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Invited Review

Oxidative damage and brain atrophy in alcoholics

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ABSTRACT

Generalized brain atrophy, especially affecting frontal lobes, hippocampus and cerebellum, is frequently observed in alcoholics. This alteration leads to cognitive dysfunction (that may affect 50-80% of alcoholics, even young people) and altered gait and movement disorders. Although several factors may contribute, oxidative damage, mainly due to increased production of reactive oxygen species plays an outstanding role in its pathogenesis, and will be reviewed in this manuscript. Among them, we can consider mechanisms directly dependent on ethanol metabolism; mechanisms related to increased cytokine secretion, partly dependent on ethanol-induced increased intestinal permeability, endotoxemia and micro RNA induction; mechanisms related to ethanol-mediated iron overload; mechanisms related to ethanol-derived toxic lipid synthesis; and mechanisms related to altered trace element and vitamin concentrations that can affect antioxidant systems. Despite the role of pro-oxidants, and in contrast with experimental data, no clear-cut benefit has been observed in clinical trials with antioxidants. Alcohol abstinence, together with adequate nutrition, still constitute the most effective therapeutic approach in these patients.

KEY WORDS: Encephalopathy, ethanol brain atrophy, cytokines, liver-brain axis, Wernicke's gut-brain axis

INTRODUCTION

Excessive ethanol intake leads to multisystem complications. Although liver disease is a hallmark of chronic ethanol abuse, most heavy alcoholics also show alterations of brain structure and function, which include a wide spectrum of organic diseases [1] and functional alterations [2]. Hippocampal atrophy is perhaps one of the most conspicuous manifestations of heavy alcoholism [3] and hippocampal damage is frequently provoked by experimental ethanol administration [4]. Ethanol intake also leads to generalized cortical atrophy (especially frontal lobe cortical atrophy) and cerebellar atrophy and this is perhaps pathogenetically related to hippocampal morphological and functional derangement given the central role of the hippocampus on neuronogenesis [5, 6]. These alterations lead to cognitive dysfunction (that may affect 50-80% of alcoholics) [7] and altered gait and movement disorders due to cerebellar alterations (which can be seen in about 42% of non-senile alcoholics) [8]. Possibly, cerebellum atrophy is also involved in cognitive and emotional deficiency [9]. Other entities, such as centropontine myelinolysis [10], Marchiafawa-Bignami disease [11], thiamine-deficiency derived Wernicke encephalopathy [12], and/or other vitamin-deficiency states are common [13]. In this sense, synergistic effects of ethanol, liver disease and nutritional alterations may be observed [14]. Overlapping features may occur: many alcoholics with thiamine deficiency also show cerebellar atrophy, brain atrophy and corpus callosum atrophy, without differences with those with normal thiamine levels [15]. In addition, alcoholics are prone to suffer ischemic stroke and subdural and intraparenchymal hemorrhage, which is perhaps also related to brain atrophy, as we will discuss later. Altered blood flow [16], which may improve after long-term abstinence [17], may also contribute to brain atrophy.

Brain atrophy involves both gray matter and white matter. Gray matter atrophy may be interpreted as the result of an imbalance between decreased neurogenesis and increased neuron degeneration. In murine models there is clear-cut evidence that ethanol alters neuronogenesis [18], a result in accordance with many observational studies in human beings [19]. However, other studies argue against this [20]. Impaired neurogenesis primarily affects the hippocampus, an area that harbours active neurogenesis [21] during the whole life span, although maximal activity is observed during adolescence and young adulthood [22]. This age interval coincides with that in which binge drinking is more common, which explains the severe alterations in brain structure and function observed among adolescent binge drinkers [23].

The mechanisms underlying brain atrophy are only partially known, although considerable research developed in the last two decades has shed light on several pathways that become directly or indirectly altered by ethanol. Most of these pathways lend support to the conclusion that oxidative damage plays a main role. In this review we will summarize some of the recent concepts regarding this topic.

WHY DOES ETHANOL CAUSE BRAIN DAMAGE THROUGH OXIDATIVE PATHWAYS?

