsynaptic GABA receptors, notably $GABA_A$ receptors, may play a central role in development of addiction and withdrawal symptoms [113,169].

$GABA_A$ receptors are unique because they cause neuro-inhibition in alcohol-naïve subjects, but cause neuro-excitation in alcohol deprived alcoholic subjects by recruiting different pathways [170]. Chronic alcohol drinking may switch $GABA_A$ receptor function from inhibitory to excitatory, facilitating the withdrawal symptoms [171-173]. An increase in DA in the brain may augment craving for alcohol [174,175], while an increase in NA and activation of the HPA axis increases the stress response and anxiety, while a decrease in opioid and 5-HT receptors enhance the feeling of despair [175,176].

Earlier studies, using linkage-based genome scans of chromosomes, have identified markers of alleles that predispose to alcohol addiction and withdrawal symptoms [177-182]. Long, et al. [183] and Buck, et al. [177] have shown that the risk for alcohol withdrawal highly correlat-

ed with markers located at chromosomes 1, 2, 4 and 11. In chromosome 5, the marker was found at 38-42 cM from the centromere of chromosome 4 (Figure 13) in mouse that is syntonic with human 9p21-p23 and 1p32-p22.1. Buck, et al. [177] also detected a QTL near *Gad 1*, α-subunit of brain sodium channels (*Scn1a, Scn2a, Scn3a*) and a glial-specific sodium channel (*Scn7a*) of chromosome 2. *Gad1* may be related to a candidate gene responsible for GABA synthesis. The differences in alcohol withdrawal severity among mice of different strains could be associated with differences in GAD enzyme activity and/or gene expression. Chromosome 11 contained a QTL in proximity to genes encoding the α_1, α_6, and γ_2 subunits of $GABA_A$ receptors [184] that correlated with severity of the withdrawal syndrome.

Alcohol withdrawal, in addition to the rapid-onset withdrawal symptoms, also cause long-lasting post-abstinence changes including, but not limited to, sleep disturbances, cognitive deficits, anxiety, mood swings, depression mostly in females, panic disorder and suicide behavior [130,185-192]. Zorrilla, et al. and Koob [193,194] have shown that protracted withdrawal from ethanol or cocaine is associated with altered limbic CRF-LI and circulating CORT levels beyond the detoxification stage. These may play some role in the development of the delayed symptoms.

Conclusions

Alcohol exposure in alcohol-naive subjects elicits euphoric and relaxing responses that are attributed to (i) an increase in $GABA_{ergic}$ (inhibitory signals), OP_{ergic} and $5HT_{ergic}$ (euphoric effects) neuronal activities and (ii) a decrease in DA_{ergic} ('want' signal or craving), Glu_{ergic} (excitatory signals),NE_{ergic} (stress signals) neuronal, and the HPA axis (stress hormones) activities. If alcohol drinking continues, the receptors are sensitized, resulting in development of tolerance when alcohol drinking must be increased to achieve desired effects (Figure 14). In *genetically predisposed* subjects, chronic alcohol drinking results in the development of addiction, characterized by a condition when alcohol caseation results in rapid onset of withdrawal symptoms including, but not limited to, alcohol craving and moderate to severe discomfort such as tremors, seizures, hallucinations, DT and, in extreme cases, death. Although mechanisms are not fully understood, in alcohol withdrawal, the neurochemical changes are opposite to those during the acute exposure phase: Glu_{ergic}, DA_{ergic}, NA_{ergic} and HPA activities are elevated, while $GABA_{ergic}$ activity is reduced. Alcohol drinking rapidly reverses the withdrawal symptoms. Taken together, these observations suggest that alcoholism is a multifaceted disease, affecting almost every system in the body, including neurological, physiological/hormonal, and cardiovascular systems. Because of this, there is a great need to improve the success rates of all forms of treatment of alcoholism including prevention of relapse, curbing active alcohol consumption and craving and treatment of the disease.

