Status of Oxidative Stress in Alcohol Dependence

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Alcohol-induced oxidative stress (OS) plays a pivotal role in the pathophysiology of alcohol dependence (AD). The opposite trends in the level of SOD and GPx activities in serum/plasma and erythrocytes of male patients could be used as the biomarker of alcohol-induced OS injury, and the synergistic changes of MDA, vitamin B12, albumin, bilirubin, and homocysteine levels should also be considered.

alcohol dependence oxidative stress antioxidant

1. Introduction

Alcohol dependence (AD) or alcoholism is a complex and serious psychiatric disorder that can lead to perturbations in daily physical, psychological, and social functions ^[1]. Currently, AD accounts for a prevalence rate of about 2.6% in the general population ^{[2][3][4]}. The lack of effective prevention strategies, treatments, and rehabilitation programs are the major contributing factors to the increasing global health burden of AD ^[5]. AD pathogenesis is highly complex and involves multifaceted etiological factors, including altered neuroplasticity, neuropsychiatric disorders, disoriented socio-environmental interactions, and genetic inheritance.

The imbalance between the rate of generation of toxic free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) and compromised or insufficient antioxidant defense response can cause chronic oxidative injury to the human body. Although low levels of ROS and RNS play a vital role as secondary signal transducers and gene activators under normal physiological conditions ^{[G][Z]}, persistently accumulating non-neutralized excess free radicals lead to a broad spectrum of oxidative damages to almost all types of major macromolecules, such as DNA, RNA, proteins, and lipids, thereby inducing a number of chronic neuropsychiatric and neurodegenerative diseases ^[B], including mild cognitive impairment (MCI), dementia ^[9], schizophrenia ^[10], and Parkinson's disease (PD) ^[11]. Normally, the human body, especially the brain, possesses excellent antioxidant defense machinery to prevent damages caused by free radical toxicities. However, this preventive mechanism can be compromised under diseased or abnormal health conditions ^{[12][13][14]}.

In the brain, ethanol is oxidized to acetaldehyde through the action of catalases (CATs) ^{[15][16]}, cytochrome P450 enzymes (CYP2E1) ^[17], and alcohol dehydrogenase (ADH) ^{[18][19]}. Notably, CAT and CYP2E1 play major roles in catalyzing the biochemical conversion of ethanol to acetaldehyde ^[20]. It has been found that the expression of CYP2E1 is induced by long-term drinking habits or AD ^[21]. The mechanistic functions of CYP2E1 and ADH

reportedly produce RNS and ROS, which in turn activate downstream enzymes such as nitric oxide synthase, nicotinamide adenine dinucleotide phosphate (NADP) oxidase, and xanthine oxidase [17]. Furthermore, acetaldehyde consumes reduced glutathione (GSH), perturbing the intracellular redox balance, resulting in oxidative stress (OS) [22]. Therefore, alcohol and its toxic metabolites may be the sole cause of increased cellular burdens of ROS/RNS and other types of highly reactive free radicals and superoxides, leading to the OS injuries to the vital organs of the body ^[23]. It has been demonstrated that an initial high level of OS can activate the antioxidant defense to scavenge free radicals and prevent lethal free radical chain reactions [24]. Hence, increased activity of antioxidant enzymes, including glutathione peroxidase (GPx), superoxide dismutase (SOD), glutathione reductase (GR), and CAT, is observed in AD patients [25][26]. Moreover, during the process of ROS/RNS neutralization and prevention of systemic free radical chain reactions [27][28], the levels of non-enzymic antioxidants such as vitamin B9 (folate), vitamin B12 ^[29], GSH ^{[30][31]}, bilirubin ^[30], and homocysteine ^[29] are significantly increased. On the other hand, levels of certain antioxidant enzymes (SOD, CAT, GPX) [30][32] and non-enzymatic molecules (vitamin E/ α -tocopherol, albumin, vitamin C/ascorbic acid) ^[33] remain unchanged or decrease under OS. Ethanol-induced ROS causes oxidative damages in multiple ways, including oxidation of DNA/RNA/protein/lipid molecules, covalent adduct formation between acetaldehyde and membrane lipids [34] initiating lipid peroxidation and malondialdehyde (MDA) production [35][36][37], protein carbonylation [38], and generation of 8-hydroxy-2'deoxyguanosine (8-OHdG) as a marker of oxidative DNA damage ^[35]. Therefore, chronic exposure to alcohol or persistent AD can lead to OS-mediated pathological alterations in brain microstructures and the functional connectivity among neuronal circuitry, resulting in cognitive impairment [39][40][41], which may turn into Wernicke's encephalopathy (WE) [42] or Korsakoff syndrome (KS) [43][44] in the long run. Alcohol-induced OS may also induce pathogenesis of major diseases [45][46][47]. Therefore, due to the inconsistent changes in OS markers and the possible serious health complications of AD patients, it is of utmost importance to delineate the actual level of OS induction in AD subjects.

