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Hydrogen sulfide, endoplasmic reticulum stress and alcohol mediated neurotoxicity

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Abstract

Alcohol is one of the most socially accepted addictive drugs in modern society. Its abuse affects virtually all organ systems with the central nervous system (CNS) being particularly vulnerable to excessive alcohol exposure. Alcohol exposure also causes profound damage to both the adult and developing brain. Excessive alcohol consumption induces numerous pathophysiological stress responses, one of which is the endoplasmic reticulum (ER) stress response. Potential mechanisms that trigger the alcohol induced ER stress response are either directly or indirectly related to alcohol metabolism, which include toxic levels of acetaldehyde and homocysteine, oxidative stress and abnormal epigenetic modifications. Growing evidence suggests that H_2S is the most recently recognized gasotransmitter with tremendous physiological protective functions against oxidative stress induced neurotoxicity. In this review we address the alcohol induced oxidative stress mediated ER stress and the role of H_2S in its mitigation in the context of alcohol neurotoxicity. Interruption of ER stress triggers is anticipated to have therapeutic benefits for alcohol mediated diseases and disorders.

Keywords

Endoplasmic reticulum stress; Alcohol; Homocysteine; Unfolded protein response; Reactive oxygen species; Hydrogen sulfide

1. Introduction

Alcohol is one of the most socially accepted addictive drugs in modern society. Alcohol abuse can have devastating effects on individuals' health, careers and relationships (Cheng, 2012). Excessive alcohol use is the third leading cause of preventable death in the United States and is responsible for 3.8% of deaths worldwide (Gunzerath et al., 2011; Rehm et al., 2009). Alcohol is readily spread throughout the body in the blood stream and crosses biological membranes which, affects virtually all biological processes. Continual alcohol abuse leaves profound effects in virtually all organ systems with the central nervous system (CNS) being particularly vulnerable to excessive alcohol exposure. Alcohol exposure also causes profound damage to both the adult and developing brain (Yang and Luo, 2015).

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Excessive alcohol consumption induces numerous pathophysiological stress responses part of which, is the endoplasmic reticulum (ER) stress response. ER stress, a condition under which unfolded/misfolded proteins accumulate in the ER, contributes to alcoholic disorders of major organs such as the liver, pancreas, heart and especially the brain. Potential mechanisms that trigger the alcoholic ER stress response are either directly or indirectly related to alcohol metabolism which, include toxic levels of acetaldehyde and homocysteine, oxidative stress and abnormal epigenetic modifications (Cheng, 2012).

The ER is a regulator of posttranslational protein processing and transport. The accumulation of unfolded or misfolded proteins in the ER lumen triggers ER stress inducing the unfolded protein response (UPR) which, is mediated by three transmembrane ER signaling proteins: pancreatic endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6) (Yang and Luo, 2015). UPR is initiated to protect cells from overwhelming ER protein loading and sustained ER stress may result in cell death. ER stress has been implied in various CNS injuries including brain ischemia, traumatic brain injury and aging-associated neurodegeneration such as vascular dementia (VAD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD). However; the effects of alcohol on ER stress in the CNS receive less attention (Yang and Luo, 2015). In this review we address the alcohol induced oxidative stress mediated ER stress and the role of H_2S in its mitigation in the context of alcohol neurotoxicity. Interruption of ER stress triggers is anticipated to have therapeutic potential to manage alcohol related diseases and disorders.

