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Effect of Alcohol on Brain Development

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Abstract

In the world, 3.3 million deaths occur every year due to harmful use of alcohol; this represents 5.9% of all deaths. Ethanol metabolites' production and their post-translation modification are one of the proposed mechanisms that lead to neuronal toxicity. The projected neurochemical changes in chronic alcohol drinkers may be due to an imbalance between excitatory and inhibitory neurotransmitters. Interaction of alcohol with GABA and glutamate receptors (NMDA and AMPA) resulted in diverse adaptive changes in gene expression through neuronal pathways leading to alcohol toxicity. Alcohol consumption in an individual leads to biochemical changes that are correlated with complex inflammatory signaling pathways such as phosphorylation of proteins, synthesis of nitric oxide (NO), NF-kappaB and MAP kinase pathways in certain regions of the brain. Ethanol exposure activates neurons and microglial cells that lead to release of neuroimmune factors like high-mobility group box 1 (HMGB1), toll-like receptor 4 (TLR4) and certain cytokines involved in immune responses leading to neuroimmune signaling in the brain. Epigenetic modification of DNA and histones may lead to neuronal gene expression, thus regulating ethanol toxicity. Researchers attempt to modulate therapies that can help to foil alcohol toxicity and support the development of original neuronal cells that have been injured or degenerated by alcohol exposure.

Keywords: brain, alcohol, epigenetic, alcohol-responsive genes (ARGs), immune responses

1. Introduction

1.1. How alcohol is absorbed into the body?

Some people drink socially and do not get addicted while others do. The ground behind the alcohol drinking is related to psychological, physiological, genetics and social factors.

When people consume alcohol, about 20% is absorbed in the stomach and almost 80% is absorbed in the small intestine. Alcohol absorption is related to the two main factors:

- a. concentration of alcohol and
- b. heavy meal consumption before drinking. An empty stomach will fasten the alcohol absorption.

Absorbed alcohol enters the blood stream and is carried all through the body. Upon reaching the body, simultaneously the body works to eliminate it. The 10% of alcohol is removed by the kidneys (urine) and lungs (breath). Left-out alcohol is oxidized by the liver, converting alcohol into acetaldehyde first and then further converted to acetic acid.

1.2. Alcohol metabolism and distribution

Alcohol is absorbed in the stomach and intestines through the blood stream and crosses the blood-brain barrier (BBB) after consumption. Alcohol is metabolized through the mitochondrial cytochrome P450 (CYP2E1) and catalase in the liver or the brain. In the brain, alcohol metabolism by CYP2E1 produces acetaldehyde and alcohol is considered to be the only source of acetaldehyde. The rest of the acetaldehyde may go through the brain by an enzyme called alcohol dehydrogenase (ADH) which is found in the liver and helps in conversion of alcohol to acetaldehyde. Target of alcohol is considered to be ADH. Alcohol binds through its hydroxyl (—OH) group and zinc atom on ADH [1]. Disulfiram (antabuse), one of the first approved treatments for alcoholism, showed its mechanism by inhibiting the ADH enzyme. When taken regularly, disulfiram decreases the drinking capacity because of the aversive effects [2].

2. Alcohol and the brain

2.1. How does alcohol act at the neurological level?

Brain chemistry is affected by alcohol through alteration of neurotransmitters. Neurotransmitters are chemical messengers that send out the signals all through the body and control thought processes, behavior and sensation processes. Neurotransmitters are either excitatory (excite brain electrical motion) or inhibitory (decrease brain electrical motion). Alcohol increases the effects of the inhibitory neurotransmitter GABA in the brain. GABA causes the lethargic movements and garbled speech that often occur in alcoholics. At the same time, alcohol inhibits the excitatory neurotransmitter glutamate, which results in a suppression of a similar type of physiological slowdown. In addition, alcohol also increases the amount of chemical dopamine in the brain center, which creates the feeling of pleasure after drinking alcohol. Just after a few drinks, the physical effects of alcohol become perceptible. These effects are linked to blood alcohol concentration (BAC) (**Table 1**). The level of BAC rises when the body takes up alcohol faster than it can release it.

In the brain, various centers have been affected due to alcohol, both upper and lower order. As the BAC increases, more centers of the brain are affected (**Figure 1**) [3]. The order in which brain centers are affected by alcohol consumption is as follows:

1. cerebral cortex
2. limbic system
3. cerebellum
4. hypothalamus and pituitary gland
5. medulla (brain stem)

2.1.1. Long-term effect of alcohol on the brain

Continuous or excessive drinking can lead to undeviating injury, causing the brain to shrivel. This leads to deficiency in fibers that transfers the information between neuronal cells. Excessive alcohol leads to a condition called **Wernicke-Korsakoff syndrome** (deficiency of thiamine) [4]. Alcohol interference leads to this deficiency, as it blocks the way of vitamin B absorption in the body. Symptoms of the Wernicke-Korsakoff syndrome are mental perplexity, lack of fine movements, memory and learning problems.

Euphoria (BAC = 0.03–0.12%)	Excitement (BAC = 0.09–0.25%)	Confusion (BAC = 0.18–0.30%)	Stupor (BAC = 0.25–0.4%)	Coma (BAC = 0.35–0.50%)	Death (BAC more than 0.50%)
They become more self-assured or brave.	They become lethargic.	They become woozy and may walk unsteadily.	They can barely move at all.	They are unconscious.	The person usually stops breathing and dies.
Their awareness period shortens.	They have a problem in understanding or recalling things (even recent events).	They may be highly emotional, destructive, reserved or overly loving.	They may lapse in and out of consciousness.	Their reflexes are depressed.	
They may look flushed (red).	They do not respond to situations as quickly	They cannot observe clearly.	They cannot respond to stimuli.	They feel cold.	
Their conclusive power is not as good.	Their body movements are uncoordinated.	They are drowsy.	They cannot stand or walk.	Their breathing is slower and shallower.	
They have trouble with fine movements, such as writing.	They start to lose their sense of balance easily.	They have garbled speech.	They may vomit.	Their heart rate may slow.	
	Their vision becomes dim.	They have clumsy movements.		They may die.	
	They may have problems in sensing things (hearing, tasting, emotion, etc.).	They may not feel tenderness as readily as a sober person.			

Table 1. The effect of alcohol exposure on the brain.