2. Status of Oxidative Stress

Drinking alcohol is an integral part of most national cultures ^{[48][49]}. For example, drinking may be regarded as a symbol of friendship and social unity. However, uncontrolled alcohol consumption is one of the top 10 risk factors for death worldwide ^[1]. However, studies have shown that no level of alcohol consumption is good for health: that is, the safe drinking level is no drinking ^[50]. Drinking alcohol may have a variety of harmful impacts, such as interpersonal violence ^[51], suicide and self-harm ^{[52][53]}, road accident ^{[54][55]}, drowning ^[56], work injury ^{[57][58]}, and serious socio-economic burden as well. Alcohol is a commonly used psychoactive substance. Excessive consumption can cause neuropathological symptoms ^[59], cardiovascular diseases ^[60], liver diseases ^[61], intestinal diseases ^[62], liver cancers ^[63], and infectious diseases due to the weakened immune system of the body ^[64]. The main component of alcoholic drinks is ethanol, which has shown to exert oxidative damages to biological macromolecules via acetaldehyde-DNA/RNA/protein adduct formation, thereby drastically inducing cellular ROS production and systemic OS ^{[14][19][22]}. These toxic conditions can then lead to abrupt changes in the levels of antioxidant enzymes and other forms of antioxidant molecules in the body.

SOD plays a major role in antioxidant defense mechanisms ^[65], especially to protect mitochondrial, cytoplasmic, and peroxisomal membranes $\frac{[66][67]}{[67]}$ where it converts superoxide radicals into hydrogen peroxide (H₂O₂) molecules, which are then biochemically degraded into water and oxygen by GPx and CAT [68][69], and also regulates the superoxide free radical level in the cell [70][71]. Animal experiments have revealed that the SOD activity in erythrocytes of alcohol-fed rats is significantly lower compared with that of sham-treated animals ^[72], which is consistent with the significant decrease in SOD activity in erythrocytes of AD patients, especially males. The phenomena might be explained by the fact that there is a large amount of cytoglobin in erythrocytes, which has a function similar to SOD and can accelerate the disproportionation of superoxide radicals with the catalytic efficiency of SOD ^[72]. Therefore, cytoglobins may inhibit the enzymatic activity of SOD in RBC by competition due to the greater amount. Additionally, alcohol consumption can lead to the reduction in zinc, which is an essential trace element in the human body as well as an important cofactor of SOD and many critical transcription factors ^[73]. Alcohol intake also causes deficiency of vitamin D in humans ^[74], leading to suppressed mRNA expression and enzymatic activity of SOD1 ^[75]. Other studies have reported that free radicals produced by ethanol metabolism can react with copper and zinc SODs, resulting in their functional inactivation ^[76]. Researchers noticed that the activity of SOD in serum/plasma samples of AD patients was significantly increased, which might be due to the large pool of toxic ROS and the resulting OS, caused by the degradation of alcohol in the human body. This situation can induce the activation of antioxidant factors, including SOD, to neutralize those free radicals. The hemolysis caused by RBC membrane rupture may also be another reason for the increased SOD or GPx activity in serum/plasma of AD patients. However, it has been shown that the SOD activity in serum/plasma [77], synaptosomes [78], kidney, and liver ^[78] decreases during the long-term feeding of an alcohol diet to the experimental animals. This inconsistency may indicate that serum/plasma SOD activity in animal experiments may not represent the actual pathobiological scenario in human AD patients, or it could be individualized effects. Furthermore, the activity of SOD in plasma/serum is too low, and the measuring methodology should be essential for precising detection.