2. Homocysteine and alcohol mediated neurotoxicity

Homocysteine (Hcy) is a normal intermediate involved in the metabolism of the essential amino acid methionine. Alcohol interferes with the Hcy metabolism in multiple ways (Fig. 1) which leads to increased accumulation of Hcy in plasma, inducing hyperho-mocysteinemia (HHcy) (Gibson et al., 2008). Along with alcohol, dietary methionine drives a transient increase in methionine, S-adenosylmethionine (SAM) and Hcy (Finkelstein and Martin, 1986). HHcy is reportedly associated with insulin resistance (Meigs et al., 2001) and it is a common risk factor in Type 2 Diabetes (Qureshi et al., 2003). HHcy is an independent risk factor in cardiovascular, neuroinflammatory and neurodegenerative diseases, obesity and hepatic steatosis (Seshadri et al., 2002). HHcy is also associated with damage to the vascular system by a mechanism related to oxidative stress resulting in a build-up of damaging free hydrogen radicals (Tyagi et al., 2005). Different investigations have shown that alcohol consumption, particularly in actively drinking alcoholics, is closely associated with elevated plasma Hcy levels. Human studies suggest that Hcy plays a role in brain damage including a decline in cognitive functions and memory. Mild to moderate HHcy is a known risk factor for neurodegenerative and neurovascular diseases. Hcy or folate and vitamin B12 deficiency can cause disturbed methylation and/or redox potentials thereby, promoting calcium influx, amyloid and tau protein accumulation, apoptosis and neuronal death. Hcy promotes neuronal degeneration contributing to psychiatric and age-related neurodegenerative diseases. Hcy metabolism in relation to neurodegenerative diseases arises from the fact that plasma concentrations of Hcy increase with age (Herrmann et al., 1999) and it is considered a risk factor for vascular disease as well as brain atrophy (den Heijer et

al., 2003). Total fasting Hcy (tHcy) concentrations greater than 11.9 μmol/L were associated with a higher risk for white matter damage when compared to concentrations below 8.6 μmol/L (Wright et al., 2005). The epidemiological and longitudinal studies of Nurk et al. (2005) suggested a causal link between Hcy and cognitive impairment. This link might be due to cerebrovascular as well as direct neurotoxic mechanisms (Sachdev, 2005). Changes in Hcy levels are also predicted to cause a decline in memory scores in elderly subjects (Nurk et al., 2005). Several follow up studies demonstrated a positive association between the level of Hcy and cognitive functions (Seshadri et al., 2002). Alcohol induced genetic alteration and its consequences lead to decreased expression of Hcy-metabolizing enzymes such as cystathionine β-synthase (CBS), cystathionine-7-lyase (CSE), methylene tetrahy-drofolate reductase (MTHFR) and methionine synthase (MS) thus, inducing HHcy (Dayal et al., 2004). Changes in plasma Hcy concentrations reflect one aspect of the metabolic consequences of methyl group deficiencies. Folic acid supplementation helps to alleviate these deficiencies because betaine works as a methyl donor. Betaine is a significant determinant of plasma Hcy particularly in cases of folate deficiency, methionine overload or alcohol consumption. Betaine supplementation has a lowering effect on methionine load and high Hcy levels. Increasing choline or betaine levels can reduce hypomethylation and lower Hcy levels. Folic acid supplementation also lowers the risk factor for stroke by reducing tHcy levels. Increased levels of Hcy can cause elevated blood pressure and are considered a risk factor for cerebrovascular dysfunction. In particular, Hcy levels are increased in the body when metabolism of cysteine or methionine is impaired. This often occurs due to dietary deficiencies in B vitamins such as vitamin B6, vitamin B12 and folic acid. Chronic alcohol consumption negatively impacts dietary choices and significantly reduces absorption of B vitamins. It has been shown that Hcy is regulated through a series of pathways which, are dependent on B vitamins particularly folate (Halsted et al., 2002). However; it remains obscure whether alcohol dependent patients benefit from Hcy lowering strategies through folate, vitamin B6 or B12 supplementation particularly, in those who have a low folate status. Reports have also suggested that consumption of alcohol along with a folate-deficient diet is associated with increased levels of Hcy (Halsted et al., 2002). Thus, it may be concluded that increased alcohol intake and a low folate diet may lead to HHcy. Previous studies imply, excess accumulation of Hcy in the body causes cell damage and promotes vascular and microvascular disorders that lead to cerebrovascular dysfunction (Dayal et al., 2004; Kamat et al., 2013).

3. ER stress and alcohol mediated neurotoxicity

The efficient functioning of the ER is indispensable for most cellular activities and survival, as it involves the synthesis, folding, modification and transport of newly synthesized transmembrane and secretory proteins. The accumulation of unfolded or misfolded proteins in the ER lumen induces UPR which, triggers ER stress that is mediated by three transmembrane ER signaling proteins: PERK, IRE1 and ATF6. UPR is initiated to protect cells from overwhelming the ER with protein loading. However; sustained ER stress may result in cell death. ER stress has been implied in various CNS injuries, including brain ischemia, traumatic brain injury and aging-associated neurodegenerative and neurovascular disorders. However; the effects of alcohol on ER stress in the CNS receive less attention.