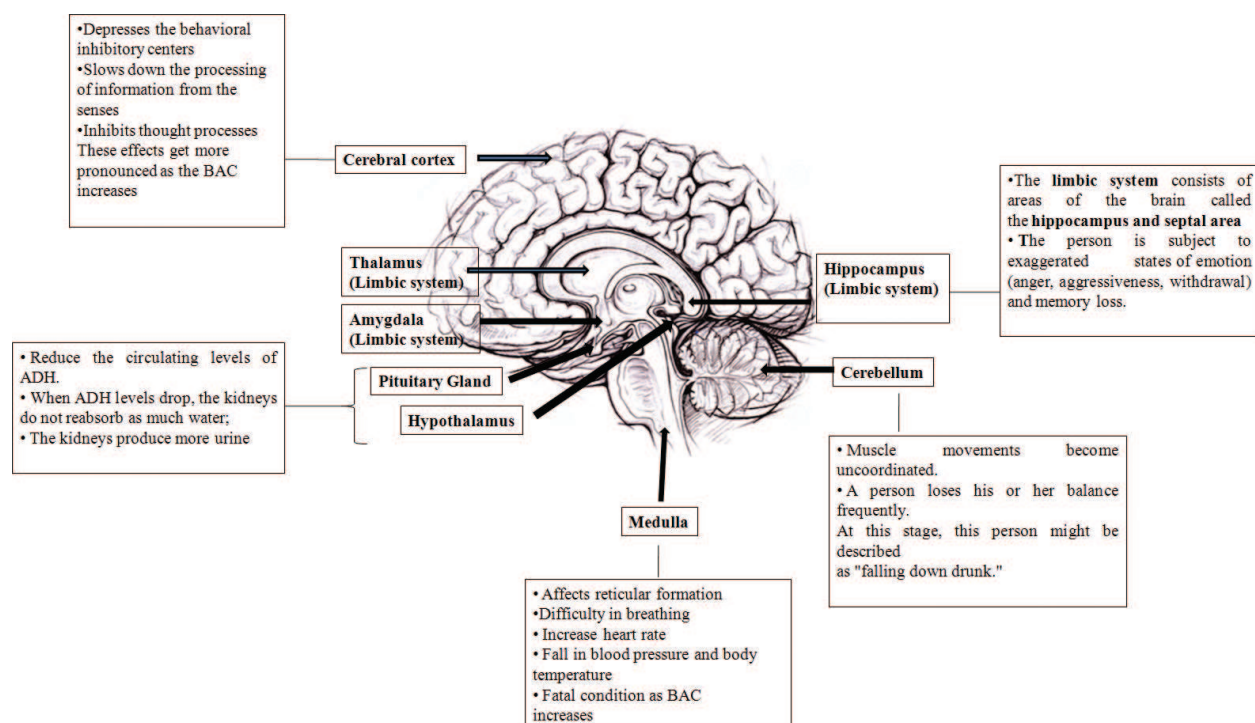


Figure 1. Effect of alcohol on various brain centers.

Heavy or continuous consumption of alcohol can lead to the liver injury. The liver is the chief organ responsible for converting alcohol into nontoxic byproducts and taking them out of the body. Excessive alcohol consumption leads to prolonged liver dysfunction which may also harm the brain, leading to a severe fatal brain disorder known as **hepatic encephalopathy** [5]. Studies have confirmed that at least two toxic substances, **ammonia and manganese**, play an important role in the progress of hepatic encephalopathy.

Treatment—Strategies that have been used to treat or prevent the development of hepatic encephalopathy are as follows:

1. L-ornithine L-aspartate: it lowers the concentration of blood ammonia
2. Artificial livers: it clears patients' harmful toxins present in the blood [6]
3. Liver transplantation [7]

2.1.2. Alcohol and the developing brain

Alcohol consumption during pregnancy can lead to changes in the physical, learning and behavioral effects in the developing brain and it is known as **fetal alcohol syndrome (FAS)** [8]. The brains of these people may have less size (i.e., microencephaly) and also a small amount of brain cells (i.e., neurons) that function accurately resulting in long-lasting problems in learning and behavior.

Treatment: Researchers are looking forward to treat or prevent brain damage, such as associated with FAS.

1. In-vivo studies yielded a result showing antioxidant therapy and vitamin E which is used for treating FAS.
2. Treatment with 1-octanol (paradoxically an alcohol itself) on developing mouse embryos significantly reduced the rigorousness of alcohol's effects [8].
3. NAP and SAL have the same property as octanol. They both help in protecting nerve cells against a variety of toxins [9].
4. A compound called MK-801 that blocks glutamate that helps with alcohol withdrawal [10].

2.2. Alcohol-induced neurotransmitters and its effect on the neurons

2.2.1. Glutamate

Glutamate receptors include metabotropic glutamate receptor (mGlu), *N*-methyl-D-aspartic acid (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Glutamate exhibits its action on binding to these receptors, resulting in the activation of G-proteins which further leads to amplification of phospholipase C, diacylglycerol (IP3DAG) and calcium-dependent protein kinases [11].

During alcohol drinking, there is a release of excessive glutamate leading to neuronal cell death. This occurs through two pathways:

1. Activation of glutamate receptors causes toxicity [12], resulting into Ca^{+2} ion influx, Na^{+} influx, nitric oxide (NO) generation and depolarization of mitochondria. This will lead to untenable elevations in ATP, mitochondrial collapse, dendritic beading and depolymerization of microtubule [13].
2. Oxidative toxicity to glutamate [14].

A study has been carried out on 13 abstinent young alcoholics showing a major increase in glutamate to creatine ratio by proton magnetic resonance spectroscopy and magnetic resonance imaging [15]. Furthermore, an alteration in glutamate is linked to altered short memory loss. Immediate administration of alcohol (acute dose) prior to the microdialysis experiment would end up into an increased glutamate release. Earlier studies showed that administration of either 2 or 3 g/kg ethanol to immature rats elicits a decrease or no modification in the release of glutamate into the N-acetyl cysteine (NAC) [16]. Researchers showed that there is a genetic component that probably contributes to the brain injury occurring in "binge drinking" alcoholics [17]. In binge drinking, alcohol models, there are no reports of increased NMDA receptors [18]. In one study, "binge- drinking" individuals with compensated alcoholic cirrhosis, dosing 80 g of ethanol, showed a transient increase in serum nitrates and nitrite resulting in an increase in NO production in certain tissues (liver and brain) [19]. During the period of chronic alcohol toxicity, basal concentration of glutamate seems to be normal in various regions of the brain though blood alcohol levels are high as 2 g/l [20].