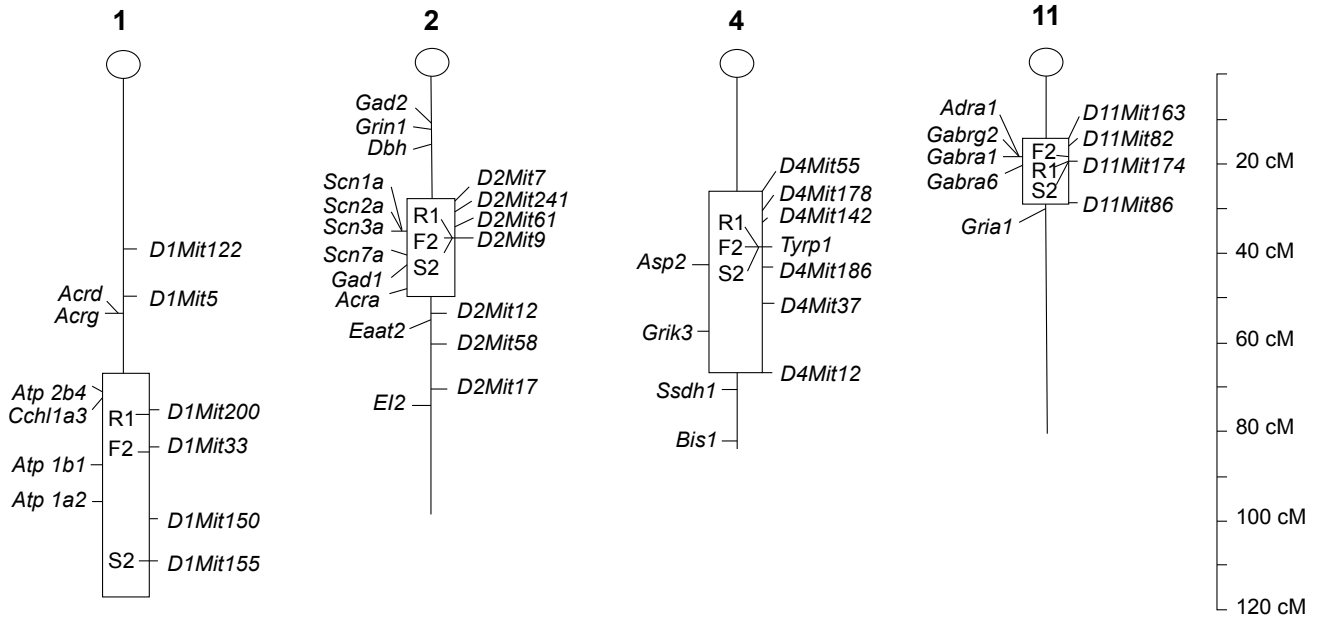

Figure 13: Application of QTL in search for candidate genes responsible for alcohol withdrawal on chromosomes (Chrs) 1, 2, 4, and 11. Results for the B6D2 F2 mouse population (a cross of alcohol preferring C57BL/6J (B6) and alcohol avoiding DBA/2J (D2) mouse with high and low alcohol withdrawal, HAW and LAW, respectively) are shown. The markers, map positions indicated in centiMorgans from the centromere (at 0 cM). Estimated 1.0 LOD confidence intervals for the positions of QTL on mouse chromosomes 1, 2 (*proximal*), and 11 are also shown (*boxed regions*). For chromosome 4, QTL actually extends beyond the range of markers examined. For chromosome 2, the 1.0 LOD confidence intervals is shown only for the proximal QTL. The position of the best correlated marker for each separate experiment (i.e., RI, F2, or S2) is also indicated within each *boxed region*. Candidate genes located within or near the 1.0 LOD confidence intervals are also shown [177].

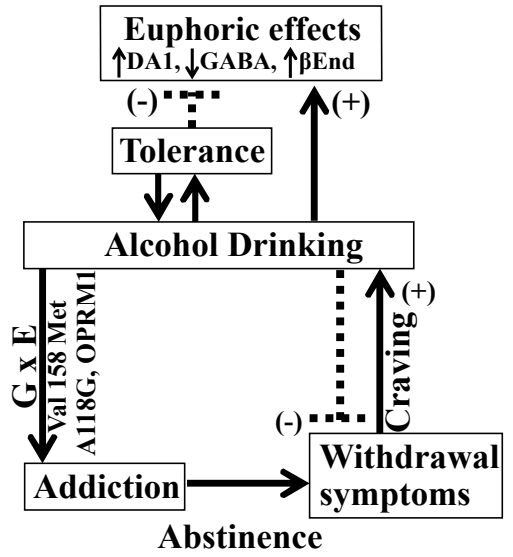

Figure 14: Overall mechanisms underlying the addictive effects of chronic alcohol drinking.

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