The ER also has important roles in the storage of intracellular Ca^{2+} and regulation of Ca^{2+} homeostasis. The integrity of the Ca^{2+} homeostasis in the ER lumen is vital for proper folding of proteins. A downregulation of ER Ca^{2+} could result in an increase of unfolded or misfolded proteins and ER stress. The ER stress response constitutes a cellular process that is triggered by a variety of conditions that disturb the folding of proteins in the ER. It has been observed that activated ER stress pathways contribute to the pathogenesis of important diseases including diabetes and cancer (Wang and Kaufman, 2012). Altered regulation of ER stress has also been revealed in various forms of CNS injury including brain ischemia, traumatic brain injury, spinal cord injury, epilepticus as well as neurodegeneration encompassing PD, ALS, AD and HD (Placido et al., 2015). The expression of ER stress markers, such as GPR78, PERK, EIF2 and IRE1 are altered in AD patient samples (Hoozemans et al., 2009). The accumulation of ER stress-associated proteins such as, Hrd1p/Der3p (HRD1) that enhance ubiquitination, have been observed within neurons of brain tissue in PD patients (Nakashima et al., 2012). Enhanced ER stress stimulates production of reactive oxygen species (ROS) in multiple pathways. This interruption of ER stress triggers is anticipated to have immense therapeutic benefits and clinical potential for alcohol related disorders.

4. Oxidative stress and alcohol mediated neurotoxicity

Cells have basal levels of ROS for signaling and normal functioning. In contrast, ROS levels increase upon stress or during enzymatic reactions e.g., mitochondrial respiratory chain reactions, arachidonic acid pathway, cytochrome P450 family and those involving glucose oxidase, amino acid oxidase, xanthine oxidase, NADP/NADPH oxidase, NO synthases (Malhotra and Kaufman, 2007), protein disulfide isomerases, endoplasmic reticulum oxidoreductin-1(ERO-1) and NADPH oxidase (Santos et al., 2009). Both oxidative stress and ER stress increase the leakage of Ca^{2+} from the ER lumen (Berridge et al., 2003). Increases in cytosolic Ca^{2+} can stimulate mitochondrial ROS production. Oxidative stress has been proposed as a major contributor to alcohol induced multiorgan damage, including CNS pathogenesis (Comporti et al., 2010).

ROS is generated during alcohol metabolism (Fig. 2) or Hcy can undergo autoxidation thus, causing the disruption of redox homeostasis and effecting redox signaling pathways (Zou and Banerjee, 2005). Hcy has also been found to induce neurological dysfunction via oxidative stress (Ho et al., 2001). Antioxidant treatment restores several of the toxic effects Hcy has on neurological function (Jara-Prado et al., 2003). The role of oxidative stress in neurodegeneration has previously been intensively studied. Oxidative stress was one important mechanism for Hcy toxicity in neuronal cells (Ho et al., 2003). Hcy directly increased the neurotoxicity of amyloid-β peptide (Aβ) by inducing oxidative stress (Ho et al., 2001). The cytotoxicity of Hcy was mitigated by antioxidants like N-acetyl cysteine, vitamin E or vitamin C (Ho et al., 2001). Antioxidants (vitamin E or vitamin C) also prevented memory dysfunction and ATPase activity caused by HHcy in rats. Other studies by Ho et al. (2003) showed the effect of folate deficiency on the CNS (Kruman et al., 2005). Folate deprivation induced a marked increase in Hcy, ROS, and Aβ-induced apoptosis, while folate supplementation prevented the generation of ROS by Aβ (Ho et al., 2003). Treatment with the S-adenosyl hydrolase inhibitor, 3-deaza adenosine, provided neuroprotection in

normal and apolipoprotein E-deficient mice, as well as in cultured neuronal cells deprived of folate and vitamin E subjected to oxidative challenge (Tchantchou et al., 2004). Thus, it is evident that conscious intervention to reduce ROS mitigates ER stress and consequently neuronal cell survival.