During chronic alcohol consumption, NMDA receptor (NMDAR1 and NMDAR2B) levels seem to be increasing in numbers and decreasing in sensitivity [21] in the nucleus [22], the striatum [23] and the hippocampus [20].

2.2.2. *Gamma-amino-butyric acid*

It is a chief inhibitory neurotransmitter. GABA binds to GABA_A receptors, resulting in hyperpolarization of the cell membrane and inhibition of neural activity. Increased GABA release upon alcohol administration results due to inhibiting its degradation [24]. Alcohol intoxicity and alcohol's anti-anxiety reduce due to decrease in GABA_A receptor activity. Chronic alcohol exposure decreases extrasynaptic GABA-mediated tonic current recorded from neurons in the hippocampus and cortex [25], and this corresponds to a decrease in extrasynaptic GABA_A receptors containing the δ subunit in hippocampus [26]. Benzodiazepines (the positive allosteric modulator of GABA_A) are considered to be a standard for treating alcohol detoxification owing to their anticonvulsant and anxiolytic pharmacological profile. Improper alcohol interactions have shown some concern about their abuse and dependence responsibility. Therefore, researchers are trying to find out potential anticonvulsant agents as alternatives, that is, gabapentin and topiramate [27, 28].

2.2.3. *Dopamine*

Transmission of dopamine is linked via two groups of G-protein-linked receptors: D1-like (D1 and D5 receptors) and D2-like (D2, D3 and D4 receptors). These receptors are classified on the basis of adenylatecyclase activity (stimulation or inhibition). Dopamine plays a central role in mediating alcohol compensation through mesocortical and mesolimbic pathways [29]. During chronic alcohol consumption, the release of dopamine depends on the large amount of the alcohol consumption, which gives pleasurable effect of alcohol intake. Reduction in dopamine release is observed during alcohol withdrawal. This ultimately reduces noticeable neuronal cells, leading to dysphoria and depression as a major part in the motivational and behavioral changes [30]. Chronic alcohol drinking has been reported to produce constant neurological changes in transmission of dopamine within the mesoaccumbens reward circuitry, including increased basal extracellular levels of dopamine in the NAC [31], increased firing rate in the ventral tegmental area (VTA) dopamine neurons [32] and changes in the function of dopamine receptor [33]. In comparison, withdrawal from chronic alcohol drinking due to increased dopamine uptake levels resulted in decreased VTA dopamine neuronal activity [34], and reduced basal levels of dopamine in the ventral and dorsal subregions of the striatum, possibly due to enhanced dopamine uptake [35]. The aripiprazole (D2 dopamine receptor agonist) has shown some effectiveness in treating dependence of alcohol [36].

2.2.4. *Serotonin*

Serotonin exerts its known role in regulating various behaviors (e.g., feeding, sleep/arousal, aggression), mood and emotional behavior [37] via several metabotropic (5-HT₁ and 5-HT₂ subtypes) and ionotropic (5-HT₃) receptors throughout the brain depending on the consumption of alcohol [38]. Alcohol elevates serotonin release in the central nervous system (CNS) affecting emotion, temper and thoughts. The 5-HT₃ receptor function is altered by ethanol consumption through its actions on receptor proteins [39]. Chronic alcohol exposure reduces serotonin levels in several brain regions [40]. Researchers have focused on the treatment for alcohol dependence and comorbid depression [41], post-stress disorder [42] and anxiety [43].

Inhibition of serotonin reuptake was done through fluoxetine. The milnacipran blocks both serotonin and norepinephrine reuptake. Both fluoxetine and milnacipran are found to be effective in reducing alcohol consumption in the rats model [44]. Consumption of alcohol (5%) every third day for 18 days leads to disturbance in serotonin function within the nucleus accumbens [45] (Tables 2 and 3).

2.3. Biochemical changes associated with alcohol intoxicity

Alcohol consumption in an individual leads to biochemical changes that are correlated with complex signaling pathways such as phosphorylation of proteins, synthesis of nitric oxide (NO), NF κ B and MAP kinase pathways in certain regions of the brain [48].

2.3.1. Generation of free radicals

Alcohol-induced brain damage may occur due to generation of free radicals [49] by acetaldehyde intoxicity [50] or microsomal ethanol oxidizing system (MEOS) [51]. This can be minimized, if there would be a reduction in glutathione (cytoprotection) in the specific regions of the brain which is affected.

2.3.2. Changes in phosphorylation

Cell signaling events depend on phosphorylation of proteins (phosphorylation: protein kinase and dephosphorylation: protein phosphatases). During intoxication in hippocampal dentate gyrus,

Neurotransmitters	Effect of alcohol in the brain	References
Glutamate	Inhibits glutamate receptor function	[13, 14]
GABA	Potentiates GABA receptor function	[24]
Dopamine	Increases dopamine concentration	[31]
Serotonin	Decreases serotonin neurotransmission	[39]

Table 2. Neurotransmitters and its effect on the brain system.

Neurotransmitters	Drug found to reduce alcohol consumption	References
Glutamate	Amitriptyline	[46]
GABA	Benzodiazepines (positive allosteric modulator of GABA _A)	[27, 28]
	Gabapentin (anticonvulsant)	
	Topiramate (anticonvulsant)	
Dopamine	Aripiprazole (D2 dopamine receptor agonist)	[36]
Serotonin	Fluoxetine and milnacipran	[44]
	Dansetron (5-HT ₃ receptor antagonist)	[47]

Table 3. Neurotransmitters-associated drug to reduce alcohol toxicity in the brain.

the total phosphorylated c-AMP response element-binding protein (CREB) immunoreactivity is reduced in both chronic or binge drinking. In rat cerebellum, the dose of 3 g/kg alcohol (acute) shows an increase in a phosphorylated form of CREB. Research showed that protein phosphatase inhibitor (DARPP-32), when it undergoes phosphorylation changes, plays a crucial role in reducing ethanol inhibition of NMDA receptors [52].

2.3.3. Transcription factors

They are the first signaling proteins which are regulated through sensitive cysteine residues, which need to be reduced to its function. Earlier studies showed that production of reactive oxygen species (ROS) is responsible for the activation of NFκB [53]. Later *in vitro* studies showed that exogenous hydrogen peroxide is responsible for NFκB activation [54]. In the cortex, one study reported activation of NFκB in chronically alcoholized rats [55]. It was quite clear that NFκB was down-regulated in comparison to acute alcohol drinking. One study showed no NFκB activation in binge alcohol drinking models, when given anti-oxidants (furosemide and butylatedhydroxytoluene) to prevent neuronal degeneration [56].