GPx commonly refers to the members of glutathione isozyme families that use reduced GSH as an electron donor to break down H₂O₂ or organic hydroperoxide into water or corresponding alcohol ^[79]. The expressions of different subtypes of GPx in different tissues of the human body have their specificities ^{[80][81]}. GPx enzymes coordinate with several other signaling molecules to mediate the antioxidant defense processes and inhibit inflammatory responses ^[80]. GPx plays an important role in promoting the repair of vascular endothelial cells and functionally damaged neurotransmitters following the OS injury and thus helps in delaying cellular aging ^[82]. The results showed that the enzymatic activity of GPx in RBCs of AD patients, especially males, was significantly decreased, which was consistent with the findings of a previous study ^[71]. One possible explanation might be the increased level of acetaldehyde under the OS condition and the resulting inhibition of activities of both GSH and GPx. Other animal experiments have also supported the fact that ethanol exposure can significantly increase the GPx activity of male Wistar rats in the epididymis (21 days) ^[83] or liver tissues (63 days) ^[84], which were again consistent with the results of the meta-analysis using human AD patients. Hemolysis-mediated RBC breakdown might increase the GPx activity in serum/plasma of AD subjects. However, the GPx activity in the liver of female mice was significantly decreased after 30 days of ethanol exposure ^[85] and also in the kidney and liver of male rats ^[78]. suggesting that

the effects of alcohol-induced GPx activity may vary in a tissue type and gender-specific manner. Taken together, these factors may partly explain the non-statistically significant changes in plasma GPx activities in AD patients.

It was found that the activities of SOD and GPx were enhanced in plasma/serum samples and diminished in erythrocytes of AD patients, while these two enzymes often produced synergistic effects on OS ^[86]. Therefore, it could be considered in the future as a combined biomarker of OS levels in such patients. Although animal experiments have shown that female and male animals may have different levels of OS during alcohol exposure and that females are more susceptible to alcohol damage ^[87], due to the lack of sufficient clinical data in female patients, researchers could not recapitulate that analysis. In the future, a large number of studies are needed to explore whether this observation leads to a different mechanism of OS management in female AD patients than in males.

CAT is a key enzyme in the metabolism of H_2O_2 and RNS. In a study, no significant changes in CAT activity were found in serum/plasma or erythrocytes, possibly because CAT could be involved in the oxidative metabolism of ethanol on the one hand ^{[15][16]}, and in the metabolism of H_2O_2 on the other hand, which may have a competitive inter-relationship. In addition, studies have demonstrated that there are no adaptive changes in CAT activity in the myocardium and brain of alcohol-fed rats ^{[88][89]}, which seems to indicate that alcohol may not affect CAT activity in humans.

MDA, a toxic by-product and one of the biomarkers of OS ^{[90][91]}, is the most studied product of polyunsaturated fatty acid (PUFA) peroxidation ^[92]. The results showed that the most severe lipid-peroxidation-mediated oxidative damages were found in the serum/plasma and erythrocyte membranes of AD patients compared to that in control subjects, which was in agreement with the increased MDA levels observed in the 60-day alcohol-fed albino Wistar rats ^[71]. In vivo studies have further confirmed that OS-induced lipid peroxidation causes the maximum damage to the erythrocyte membranes of alcohol-exposed rats ^{[71][93]}, which was in line with the previous results ^{[94][95]}. Notably, there could be certain technical artifacts that could influence the above finding. First, hemolysis might become activated during the isolation of erythrocytes from plasma/serum samples, which could then increase the MDA level in the respective samples. Second, membrane phospholipids could undergo rapid peroxidation during the preparation of tissue homogenates, resulting in the overestimation of MDA levels in the downstream analysis. Hence, it is necessary to take preventive measures to avoid any unwanted production of aldehydes in the process of organelle separation ^[96]. Third, an inappropriate diet (e.g., high protein or fat) can also lead to OS, manifested as an increased level of urinary MDA ^{[97][98]}. Moreover, the level of MDA is associated with gender, age ^[99], vitamin status, and smoking habits ^[100]. Considering the above possibilities, the MDA level may be considered as the OS biomarker for evaluating the status of erythrocyte membrane damage in AD patients.

Bilirubin is a potent scavenger of ROS and RNS/NO ^{[101][102]}. It can modulate the levels of pro-inflammatory cytokines, thereby inhibiting the migration/infiltration of activated immune cells to the lesion sites ^[103]. Experiments in albino male Wistar rats chronically treated with an alcohol diet for 28 days ^[104] or 60 days ^[105], as well as 30 days of alcohol exposure to ICR mice ^[106], consistently demonstrated a significant increase in the total plasma/serum bilirubin levels, which were in line with the observations in the present study. Bilirubin inhibits the