(I) Increased reactive oxygen species (ROS) production

We can consider mechanisms directly dependent on ethanol metabolism; mechanisms related to increased cytokine secretion, partly dependent on ethanol-induced increased intestinal permeability, endotoxemia and micro RNA induction; mechanisms related to ethanol-mediated iron overload; mechanisms related to ethanol-derived toxic lipid synthesis; and mechanisms related to altered trace element and vitamin concentrations that can affect antioxidant systems (Figure 1). Several other alterations frequently observed among alcoholics heavily influence these mechanisms, especially protein-calorie malnutrition [24], the effect of liver disease [25], hepatic encephalopathy [26], or that of concurrent tobacco consumption [27]. They will not be discussed in depth in this review.

Direct effects of ethanol/acetaldehyde

Brain ethanol metabolism and ROS generation

In contrast with previous ideas, it was shown that acetaldehyde is formed in brain (microglia, astrocytes and neurons) after ethanol consumption, playing important roles in the neurobehavioral effects of ethanol [28, 29]. The acetaldehyde that is formed in brain derives mainly from the activity of catalase and the microsomal fraction cytochrome P450 2E1 (CYP2E1) [30], a metabolic pathway strongly activated by chronic ethanol intake [31]. Ethanol metabolism by CYP2E1 is coupled with increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a potent source of ROS [31] that is able to generate a superoxide anion when an electron is transferred from NADPH to oxygen. It was shown that ethanol leads to up-regulation of NADPH oxidase in microglia, neurons, and astrocytes [32] and that acetaldehyde is directly involved in this effect [33]. The increased production of ROS associated with ethanol intake activates nuclear factor-κB (NFκB) [34], a key transcription factor composed of several subunits [35] that is heavily involved in pro-inflammatory cytokine synthesis, especially tumor necrosis factor (TNF)-α [36].

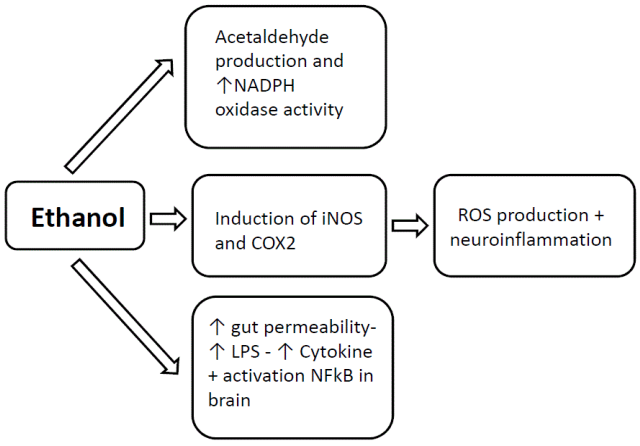

Figure 1. The increased production of reactive oxygen species (ROS) associated with ethanol intake activates nuclear factor-κB (NFκB) which activates synthesis of tumor necrosis factor (TNF)-α, which in turn increases production of ROS.

In vitro studies have shown that ethanol is also able to induce the synthesis of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 enzymatic systems [37], leading to increased prostaglandin synthesis and inflammation, and to increased production of highly reactive peroxynitrite which contributes to oxidative stress. In turn, oxidative stress increases blood brain barrier permeability [38], and causes cell injury [39] and mitochondrial alteration [40] that may exert a negative influence on ROS production . On the other hand, it is well known that TNF-α is a potent inductor of ROS generation [41], and, in conjunction with interferon gamma (IFN-γ), also increases the synthesis of reactive nitrogen species [42]. Therefore, ethanol metabolism itself is sufficient to cause oxidative stress in the central nervous system, closing a positive feed-back loop (Figure 2). In addition, several other mechanisms are involved.