2.4. Epigenetic mechanism

It is an efficient mechanism for gene regulation by altering the packaging of DNA within chromatin through interactions with histones. CREB requires phosphorylation to initiate transcription of pro-survival neuronal factors (**Figure 2**). A study revealed an increase in CREB (a regulator for plasticity of neurons), increase in H3-H4 (a central histone tetramer) acetylation and inhibition of HDAC (histone deacetylases) activity in a rat amygdala when given an acute dose of ethanol for 15 days. A trichostatin (HDAC inhibitor) was used to treat the rats, resulting in deacetylation of H3-H4, CREB inhibition, reduced NPY expression and HDAC activation in the rat amygdala [57].

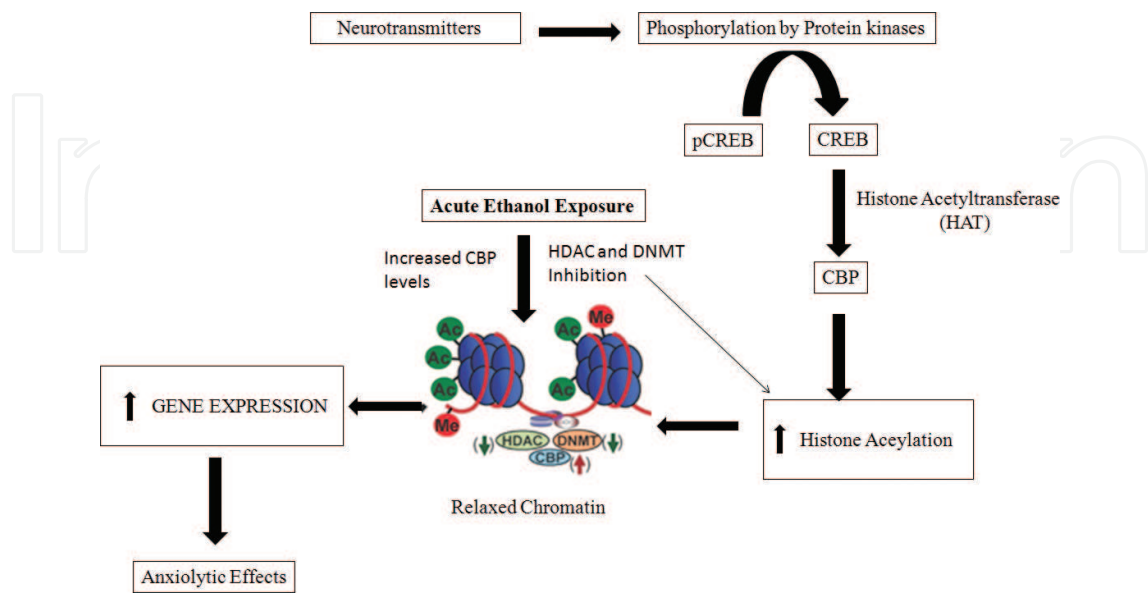


Figure 2. Epigenetic modifications associated with alcoholism.

2.5. Genome profiling of alcohol-responsive genes

With recent technologies like direct sequencing and gene microarray, studying individual genes along with entire genome of an organism has been made possible.

2.5.1. Microarray study

First genome microarray studies were performed in post-mortem alcoholics' human brain; results revealed that myelin related genes expressed in oligodendrites (from frontal cortex) showed downregulation in the brains of human alcoholics compared with brains from control individuals [58], suggesting neuronal dysfunction. In the prefrontal cortex area of the brain, there were 54 genes which were upregulated and those belong to the class of heat shock protein, including *HSP70-2*, *CRYAB*, *HSP27-1* and *HSP40-1* in alcoholic abusive individuals [59]. An old study revealed that 100 mM ethanol (2 days) given to NG108-15 hybrid cell line determined that a number of genes were induced by heat shock and a few were induced by ethanol only. Heat-shock cognate proteins *Hsc 70* and *Hsc 110* were recognized as ethanol-inducible genes [60]. When *C. elegans* was given a high dose of ethanol, it showed activation of *glr-2*, a gene that encodes a subunit of the AMPA glutamate receptor subunit (homologous to mammalian GluR2) within 15 min [61]. Cultured cortical neurons given 75 mM of ethanol for 5 days showed increased levels of gene expression of *Hsp84*, *Hspa8* and *Hsp70* [62]. In a whole brain, when C57BL/6J and DBA/2J mouse strains were given acute doses of different ethanol preferences, they revealed downregulation of *ErbB3*, *Mobp* and *Nkx2-2* (myelin-related genes) [63].

The researcher performed a genomic level along with a microarray experiment on neurons of mouse corticals given 60 mM ethanol or heat treatment at 42°C. Microarray results showed upregulation of a large number of genes by ethanol and heat shock [64]. Among the pool of genes, there were nine genes which showed greater than 50% stimulation. It includes.

- gene-encoding proteins involved in synaptic neurotransmission: *Syt1* and *Spnb2*;
- gene-encoding proteins involved in synaptic plasticity and synaptic formation: glycoprotein m6a (*Gpm6a*), neurogranin (*Nrgn*) and cadherin 13 (*Cdh13*);
- and gene-encoding proteins involved in microtubule assembly, microtubule-associated protein 1B (*Mtap1b*) [64].

2.5.2. Analysis of quantitative trait loci

A quantitative trait loci (QTL) refers to the trait that varies in degree and can be attributed to the interactions between two or more genes and their environment. Possible QTLs have been identified through microarray studies for alcohol uptake. An analysis is done across inbred mouse strains identified a group of genes for alcohol preference QTL on chromosome 9. These genes include *Arhgef12*, *Carm1*, *Cryab* (heat shock protein), *Cox5a*, *Dlat*, *Fxyd6*, *Limd1*, *Nicn1*, *Nmnat3*, *Pknx2*, *Rbp1*, *Sc5d*, *Scn4b*, *Tcf12*, *Vps11* and *Zfp291* [65].

2.6. Activation of multiple neuroimmune genes in human alcoholic brains

In human brain-slice cultures, multiple ethanol-induced cytokines are released. Among all, monocyte chemotactic protein-1 (MCP-1) showed increased levels in the amygdala, nucleus accumbens, VAT and hippocampus [66]. In alcoholic brains, elevated levels of TLR 2, TLR3, TLR4 and HMGB1 (high-mobility group box 1) were found in the orbital frontal cortex (OTC) [67]. Release of HMGB1 leads to disruption of synaptic plasticity which causes hyperexcitability of neurotransmitters due to ethanol exposure. There is an increased level of IL-1 β inflammatory marker in an alcoholic brain (hippocampus) causing neuro-degeneration [68]. RAGE (HMGB1 receptor) has shown an increased level in an alcoholic brain [69].