5. Hydrogen sulfide protection against ethanol mediated neuronal damage

Production of gaseous transmitters by mammalian cells has attracted much attention in recent years. The accumulating evidence suggests that despite it being previously seen as a noxious gas, H_2S is rapidly emerging as a gaseous transmitter in addition to nitric oxide (NO) and carbon monoxide (CO) (Hosoki et al., 1997). The latter two molecules are endogenously produced gaseous transmitters that reportedly carry out a tremendous physiological role against free radical mediated oxidative damage in neurodegenerative diseases (Rosselli et al., 1998; Wu and Wang, 2005; Uttara et al., 2009). The third gaseous transmitter, H_2S contributes to the regulation of cardiac function, systemic and pulmonary blood pressure and vasomotor activity, inflammation and angiogenesis (Kohn et al., 2012). All three gasotransmitters CO, NO H_2S have attracted attention because they exert fine modulatory control over cellular functions by influencing an array of intracellular signaling processes (Sen, 2016). H_2S was found to be produced endogenously in various parts of the body such as the heart, blood and CNS (Zhao et al., 2001) by two pyridoxal-5′-phosphate-dependent enzymes. These enzymes are responsible for metabolism of l-cysteine which is a by-product of l-methionine, Hcy and cystathionine. CBS, CSE and a newly identified enzyme 3-mercaptopyruvate sulfurtrans-ferase (3MST) (Sen et al., 2012) are involved in the generation of H_2S. CBS is the major H_2S producing enzyme in the brain (Abe and Kimura, 1996). H_2S can easily penetrate the plasma membrane thus, inducing a wide spectrum of signaling cascades in target cells. Until recently, H_2S was the least appreciated among the three gasotransmitters nevertheless; growing evidences suggests that it may emerge as the most important one. Particularly due to its ability in signaling activity by sulfhydrating target proteins (Sen, 2016). Some studies in cellular and animal models have suggested several mechanisms to explain the protection associated with H_2S including promoting anti-inflammatory responses (Calvert et al., 2010), antiapoptotic effects (Yang et al., 2007), improving mitochondrial action (Kimura et al., 2010), cardiac systolic function, sensory transduction, vasodilation and neuroprotection (Wang, 2012). Endogenous H_2S acts as a potent regulator of various biological processes mainly related to vasomotor function. H_2S regulates intracellular calcium concentrations via L-type calcium channels, T-type calcium channels, sodium/calcium exchangers, transient receptor potential channels, β-adrenergic receptors and NMDA in various cells (Zhang et al., 2015). Physiological concentrations of H_2S enhance the NMDA receptor-mediated responses and modify long-term potentiation (LTP) (Abe and Kimura, 1996). H_2S is able to regulate the activity of several sirtuins and enhance AP-1 binding activity with the SIRT3 promoter, reducing oxidant-provoked vascular endothelial dysfunction (Xie et al., 2016). H_2S and NO signaling pathways have been described to offer protection against AD associated amyloid vasculopathy and neurodegeneration. There are reports of H_2S induced endothelial proliferation and migration as well as enhanced VEGF gene expression. H_2S normalizes intracellular ethanol mediated reduced levels of GSH, the major intracellular antioxidant in the biological system (Kimura

et al., 2006; Kimura and Kimura, 2004; Chen et al., 2016), alleviating ER stress thus, promoting neuronal protection and improving brain function (Fig. 3). H_2S also plays a role in ER stress mitigation by sulfhydration (Krishnan et al., 2011) or scavenging the reactive carbonyl group (Koike and Ogasawara, 2016). There is a growing amount of evidence demonstrating that H_2S is a potential therapeutic molecule that carries tremendous physiological functions.