Ethanol and iron excess

Brain iron accumulation may be another important factor involved in ethanol-mediated brain injury. Hypoxia inducible factors (HIF) constitute a family of heterodimeric proteins with two subunits: an oxygen-regulated α subunit (three different α (termed HIF-1α, -2α, -3α) subunits have been described until now [43]), and a stably expressed β subunit [44]. Under conditions of normal oxygen tension, the α subunits are hydroxylated at proline residues. Proline hydroxylation of the HIF-1α subunit promotes ubiquitination and its rapid proteosomal degradation [45]. On the contrary, hypoxia inhibits proline hydroxylation,

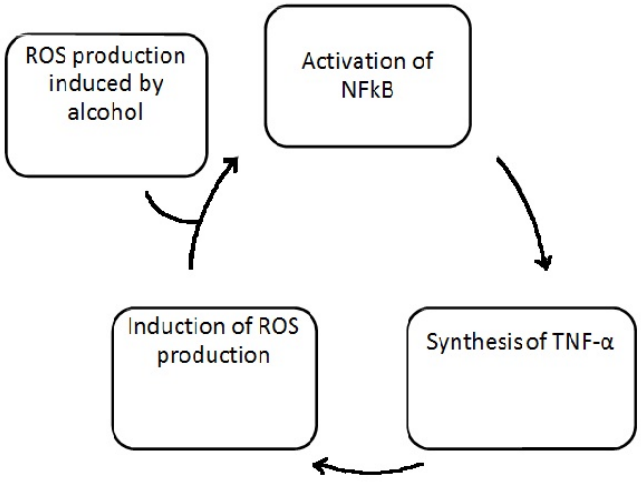

Figure 2. Ethanol metabolism is coupled with increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a potent source of reactive oxygen species. Ethanol also activates the synthesis of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 enzymatic systems which also lead to oxidative damage. Increased gut permeability caused by alcohol intake leads to the presence of endotoxin in brain which activates cytokine secretion and NFκB activation. All of this leads to neuro-inflammation and brain damage.

favoring coupling of the α subunit with the β subunit and allowing the heterodimer to bind to the hypoxia-responsive element in the promoter regions of the target genes that code for proteins involved in the adaptive response to hypoxia [46].

Induction of CYP2E1 by chronic alcoholism is accompanied by an increase in HIF-1α expression in relation to the enhanced oxygen consumption promoted by CYP2E1 activation, as shown by Wang et al [47] using CYP2E1 knock-out and knock-in mice. The increase in HIF promoted by ethanol metabolism has several consequences: HIF is involved in the synthesis of pro-inflammatory cytokines such as TNF-α, in the synthesis of NO [48, 49], in the induction of NADPH oxidase [50], and it also upregulates transferrin receptor 1 and increases iron cell accumulation [51]. In addition, interleukin (IL)-6, a cytokine that has been found increased in inflammatory conditions, enhances expression of hepcidin, a protein that blocks iron efflux from the cell [52].

However, this is not the only mechanisms which may lead to increased brain iron accumulation. After intraparenchymal hemorrhage, iron concentration increases several fold. This causes early edema and subsequent brain atrophy [53]. Patients with alcoholism usually present head injuries of variable severity, including those that cause intraparenchymal hemorrhage. In addition, although Marshall et al [54], failed to find increased permeability of the blood brain barrier in a 4-day binge drinking model, others did find that ethanol may induce blood-brain barrier leakage [55], that leads to extravasation of red blood cells to interstitial tissue, where they are destroyed, releasing heme and free iron, which in turn increases ferritin. Free iron is a dangerous compound that generates ROS and easily causes lipid peroxidation [56, 57], therefore causing further neuronal damage; ROS also cause a further increase in blood brain barrier permeability. Regarding the increased ferritin secretion, we have recently found a direct relationship between ferritin and brain and cerebellar atrophy in a group of 62 alcoholic patients [58]. Given the lifestyle of many alcoholics, the development of a recently described degenerative process characterized by abnormal accumulation of a tau protein is theoretically possible. The pathogenesis not completely known, and the disease has been described in athletes and soldiers who suffer repetitive brain trauma that leads to progressive brain function impairment [59].

Microglia activation

Chronic ethanol treatment in rats induces microglial activation [60], especially at the cortex and hippocampal dentate gyrus. Upon activation, these cells exhibit morphological changes that evolve in several stages, during which the cells change their phenotype and function [61]. There is some controversy regarding the consequences of such activation. In a binge drinking model, Marshall et al [54] described that although microglia was activated by ethanol, activation was only partial, leading to secretion of the antiregulatory cytokines IL-10 and transforming growth factor (TGF)-β, so that the function of microglia activated at that stage was rather protective than harmful. In contrast, Drew et al [62] showed in a neonatal murine model that the addition of ethanol during postnatal days 4 to 9 led to microglia activation and transformation of the cells into a pro-inflammatory phenotype, with increased secretion of IL-1β, TNF-α, and MCP-1. Hippocampus and cerebellum were the most involved areas. These pro-inflammatory cytokines and chemokines are all related to generation of more ROS, so that ethanol-mediated microglia activation also constitutes a main source of ROS.