2.6.1. Role of microglia

Exposure to alcohol causes activation of microglia along with the proinflammatory cytokines, leading to neuronal inflammation and toxicity [70]. Alcohol exposure causes accumulation of microglia in the brain which occurs through activation of TLRs leading to increased HMGB1 expression [71]. Alcohol-induced neuronal apoptosis leads to stimulation of the transcription factor AP-1 and release of IL-1 β , IL-6 and transforming growth factor β (TGF- β 1) [71]. An in vitro study revealed that microglial TNF- α production plays an important role in neuronal toxicity [72]. Neuronal cell death occurred due to chronic alcohol exposure which leads to upregulation of the NF- κ B expression, which in turn leads to release of TNF- α resulting in neuronal apoptosis [73].

In vivo studies in the cortical and hippocampus region of the brain showed increased levels of NADPH oxidase, superoxide and microglial activation, which is correlated with alcohol-induced ROS production [74]. In vitro studies revealed that upon alcohol exposure, microglia-conditioned cells showed increased ROS production and induced oxidative stress in cultured hypothalamic neuronal cells; this leads to neuronal apoptosis [75]. Alcohol-induced elevation of TGF- β 1 levels in neuronal cells is accompanied by a host of molecular and chemical changes such as increase in E2F1 protein expression, mitochondrial proapoptotic proteins bak, bad and bcl-xs and E2F1 protein expression and simultaneously decrease in cyclin D1, cyclin-dependent kinase-4 expression and antiapoptotic protein bcl-2 leading to neuronal apoptosis [76] (**Figure 3**).

2.7. The brain and immune responses

The interface between the brain and the immune system is bidirectional. Recent findings have revealed that alcohol causes the release of HMGB1 in the gut, which in turn activates TLR4

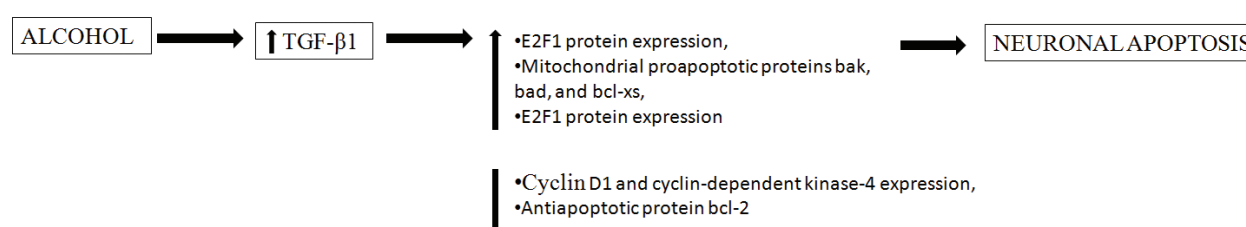


Figure 3. Alcohol-induced elevation of TGF- β 1 levels in neuronal cells is accompanied by a host of molecular and chemical changes related to cell death.

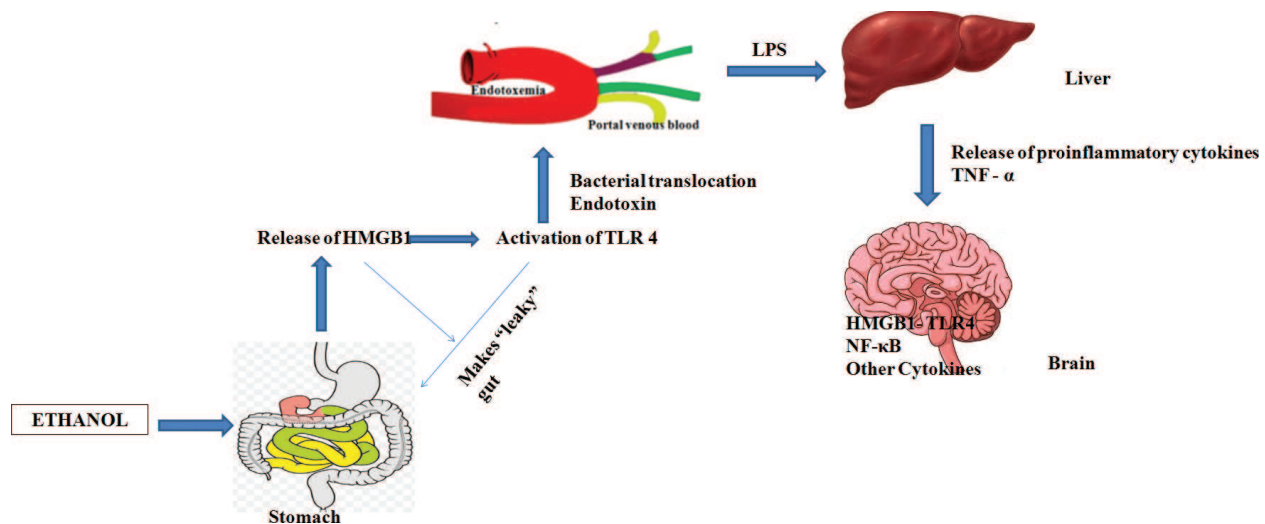


Figure 4. Alcohol influences neuroimmune signaling via its effects on the gut.

resulting in an increased gut permeability. As a result, there is activation of proinflammatory cytokines in the liver, which leads to induction of TNF- α and other cytokines in the blood. Researchers found that LPS induced increases in serum TNF- α as well as proinflammatory cytokines, leading to induction of the gene in the brain [77]. This proinflammatory cytokines in the blood are then transported across the blood–brain barrier (BBB) by their receptors [78]. For example, 2 to 3 g/kg ethanol when administered into the stomach results in the activation of innate immune response in the gut [79]. This damages the tight junction present in the gut resulting in an opening of the sites where gut bacteria and their endotoxins (LPS) can easily enter the blood stream leading to the liver, where they can activate proinflammatory cytokines (**Figure 4**). Increased proinflammatory cytokines responses, which affects the brain through TNF- α and other cytokines [80]. The brain response to the proinflammatory cytokine MCP-1 is quite longer than that found in the liver and blood [81]. An in vivo study showed an increased LPS induction of proinflammatory cytokines (TNF- α , IL-1 β and MCP-1) only in the brain but not in the liver and blood after ten daily doses of alcohol [81]. In the liver, the researcher suggested that the anti-inflammatory cytokine (IL-10) inhibits NF- κ B which was increased after 1 week of ethanol treatment but decreased in the brain [81]. After 10 days of ethanol (5g/kg/day) administration to mice model, this study showed sensitization to TLR3 agonist Poly:IC which induces proinflammatory cytokines in the brain for 24 hours [74].