6. Discussion and future prospective

Unhealthy alcohol consumption remains a principal problem for the public health of individuals and is responsible for high morbidity rates by affecting various organs and organ systems, especially the brain. The mammalian cell has evolved a complex and intertwined set of signaling pathways to respond to both physiological and pathological ER stress. Although these pathways are not yet fully characterized, it is becoming clear that ER stress induced ROS generation and UPR are intimately involved in neuronal damage and various neuronal diseases. Interruption of ER stress triggers is anticipated to have therapeutic benefits for controlling alcohol associated neuronal damage. Studies show that H_2S has remarkable potential as a therapeutic tool by exploiting ways to increase the endogenous level of H_2S. Extensive research on the mechanisms of H_2S and its role in modulation of cellular signaling will provide new insights into the physiological functions of H_2S.

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Abbreviations

CNS	central nervous system
ER	endoplasmic reticulum
Hcy	homocysteine
tHcy	total fasting homocysteine
HHcy	hyperhomocysteinemia
CBS	cystathionine β-synthase
BHMT	betaine methyltransferase
UPR	unfolded protein response
MTHFR	methylene tetrahydrofolate reductase
PERK	pancreatic endoplasmic reticulum kinase
HD	Huntington’s disease
ALS	amyotrophic lateral sclerosis
IRE1	inositol-requiring enzyme 1

ATF6	activating transcription factor 6
GPR 78	G-protein coupled receptor 78
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
VAD	vascular dementia
PD	Parkinson's disease
DNMTs	DNA methyltransferases
MetS	methionine synthase
CSE	cystathionine-γ-lyase
PERK	pancreatic endoplasmic reticulum kinase
IRE1	inositol-requiring enzyme
EIF2	eukaryotic initiation factor 2
ROS	reactive oxygen species
NADP	nicotinamide adenine dinucleotide phosphate
NMDA	N-methyl-D-aspartate receptor
LTP	long-term potentiation
GSH	glutathione
H2S	hydrogen sulfide
AD	Alzheimer's disease

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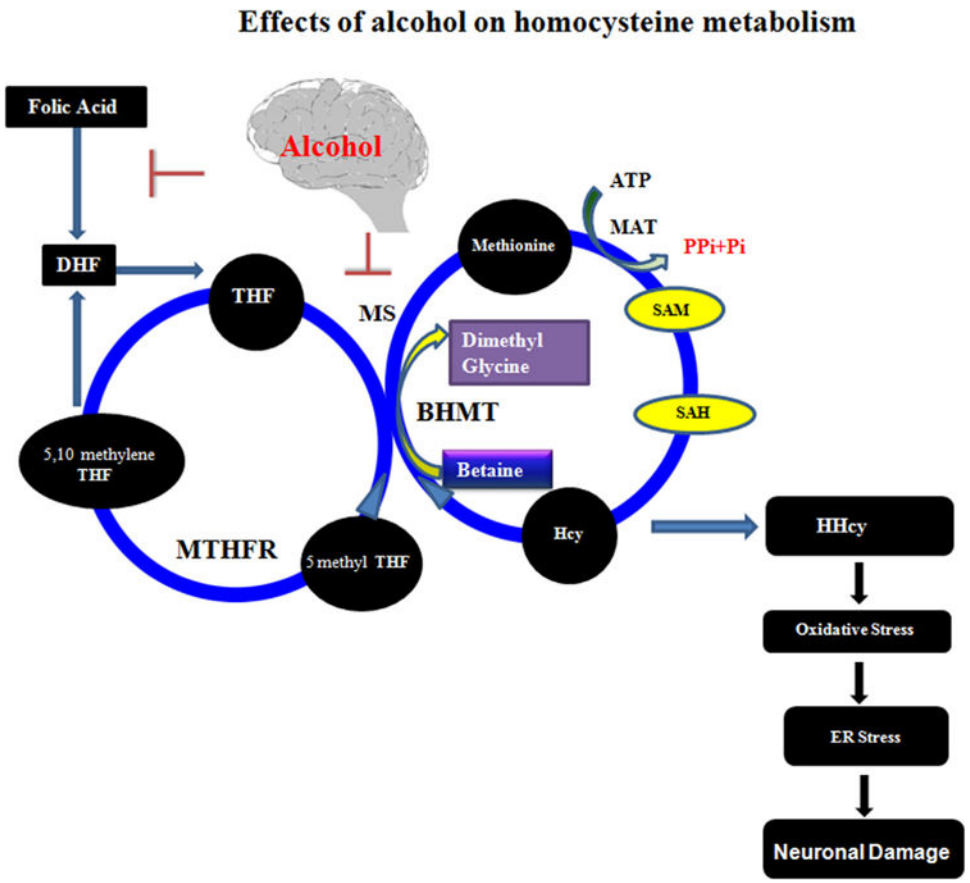

Fig. 1.