The effect of ethanol itself, pro-inflammatory cytokines and ROS damage brain cells. Several families of sensors become activated by tissue injury (and/or microbial structures). Among them, the best known are the toll-like receptors, located on the surface of the cells, and the nucleotide binding oligomerization domain (NOD)-like receptors (NLR), that detect pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs) within the cell (in the cytosol). There are several NOD-like receptors (the best characterized is NLRP3) that can lead to the formation of inflammasomes, structures composed of several proteins able to activate caspases, that can be further classified into pro-inflammatory (for instance, Caspase-1) or pro-apoptotic. Caspase-1 induce the secretion of pro-inflammatory cytokines IL-18 and IL-1β. ROS can activate NLPR3 [63]. In vitro studies have also shown that astrocytes (especially at the dentate gyrus and corpus callosum) become activated by ethanol, probably via increased ROS generation by mitochondria. These astrocytes express enhanced NLPR3 inflammasome, and consecuently, more IL-1β and IL-18, contributing to increased inflammation, as shown by Guerri's group [64]. The same group also reported activation of TLR-4 directly by ethanol [65]. Strikingly, activation of NLRP3 did not take place in TLR-4 knock-out mice, suggesting that both sensor systems (TLRs and NLRs) are necessary to orchestrate an inflammatory response.

Ethanol and cytokine production: direct effects and the gut-brain axis

As mentioned above, pro-inflammatory cytokines (and also regulatory ones) are released during ethanol treatment in many experimental models, and raised levels have been also reported for alcoholic patients [66-68], also in spinal fluid [69]. Pro-inflammatory cytokines exert protean and sometimes antagonistic effects in the inflammatory response, also including increased ROS generation, so they are involved in oxidative damage. As mentioned in the aforementioned studies [64,65], it was shown that ethanol may directly activate TLR-4, an activation that in turn leads to increased expression of NFκB (adding to the direct effect

of ROS) and secretion of pro-inflammatory cytokines, such as IL-1β, TNF-α, monocyte chemoattractant protein (MCP)-1and IL-6 [70], whereas IL-8 and additional IL-1β derives from activation of NLRP3. Moreover, in an experimental in vitro model, Davis and Syapin [71] showed that ethanol potentiates the induction of NFκB mediated by cytokines. Ethanol consumption leads to a greater binding of NFκB to DNA, therefore favoring transcription of pro-inflammatory agents, and a reduced binding of the pro-survival, anti-apoptotic transcription factor c-AMP responsive element-binding protein (CREB) to DNA, coinciding with ethanol activation of oxidative stress [72]. CREB immunoreactivity shows a dramatic increase in dentate gyrus after 72 h of abstinence in experimental murine models [73].

As explained above, there is a local brain production of cytokines, and consequently ROS, but there are at least two additional mechanisms that contribute to a marked inflammatory effect in brain tissue in alcoholics. One of these mechanisms is related to direct activation of TLR-4 by (gut-derived) lipopolysaccharide, and a second one, from the effect of cytokines produced in distant organs that are transported to brain. These cytokines are able to cross the blood brain barrier [74] and to stimulate brain endothelial cells to produce additional cytokines [75].