3. Conclusion(s)

Alcohol is an anxiolytic and soothing drug. Chronic alcohol consumption leads to determined molecular and cellular modification in the brain system. It is comprehensible that GABA and glutamate neurotransmitters play a crucial role in alcohol toxicity, neuronal toxicity and neuronal cell death. Ethanol exposure triggers the activation of various gene expressions involved in apoptosis, in oxidative stress and in the cell cycle. Upregulation of genes by ethanol includes heat shock proteins and proteins related to synaptic neurotransmission,

synaptic plasticity and synaptic formation. Downregulation of genes by ethanol includes protein synthesis, myelination and the ubiquitin-proteasome pathway. Chronic ethanol exposure increases HMGB1–TLR4 and NF- κ B signaling which leads to improved NF- κ B target genes' expression. This results in determining neuroimmune responses to ethanol toxicity that releases HMGB1 or directly stimulates TLR and/or NMDA receptors. An epigenetic mechanism will show potential towards drug dependence by changing the DNA protein structure. Microglial cells will arbitrate the effect of alcohol toxicity on neurogenesis. The progression towards the neurobiologic techniques including micro array, QTL and proteomics will provide some anticipation for researching the molecular and cellular mechanisms that act as a keystone for the understanding of neuronal toxicity and enlightening new therapeutic gene targets for this public health burden.

Conflict of interest

We have no conflict of interest to declare.

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References

- [1] Zakhari S. Overview: How is alcohol metabolized by the body? *Alcohol Research & Health*. 2006;**29**(4):245-254
- [2] Barth KS, Malcolm RJ. Disulfiram: An old therapeutic with new applications. *CNS & Neurological Disorders—Drug Targets*. Mar 2010;**9**(1):5-12
- [3] Oscar-Berman M. Neuropsychological vulnerabilities in chronic alcoholism. In: Noronha A, Eckardt MJ, Warren K, editors. Review of NIAAA's Neuroscience and Behavioral Research Portfolio. National Institute on Alcohol Abuse and Alcoholism (NIAAA) Research Monograph No. 34. Bethesda, MD: NIAAA; 2000. pp. 437-471
- [4] Kopelman MD, Thomson AD, Guerrini I, Marshall EJ. The Korsakoff syndrome: Clinical aspects, psychology and treatment. *Alcohol and Alcoholism*. 2009;**44**(2):148-154
- [5] Butterworth RF. Hepatic encephalopathy—A serious complication of alcoholic liver disease. *Alcohol Research & Health*. 2003;**27**(2):143-145

- [6] Mitzner SR, Williams R. Albumin dialysis MARS 2003. *Liver International*. 2003;**23**(Suppl. 3):1-72
- [7] Arria AM, Tarter RE, Starzl TE, Van Thiel DH. Improvement in cognitive functioning of alcoholics following orthotopic liver transplantation. *Alcoholism: Clinical and Experimental Research*. 1991;**15**(6):956-962
- [8] Chen SY, Wilkemeyer MF, Sulik KK, Charness ME. Octanol antagonism of ethanol teratogenesis. *FASEB Journal*. 2001;**15**:1649-1651
- [9] Spong CY, Abebe DT, Gozes I, et al. Prevention of fetal demise and growth restriction in a mouse model of fetal alcohol syndrome. *Journal of Pharmacology and Experimental Therapeutics*. 2001;**297**:774-779
- [10] Thomas JD, Fleming SL, Riley EP. Administration of low doses of MK-801 during ethanol withdrawal in the developing rat pup attenuates alcohol's teratogenic effects. *Alcoholism: Clinical and Experimental Research*. 2002;**26**(8):1307-1313
- [11] Riedel G, Platt B, Micheau J. Glutamate receptor function in learning and memory. *Behavioural Brain Research*. 2003;**140**:1-4
- [12] Michaels RL, Rothman SM. Glutamate neurotoxicity in vitro; antagonist pharmacology and intracellular calcium concentrations. *The Journal of Neuroscience*. 1990;**10**:283-292
- [13] Greenwood SM, Mizielinska SM, Frenguelli BG, et al. Mitochondrial dysfunction and dendritic beading during neuronal toxicity. *The Journal of Biological Chemistry*. 2007;**282**:26235-26244
- [14] Choi DW. Excitotoxic cell death. *Journal of Neurobiology*. 1992;**23**:1261-1276
- [15] Lee E, Jang DP, Kim JJ, et al. Alteration of brain metabolites in young alcoholics without structural changes. *Neuroreport*. 2007;**18**:1511-1514
- [16] Yan OS, Reith ME, Yan SG, et al. Effect of systemic ethanol on basal and stimulated glutamate releases in the nucleus accumbens of freely moving Sprague-Dawley rats: A microdialysis study. *Neuroscience Letters*. 1998;**258**:29-32
- [17] Crews FT, Braun CJ. Binge ethanol treatment causes greater brain damage in alcohol-preferring P rats than in alcohol-nonpreferring rats. *Alcoholism: Clinical and Experimental Research*. 2003;**27**:1075-1082
- [18] Rudolph JG, Crews FT. No change in NMDA receptor binding in rat brain following chronic ethanol treatment. *Alcoholism: Clinical and Experimental Research*. 1996;**20**:8A
- [19] Oekonomaki E, Notas G, Mouzas IA, et al. Binge drinking and nitric oxide metabolites in chronic liver disease. *Alcohol and Alcoholism*. 2004;**39**:106-109
- [20] Dahchour A, De Witte P. Effects of acamprosate on excitatory amino acids during multiple ethanol withdrawal periods. *Alcoholism: Clinical and Experimental Research*. 2003;**27**:465-470