glucuronidation of ethanol via the competitive binding with UDP-glucuronosyltransferase 1A1 [107]. Hence, it is considered an in vivo protective factor [108][109] against the pathological onset of cardiovascular diseases and type 2 diabetes in AD patients. Vitamin B12 (cobalamin) deficiency is a common cause of various neuropsychiatric symptoms [110][111]. Elevated serum B12 levels might be indicative of many serious underlying health complications such as solid tumors, liver cirrhosis, hepatic carcinoma, and chronic renal failure [112][113]. In a study, significantly elevated vitamin B12 levels suggest serious hepatotoxicity in individuals with uncontrolled alcohol consumption, resulting in the dysfunctional vitamin B12 metabolism [113][114], which could be reflected in the dramatic elevation of plasma/serum vitamin B12 levels. Therefore, vitamin B12 could be used as a biomarker to predict the status of liver lesions in this subset of patients [115]. Homocysteine is a sulfur-containing amino acid, and its metabolism is related to the cellular concentrations of folic acid and vitamin B12 [116]. Animal studies using the AD mice model have shown that chronic drinking can significantly increase the level of plasma homocysteine [117][118], which was consistent with the results. Excessive homocysteine can impair various physiological mechanisms, especially the amino acid metabolism pathways [119]. Moreover, it can induce neuronal damage by stimulating the N-methyl-Daspartate (NMDA) receptor activity and overproduction of toxic free radicals, leading to neurodegenerative conditions, brain atrophy, and withdrawal seizures in susceptible individuals [120]. Serum albumin plays potential roles in anti-inflammatory, antioxidant, anticoagulant, and anti-platelet aggregation mechanisms [121][122]. A mice study exhibited a significant decrease in the serum albumin level after 2 days of alcohol exposure [123]. Similar effects have also been observed in adult Wistar rats following 28 days of alcohol exposure $\frac{124}{2}$. Taken together, findings from these acute and chronic alcohol exposure studies were consistent with the results, suggesting that reduced albumin levels could be a risk factor for cardiovascular diseases [121], liver diseases [125], and kidney diseases [126]. Thus, changes in albumin levels in AD patients may have certain clinical implications in the diagnosis, treatment, and rehabilitation strategies.

Among the several limitations, the small number of the included research was a major drawback, which led to the fact that the individual OS-related biomarkers used in the meta-analysis could not be analyzed and corrected for the quantitative publication bias but could only be analyzed from the funnel plot. Researchers speculate that most of the reported indicators may have publication bias, which could be attributed to multiple factors, such as (1) the enrolled studies were published over a long period (1993-2019) and (2) both DSM and ICD scales have undergone significant improvement in their diagnostic standards (DMS-III/IV/V and ICD-10/11). The alcohol abuse and alcohol dependence were combined into alcohol use disorder in DSM-5; therefore, it may excluded that some recent research due to the searching strategy. However, there are some differences in status between alcohol abuse and alcohol dependence, which may affect oxidative stress status. First, alcohol abuse (ICD-10-F10.1) patients are those who have suffered physical or mental harm because of alcohol use, but some of these patients may not meet the diagnosis of alcohol dependence (ICD-10-F10.2). Second, alcohol-abuse syndrome did not have an emphasis on repetitive drinking as the cause, whereas alcohol-dependence syndrome had an emphasis on repetitive drinking as well as dependence leading to illness. The mechanism of the changes in antioxidant levels in alcohol-abuse patients at the time of admission (onset) may be different with alcohol-dependent patients; for example, the former may be a manifestation of acute physiological stress, while the latter is a manifestation of long-term alcohol effects on the body. Third, there is possible heterogeneity in patient enrollment due to the

alterations in the pathological standards. The inconsistency between the male and female ratios in some studies (particularly in some research that studied only male patients) and different geographical regions may also contribute to the existence of publication bias. Therefore, researchers chose to use the combined effect size estimation method based on the results of the heterogeneity tests. In this case, the use of the RE model ($l^2 > 50\%$) might have amplified the publication bias of the small sample size study due to the application of the equal-weight method [127][128]. Although sensitivity analyses showed relatively good stability of the effect sizes of OS biomarkers, the small number of studies, the differences in the quality of individual samples, and the use of the RE model might also lead to the poor quality of results. Additionally, the level of OS in female patients could not be studied due to the inclusion of research focusing mostly on male patients. Future investigations should be conducted involving both genders at equal ratios to eliminate the possibility of gender bias.

In summary, to obtain in-depth pathological information about the altered levels of OS markers in AD patients, special attention should be given to the number of studies and sample sizes with statistical significance, excluding other confounding factors (e.g., smoking, diabetes, etc.) and designing experimental plans with scientific rigor, including age- and gender-matched controls, as well as other possible factors.

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