Intestinal lumen harbors a great amount of Gram-negative bacteria. In normal conditions, they cross the colonic mucosa, both by receptor-mediated endocytosis and incorporated in chylomicrons [76]. This phenomenon is highly enhanced in several common diseases, notably heart failure [77], type 1 diabetes (perhaps even as a pathogenetic factor)[78], or hepatitis C virus disease [79] and among alcoholics [80]. Ethanol and, especially, acetaldehyde alter tight junctions in the intestinal mucosa, and also lead to bacterial overgrowth in the intestinal lumen [81]. An increased amount of circulating lipopolysaccharide further increases intestinal permeability [82]. Alterations in portal hemodynamics when liver disease ensues enhances this process [83]. Therefore, lipopolysaccharide reaches the portal vein and activates Kupffer cells, leading to cytokine secretion and triggering an inflammatory cascade of events that cause liver damage. The increased gut permeability, and the development of porto-systemic shunts when liver disease evolves, may overwhelm the Kupffer system, and lipopolysaccharide may enter the systemic circulation [84] and reach the brain. In the brain, endotoxin is recognized by the TLR-4, activating the NFκB cascade and leading to cytokine secretion, and ROS production. These alterations cause neuro-inflammation, and also inhibit hippocampal neurogenesis [86]. In a classic study, Qin et al [87] showed that systemic lipopolysaccharide administration caused a marked increase in brain TNF-α levels that remained high for 10 months leading to activation of microglia and increased expression of pro-inflammatory factors. Pre-treatment with ethanol markedly potentiates the effect of endotoxin on brain TNF-α, MCP-1 and IL-1β secretion [85]. Other TLRs, such as TLR-3 also become activated. In summary, this cascade of events finally leads to increased ROS production, especially in microglia and neurons of dentate gyrus and cortex, neuro-inflammation and neuro-degeneration, and is potentiated in binge drinking models [88].

At least in the liver there is an interaction between CYP2E1, lipopolysaccaride, and TNF-α, ROS derived from induction of CYP2E1 potentiate the harmful effects of the other two compounds [89]. In any case, the main ROS generated by this pathway include hydrogen peroxide and the anion superoxide [90]. When free iron is also present, more active ROS metabolites are formed, including hydroxyl radical and hydroxyethyl radicals [91]. MDA also increases [92] offering a substrate to form adducts, especially if antioxidants systems fail. Thus, these two last mechanisms may contribute to a more severe ROS derived lesion.

Micro RNA-associated oxidative stress

Considerable research has recently focused on the role of microRNAs in the inflammatory response, since it seems that they may modulate inflammation. The main target is attenuation of NFκB signaling. Indeed, certain micro(mi) RNAs negatively regulate this transcription factor, at least in endothelial cells, by targeting of TRAF6 and IRAK1, adaptor proteins acting in the metabolic pathway upstream of NFκB [93]. MiRNAs may also constitute key regulators of the blood-brain barrier function [94]. Some controversy exists regarding the effects of miRNAs on ethanol-induced brain inflammation: whereas Zhang et al [95] described an inhibition of the expression of proinflammatory factors in an in vitro study by miRNA-339-5p, others have shown that ethanol may induce (a different) miRNA production (miRNA-155) in the cerebellum, in a TLR-4 dependent fashion. This induction would lead to increased TNF- α and MCP-1 secretion by cerebellar microglia [96].

Toxic lipids: the liver-brain axis

An interesting field connecting brain damage and liver alterations resides in the potential effects of products derived from liver steatosis on brain function. Increased lipolysis and enhanced fat synthesis mediated by ethanol, together with impaired secretion of fat droplets lead to liver steatosis that may evolve to steatohepatitis. Excessive metabolism of lipids within the hepatocyte may cause stress in the endoplasmic reticulum, mainly due to excessive ROS formation. During lipolysis and sphingomyelin degradation, ceramide is formed and passes into bloodstream. It reaches the central nervous system, where it is able to cause insulin resistance by blocking phosphorylation events in the downstream insulin receptor signaling system [97], and activating pro-inflammatory cytokines [98]. In vitro studies have shown that liver derived ceramides are able to increase 4-hydroxynonenal and ubiquitin immunoreactivity in cultured neuronal cells

[99]. Even more, it seems that exogenous, liver derived ceramide can cause an increase in brain gene expression of ceramide genes.

In addition, ethanol alters the structure and permeability of cell membranes and its receptors, and this also affects insulin and insulin-like growth factor receptors in diverse areas of the central nervous system, as shown in a murine model by Cohen et al [100]. Probably, impaired receptor function was related to oxidative stress: loss of receptor expression was associated with neuronal loss and increased brain NADPH oxidase expression and altered acetylcholine metabolism [101].