Interaction of alcohol in Hcy metabolism and ER stress: Alcohol interacts with methionine synthase (MS), which is responsible for the conversion of Hcy to methionine. One of the possible reasons for HHcy during alcohol exposure may be due to inhibition of the enzyme MS by alcohol, which disallows Hcy to be converted into methionine thus leading to the condition of HHcy. On the other hand, other pathways such as transmethylation may also be affected by the inhibition of MS and may cause abrupt disturbance of S-Adenosyl methionine (SAM) and S-Adenosyl-L-homocysteine (SAH). SAM to SAH conversion is controlled by DNA methyltransferase (DNMT). If the pathway becomes disturbed, the transmethylation process also becomes disturbed. On the other hand, high Hcy also causes the low expression of cystathionine β-synthase (CBS), an antioxidant enzyme in the brain which maintains the redox system. Alcohol also interacts with folic acid pathways. Folic acid is converted into tetrahydrofolate (THF) by the enzyme dihydrofolate reductase (DHFR). THF is converted into methylene tetrahydrofolate (MTHF) by the cofactor vitamin B6. Again MTHF is transformed to THF by the key enzyme, MTHF reductase (MTHFR). In this diagram, the author speculates that alcohol may inhibit folic acid to DHF conversion and methionine synthase activity. In this mechanism, alcohol can trigger HHcy and thus affect the redox system, leading to ER stress resulting in neuronal damage that ends in impaired brain function. H_2S inhibits free-radical reactions and oxidative stress thereby, alleviating ER stress, providing neuronal protection.

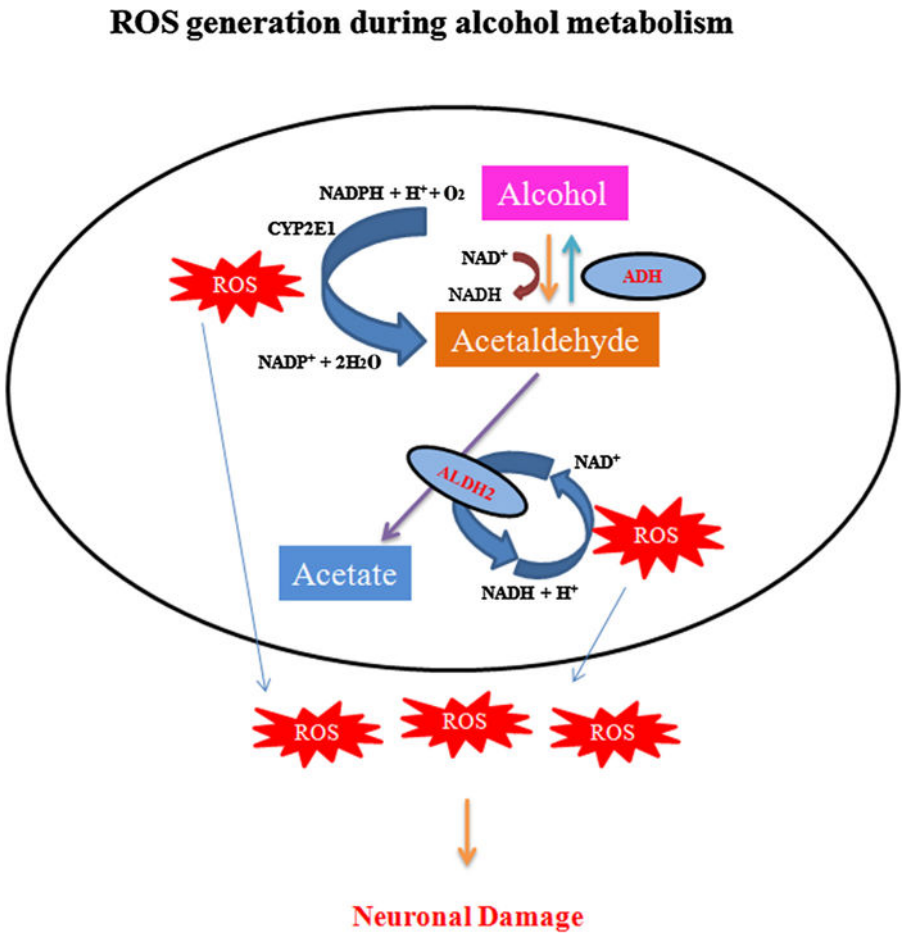

Fig. 2.