- [21] Kumari M, Anji A. An old story with a new twist: Do NMDAR1 mRNA binding proteins regulate expression of the NMDAR1 receptor in the presence of alcohol. *Annals of the New York Academy of Sciences*. 2005;**1053**:311-318
- [22] Dahchour A, DeWitte P. Excitatory and inhibitory amino acid changes during repeated episodes of ethanol withdrawal: An in vivo microdialysis study. *European Journal of Pharmacology*. 1999;**17**:171-178
- [23] Rossetti ZL, Carboni S. Ethanol withdrawal is associated with increased extracellular glutamate in the rat striatum. *European Journal of Pharmacology*. 1995;**283**:177-183
- [24] Hancher HJ, Dobson PD, Olsen RW, et al. Alcohol-induced motor impairment caused by increased extrasynaptic GABA(A) receptor activity. *Nature Neuroscience*. 2005;**8**:339-345
- [25] Fleming RL, Acheson SK, Moore SD, et al. GABA transport modulates the ethanol sensitivity of tonic inhibition in the rat dentate gyrus. *Alcohol*. 2011;**45**:577-583
- [26] Cagetti E, Liang J, Spigelman I, et al. Withdrawal from chronic intermittent ethanol treatment changes subunit composition, reduces synaptic function, and decreases behavioral responses to positive allosteric modulators of GABAA receptors. *Molecular Pharmacology*. 2003;**63**:53-64
- [27] Addolorato G, Leggio L, Hopf FW, et al. Novel therapeutic strategies for alcohol and drug addiction: Focus on GABA, ion channels and transcranial magnetic stimulation. *Neuropsychopharmacology*. 2012;**37**:163-177
- [28] Cooper E, Vernon J. The effectiveness of pharmacological approaches in the treatment of alcohol withdrawal syndrome (AWS): A literature review. *Journal of Psychiatric and Mental Health Nursing*. 2013;**20**:601-612
- [29] Spanagel R. Alcoholism: A systems approach from molecular physiology to addictive behavior. *Physiological Reviews*. 2009;**89**:649-705
- [30] Charlet K, Beck A, Heinz A. The dopamine system in mediating alcohol effects in humans. *Current Topics in Behavioral Neurosciences*. 2013;**13**:461-488
- [31] Thielen RJ, Engleman EA, Rodd ZA, et al. Ethanol drinking and deprivation alter dopaminergic and serotonergic function in the nucleus accumbens of alcohol preferring rats. *The Journal of Pharmacology and Experimental Therapeutics*. 2004;**309**:216-225
- [32] Brodie MS. Increased ethanol excitation of dopaminergic neurons of the ventral tegmental area after chronic ethanol treatment. *Alcoholism: Clinical and Experimental Research*. 2002;**26**:1024-1030
- [33] Engleman EA, McBride WJ, Li TK, et al. Ethanol drinking experience attenuates (-) sulphiride-induced increases in extracellular dopamine levels in the nucleus accumbens of alcohol-preferring (P) rats. *Alcoholism: Clinical and Experimental Research*. 2003;**27**:424-431

- [34] Bailey CP, O'Callaghan MJ, Croft AP, et al. Alterations in mesolimbic dopamine function during the abstinence period following chronic ethanol consumption. *Neuropharmacology*. 2001;**41**:989-999
- [35] Barak S, Carnicella S, Yowell QV, et al. Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: Implications for alcohol reward and seeking. *The Journal of Neuroscience*. 2011;**31**:9885-9894
- [36] Martinotti G, Di Nicola M, Di Giannantonio M, et al. Aripiprazole in the treatment of patients with alcohol dependence: A double-blind, comparison trial vs. naltrexone. *Journal of Psychopharmacology*. 2009;**23**:123-129
- [37] Carlson NR. *Physiology of Behaviour*. Boston, MA: Allyn & Bacon; 1998
- [38] Lovinger DM. The role of serotonin in alcohol's effects on the brain. *Current Separations*. 1999;**18**:23-28
- [39] Rodd ZA, Gryszowka VE, Toalston JE, et al. The reinforcing actions of a serotonin-3 receptor agonist within the ventral tegmental area: Evidence for subregional and genetic differences and involvement of dopamine neurons. *The Journal of Pharmacology and Experimental Therapeutics*. 2007;**321**:1003-1012
- [40] Petrakis IL. A rational approach to the pharmacotherapy of alcohol dependence. *Journal of Clinical Psychopharmacology*. 2006;**26**(Suppl. 1):S3-S12
- [41] Pettinati HM, Oslin DW, Kampman KM, et al. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *The American Journal of Psychiatry*. 2010;**167**:668-675
- [42] Petrakis IL, Ralevski E, Desai N, et al. Noradrenergic vs serotonergic antidepressant with or without naltrexone for veterans with PTSD and comorbid alcohol dependence. *Neuropsychopharmacology*. 2012;**37**:996-1004
- [43] Book SW, Thomas SE, Randall PK, et al. Paroxetine reduces social anxiety in individuals with a co-occurring alcohol use disorder. *Journal of Anxiety Disorders*. 2008;**22**:310-318
- [44] Simon O'Brien E, Legastelois R, Houchi H, et al. Fluoxetine, desipramine, and the dual antidepressant milnacipran reduce alcohol self-administration and/or relapse in dependent rats. *Neuropsychopharmacology*. 2011;**36**:1518-1530
- [45] Szumlinski KK, Diab ME, Friedman R, et al. Accumbens neurochemical adaptations produced by binge-like alcohol consumption. *Psychopharmacology (Berlin)*. 2007;**190**:415-431
- [46] Gardoni F, Di Luca M. New targets for pharmacological intervention in the glutamatergic synapse. *European Journal of Pharmacology*. 2006;**545**(1):2-10
- [47] Machu TK. Therapeutics of 5-HT₃ receptor antagonists: Current uses and future directions. *Pharmacology & Therapeutics*. 2011;**130**(3):338-347