Therefore, several mechanisms lead to increased production of harmful ROS. This increased production is not counteracted by an increase in antioxidant systems. On the contrary, ethanol and, especially, nutritional and liver alterations commonly observed in alcoholics strongly contribute to altered antioxidant defense. Some of these alterations will be discussed briefly below.

(II) Decreased antioxidant activity

Antioxidant systems include enzymatic pathways located within the cell and circulating molecules. Superoxide dismutases (SOD) are able to remove superoxide anion and transform it into the less toxic hydrogen peroxide [102]. Catalase and glutathione peroxidase (GPx) remove hydrogen peroxide; as mentioned above, ferritin, together with other molecules such as heme-oxygenase and ceruloplasmin are involved in removal of iron [103-105], and several other compounds including thioredoxin, glutathione transferase, metallothioneins, uric acid, bilirubin and several trace elements may also act as antioxidants [57], especially zinc (Zn), selenium (Se) and manganese (Mn), primarily as essential cofactors of antioxidant enzymes, and the antioxidant vitamins. There is some discrepancy regarding the effects of ethanol on enzyme activity. For instance, Bagheri et al [106] showed that acute ethanol administration reduced SOD significantly, whereas chronic intake increased it; they failed to find alterations in GPx, whereas catalase levels were decreased. In contrast, Ramezani et al [107] report a decrease in GPx, whereas no differences existed in SOD or catalase. On the other hand, Ibrahim et al [108] did find significant differences in these enzymes. Nordman et al [109] already stated that antioxidants were deficient in alcoholics, with SOD, alpha-tocopherol, ascorbate and selenium probably contributing to cerebellar oxidative stress and brain damage [110].

Many of the alterations in circulating antioxidants observed in alcoholics are not due to the effect of ethanol itself, but to associated conditions frequently observed in these patients, especially nutritional deficiency (for example, in the case of niacin deficiency) or liver disease (in the case of vitamin K). The unconventional lifestyle of many alcoholics, with impaired nutritional intake, probably leads to poor intake of many micronutrients, including trace elements, dietary antioxidants and vitamins. Therefore, pathogenesis of the eventual brain alterations suffered by these patients is multifactorial. It is out of the scope of this study to review in detail the antioxidant effect of each dietary antioxidant, vitamin, or trace element. Instead, we will discuss briefly the potential beneficial effects, due to its antioxidant properties, of some vitamins usually determined in the laboratory evaluation of the alcoholic patient, such as vitamin E, vitamin A, vitamin D, homocysteine, ascorbic acid and thiamine deficiency.

Vitamin E deficiency

Low levels of vitamin E have been described in alcoholics [111]. Malabsorption and poor nutrition and, perhaps, an increased demand of vitamin E by the liver [112, 113] may all contribute to this deficiency. The main effect of vitamin E is the protection of membrane phospholipids and polyunsaturated fatty acids from oxidation. Perhaps these mechanisms explain the protective effect against hippocampal apoptosis induced by a high cholesterol diet [114] against Alzheimer disease, as shown by Giraldo et al [115] both in in vitro studies and in transgenic mice, or the memory impairment observed with a high fat, high carbohydrate diet [116], among many other studies [117]. Apoptosis and deposit of β amyloid proteins take place in vitamin E deficient animals, especially affecting CA-1 pyramidal hippocampal cells [118]. Hippocampal neuronal damage was preceded by an alteration of collapsin response mediator protein 2 (CRMP-2), a cytoplasmic protein involved in normal axonal function, and enhanced expression of microtubule associated protein-light chain 3 (MAP-LC3), an autophagy-related protein, in possible relation to increased oxidative damage [119], leading to axonal dysfunction. A deleterious effect on Purkinje cells was also described [120]. In ethanol murine models Shirpoor et al [121] showed that vitamin E supplementation reverted the severe alterations observed especially in cerebellum and hippocampus in offspring's of Wistar rats treated with ethanol. A similar conclusion was obtained by Marino et al [122] who showed a partial recovery of the lack of CA-1 pyramidal cells observed in ethanol-treated pups.