Induction of oxidative pathway response during alcohol metabolism. Upon exposure to alcohol, the cellular alcohol dehydrogenase enzyme (ADH) is activated in the cytosol, which metabolizes to produce acetaldehyde. During long term exposure or chronic alcohol consumption, an enzyme in the endoplasmic reticulum, cytochrome P450 IIE1 (CYP2E1), becomes activated and alcohol gets metabolized to acetaldehyde. The derived acetaldehyde enters into the mitochondria and is further metabolized into acetate mainly by aldehyde dehydrogenase 2 (ALDH2). Thereby, it results in the formation of reactive oxygen species (ROS), which leads to neurotoxicity and damage.

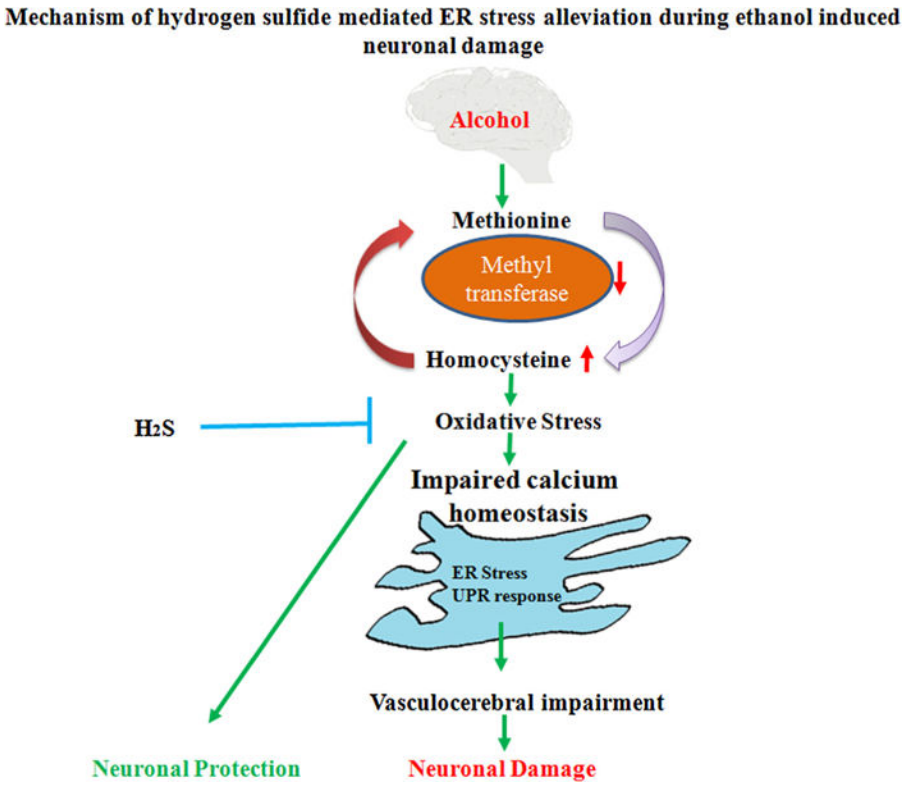

Fig. 3.

Mechanism of hydrogen sulfide mediated ER stress alleviation during ethanol induced neuronal damage. Ethanol causes deregulation of homocysteine metabolism leading to increased cellular Hcy levels. This further accelerates the oxidative pathways. Ethanol induced oxidative stress alters ER redox status and is manifested by activation of the stress response, which leads to cerebrovascular impairment or neuronal damage. H2S can potentially mitigate the cerebrovascular damage by alleviating the ER stress and thus provides neuroprotection.