- [48] Pandey SC. Neuronal signalling systems and ethanol dependence. *Molecular Neurobiology*. 1998;**17**:1-15
- [49] Pratt OE, Rooprai HK, Shaw GK, et al. The genesis of alcoholic brain tissue injury. *Alcohol and Alcoholism*. 1990;**25**:217-230
- [50] Heap L, Ward RJ, Abiaka C, et al. The influence of brain acetaldehyde on oxidative status, dopamine metabolism and visual discrimination task. *Biochemical Pharmacology*. 1995;**17**:263-270
- [51] Sohda T, Shimizu M, Kamimura S, et al. Immunohistochemical demonstration of ethanol-inducible P450 2E1 in rat brain. *Alcohol*. 1993;(Suppl 1B):69-75
- [52] Bison S, Crews F. Alcohol withdrawal increases neuropeptide Y immunoreactivity in rat brain. *Alcoholism: Clinical and Experimental Research*. 2003;**27**:1173-1183
- [53] Schreck R, Albermann K, Baeuerle PA. Nuclear factor kappa B: An oxidative stress-responsive transcription factor of eukaryotic cells (a review). *Free Radical Research Communications*. 1992;**17**:221-237
- [54] Bowie A, O'Neill LA. Oxidative stress and nuclear factor kappa B activation: A reassessment of the evidence in the light of recent discoveries. *Biochemical Pharmacology*. 2000;**59**:13-23
- [55] Ward RJ, Zhang Y, Crichton RR, et al. Expression of NF kappa B in rat brain after administration of ethanol in vivo. *FEBS Letters*. 1996;**389**:119-122
- [56] Crews FT, Collins MA, Dlugos C, et al. Alcohol-induced neurodegeneration: When, where and why. *Alcoholism: Clinical and Experimental Research*. 2004;**28**:350-364
- [57] Pandey SC, Ugale R, Zhang H, Tang L, Prakash A. Brain chromatin remodeling: A novel mechanism of alcoholism. *The Journal of Neuroscience*. 2008a;**28**(14):3729-3737
- [58] Lewohl JM, Wang L, Miles MF, Zhang L, Dodd PR, Harris RA. Gene expression in human alcoholism: Microarray analysis of frontal cortex. *Alcoholism: Clinical and Experimental Research*. 2000;**24**(12):1873-1882
- [59] Iwamoto K, Bundo M, Yamamoto M, Ozawa H, Saito T, Kato T. Decreased expression of NEFH and PCP4/PEP19 in the prefrontal cortex of alcoholics. *Neuroscience Research*. 2004;**49**(4):379-385
- [60] Miles MF, Diaz JE, DeGuzman V. Ethanol-responsive gene expression in neural cell cultures. *Biochimica et Biophysica Acta*. 1992;**1138**(4):268-274
- [61] Kwon JY, Hong M, Choi MS, Kang S, Duke K, Kim S, et al. Ethanol-response genes and their regulation analyzed by a microarray and comparative genomic approach in the nematode *Caenorhabditis elegans*. *Genomics*. 2004;**83**(4):600-614
- [62] Wang J, Gutala R, Sun D, Ma JZ, Sheela RC, Ticku MK, et al. Regulation of platelet-derived growth factor signaling pathway by ethanol, nicotine, or both in mouse cortical neurons. *Alcoholism: Clinical and Experimental Research*. 2007;**31**(3):357-375

- [63] Treadwell JA, Singh SM. Microarray analysis of mouse brain gene expression following acute ethanol treatment. *Neurochemical Research*. 2004;**29**(2):357-369
- [64] Pignataro L, Miller AN, Ma L, Midha S, Protiva P, Herrera DG, et al. Alcohol regulates gene expression in neurons via activation of heat shock factor 1. *The Journal of Neuroscience*. 2007;**27**(47):12957-12966
- [65] Mulligan MK, Ponomarev I, Hitzemann RJ, Belknap JK, Tabakoff B, Harris RA, et al. Toward understanding the genetics of alcohol drinking through transcriptome meta-analysis. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;**103**(16):6368-6373
- [66] He J, Crews FT. Increased MCP-1 and microglia in various regions of the human alcoholic brain. *Experimental Neurology*. 2008;**210**(2):349-358
- [67] Crews FT, Qin L, Sheedy D, et al. High mobility group box 1/toll-like receptor danger signaling increases brain neuroimmune activation in alcohol dependence. *Biological Psychiatry*. 2013;**73**(7):602-612
- [68] Vivivani B, Bartesaghi S, Gardoni F, et al. Interleukin-1 β enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *The Journal of Neuroscience*. 2003;**23**(25):8692-8700
- [69] Vetreno RP, Qin L, Crews FT. Increased receptor for advanced glycation end product expression in the human alcoholic prefrontal cortex is linked to adolescent drinking. *Neurobiology of Disease*. 2013;**59**:52-62
- [70] Chastain LG, Sarkar DK. Role of microglia in regulation of ethanol neurotoxic action. *International Review of Neurobiology*. 2014;**118**:81-103
- [71] Alfonso-Loeches S, Guerri C. Molecular and behavioral aspects of the actions of alcohol on the adult and developing brain. *Critical Reviews in Clinical Laboratory Sciences*. 2011;**48**(1):19-47
- [72] Boyadjieva NI, Sarkar DK. Role of microglia in ethanol's apoptotic action on hypothalamic neuronal cells in primary cultures. *Alcoholism: Clinical and Experimental Research*. 2010;**34**(11):1835-1842
- [73] Guadagno J, Xu X, Karajgikar M, et al. Microglia-derived TNF α induces apoptosis in neural precursor cells via transcriptional activation of the Bcl-2 family member puma. *Cell Death & Disease*. 2013;**4**:e538
- [74] Qin L, Crews FT. Chronic ethanol increases systemic TLR3 agonist-induced neuroinflammation and neurodegeneration. *Journal of Neuroinflammation*. 2012;**9**(130)
- [75] Boyadjieva NI, Sarkar DK. Cyclic adenosine monophosphate and brain-derived neurotrophic factor decreased oxidative stress and apoptosis in developing hypothalamic neuronal cells: Role of microglia. *Alcoholism: Clinical and Experimental Research*. 2013;**37**(8):1370-1379

- [76] Kuhn P, Sarkar DK. Ethanol induces apoptotic death of beta-endorphin neurons in the rat hypothalamus by a TGF-beta 1-dependent mechanism. *Alcoholism: Clinical and Experimental Research*. 2008;**32**(4):706-714
- [77] Qin L, Crews FT. NADPH oxidase and reactive oxygen species contribute to alcohol-induced microglial activation and neurodegeneration. *Journal of Neuroinflammation*. 2012;**9**(5):1742-2094
- [78] Banks WA, Erickson MA. The blood-brain barrier and immune function and dysfunction. *Neurobiology of Disease*. 2010;**37**(1):26-32
- [79] Ferrier L, Berard F, Debrauwer L, et al. Impairment of the intestinal barrier by ethanol involves enteric microflora and mast cell activation in rodents. *American Journal of Pathology*. 2006;**168**(4):1148-1154
- [80] Sims GP, Rowe DC, Rietdijk ST, et al. HMGB1 and RAGE in inflammation and cancer. *Annual Review of Immunology*. 2010;**28**:367-388
- [81] Qin L, He J, Hanes RN, et al. Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. *Journal of Neuroinflammation*. 2008;**5**:10