Vitamin A deficiency

Although some studies show that vitamin A may exert some pro-oxidant effects [123], carotenoids also protect unsaturated fatty acids from oxidative damage [124], and therefore, vitamin A deficiency may be involved in brain alterations. In a similar fashion to what was observed with tocopherol deficiency, reduced hippocampal neurogenesis has been reported by several groups accompanied by functional impairment [125, 126], especially affecting memory and spatial learning. Hippocampal and functional recovery was achieved, at least partially, with vitamin A supplementation [127]. In alcoholics, vitamin levels are low

due to malnutrition and malabsorption [128]. In chronic alcoholics with strong microsomal induction, accelerated vitamin A catabolism also plays a role in low vitamin levels [129]. In human beings there are data that support a relationship between cognitive impairment and vitamin A deficiency [130], and alcoholics with cerebellar atrophy showed lower serum vitamin A [131].

Vitamin D deficiency

It has been recently shown that vitamin D may act as an antioxidant in brain [132]. Vitamin D is essential in maintaining the adequate levels of calcium within the cells. An excess of calcium within the nerve cell contributes to excitotoxicity and increased generation of ROS [133]. In addition, it was observed that vitamin D supplementation (at low doses) increases neuronal glutathione levels, an effect that strongly supports an antioxidant role of the vitamin [134]. Finally, vitamin D inhibits NO synthase, which might be responsible for an increase in peroxinitrite production, lending support to its role against oxidative damage; it also acts as an anti-inflammatory agent, inhibiting microglial production of TNF-α and IL-6 [135]. Several clinical observations agree with these effects: it seems that individuals with lower vitamin D levels showed cognitive impairment compared with those with normal vitamin D levels [136,137]. Moreover, vitamin D is involved in brain development [138] and vitamin D receptors have been identified in brain [139]. In alcoholics, renal metabolism may be diverted to the synthesis of the less active 24,25dihydroxyvitamin D [140]. This fact, together with nutritional disturbances, malabsorption and decreased sun exposure may explain the frequently observed low vitamin D levels in alcoholics [141] which might a play a role in brain oxidative damage.

Vitamin B12 alterations; hyperhomocysteinaemia

Cyanocobalamin deficiency is associated with brain atrophy [142], demyelination [143] and cognitive impairment [144], although probably, the relationship between vitamin B12 and cognitive impairment fits better with a U-shaped curve [145]. Moreover, in demyelination associated with vitamin B12 deficiency, increased TNF-α and IL-6 values have been reported, linking B12 deficiency to neuro-inflammation [146].

One of the consequences of vitamin B12 deficiency is hyperhomocysteinemia. Raised levels of homocysteine have been reported in alcoholics, but often without relation to B12 levels, but with those of folate or riboflavin [147]. In fact, in alcoholic patients with cirrhosis, vitamin B12 levels are frequently high, but despite this, homocysteine levels may be also raised [148]. In any case, hyperhomocysteinemia is related to hippocampal alterations [149, 150] and cognitive impairment [151], possibly in association with oxidative damage, given its ability to down-regulate glutathione peroxidase [152].

Vitamin C deficiency

Ascorbic acid acts as a scavenger of ROS: it oxidizes to monodehydroascorbic acid and dihydroascorbic acid [153], that are later deoxidized by the glutathione reductase activity, linking its function to selenium stores, which are low in alcoholics [154]. Although decreased vitamin C levels have been reported in patients with dementia [155], its role in brain atrophy in alcoholics is unclear. However, experimental data do support a beneficial effect on ethanol induced hippocampal neurodegeneration, [156, 157].

Thiamine deficiency and Wernicke encephalopathy

Thiamine deficiency leads to the so called Wernicke-Korsakoff encephalopathy, an acute situation suffered by alcoholics with variable degree of previous brain alterations. It is heavily dependent on oxidative damage, and possibly, thiamine deficiency exerts a synergistic effect with ethanol, at least regarding white matter shrinkage (for instance, atrophy of corpus callosum [158]) or cerebellar atrophy [159]. Thiamine deficiency is very common in alcoholics with prevalence ranging from 29.7% [160] to more than 50%, depending on diagnostic criteria utilized [161]. Inadequate intake, impaired absorption, a reduced liver storage, and decreased transformation of thiamine in its active form account for this deficiency among alcoholics. Several enzymes become affected in thiamine deficiency, the most important including pyruvate dehydrogenase, transketolase; α-ketoacid decarboxylase; and α-ketoglutarate dehydrogenase [162]. The impaired function of these enzymes leads to increased ROS production and further damage to mitochondria. ROS promote increased expression of nitric oxide synthase, and also an increase in blood brain barrier permeability, allowing iron to escape to the interstitium, and the already commented generation of a more intense oxidative damage and enhanced ROS formation. Therefore, in thiamine deficiency, oxidative damage plays an important role. The increased blood brain barrier permeability also leads to brain edema [163] which is reversible after thiamine supplementation. The impossibility to convert pyruvate to acetyl coenzyme A leads to lactic acidosis that also causes cytotoxic cerebral edema and induce neuronal death [164]. Increased ROS probably mediates glutamate mediated excitotoxicity, altering the function of complexins, proteins that regulate neurotransmitter release [165]. In addition, thiamine deficiency is accompanied by increased transcription of genes coding for pro-inflammatory cytokines and chemokines [166]. All these events may explain the stupor and coma characteristic of Wernicke encephalopathy, together with cerebellar alterations

and ophthalmoplegia, and the related manifestations of Korsakoff's dementia. As shown, thiamine deficiency shares some metabolic alterations with ethanol intake.

FUNCTIONAL CONSEQUENCES

Ethanol interacts with microtubule formation, a process that is crucial for neuronogenesis, synaptogenesis and cell migration [167]. Ethanol causes DNA oxidation which impairs learning in rats [168]; and, as shown, lipid peroxidation and an inflammatory response. All of these consequences lead to increased neuronal death and decreased neurogenesis. TNF-α potentiates glutamate excitotoxicity, linked to excessive glutamate activation of N-methyl-D-aspartate (NMDA) receptor. TNF-α reduces glial glutamate transporter activity and thus may also play a role in neurodegeneration. Increased glutamate is related to an increased desire to consume ethanol. Therefore, increased TNF-α would be related not only to brain damage, but also to alcohol dependence [169]. Binge drinking impairs memory and learning. This effect is more intense when alcohol is consumed during adolescence, just when binge drinking is more common [170]. In addition, disruption of executive frontal cortical function leads to impulsive behavior and loss of control, creating an impossibility to cut with alcohol consumption. Indeed, brain atrophy may predict future relapse in drinking habits: future relapsers showed smaller brain volumes in orbitofrontal cortex and surrounding white matter than no relapsers [171].

POTENTIAL THERAPIES FOR ALCOHOL-MEDIATED BRAIN ATROPHY

As discussed previously, brain atrophy induced by alcohol is due to several factors. While ethanol itself has a direct toxic effect on the brain, other factors that arise from alcohol exposure can also lead to brain atrophy. These factors include increased cytokine secretion, increased intestinal permeability with subsequent LPS-induced endotoxemia, the induction of miRNA, iron overload in brain cells, membrane lipid peroxidation, and vitamin and trace element deficiencies. Several strategies that target each step in neurodegeneration have been studied in animal models of alcoholism. These have also been studied in models of traumatic brain injury in which oxidative damage and lipid peroxidation also play a major role. However, just as in traumatic brain injury, the effectiveness of antioxidants in alcohol-induced brain damage has been mostly studied in animal models. Therefore, clinical trials are needed in which factors such as doses and toxicity are taken into account [172]. In addition to those already cited previously, some other studies will be commented below.

ROS scavengers and inhibition of lipid peroxidation

Tiwari and Chopra [173] have studied the use of curcumin, the active ingredient in turmeric, in the treatment of chronic cognitive dysfunction in rats that were exposed to ethanol. The use of curcumin prevented cognitive alterations by inhibiting the activation of inflammatory signaling pathways mediated by oxidative stress. The authors consider that curcumin could be potentially useful in alcoholic patients with cognitive dysfunction. In another study, Tiwari and Chopra [174] have also studied the use of other components found in fruits and vegetables in the prevention of alcohol-induced brain atrophy. They studied the effect of resveratrol, a phytoalexin found in the skin of red grapes, in the prevention of cognitive deficits induced by chronic alcohol exposure. Once again, they found that resveratrol prevented cognitive dysfunction and this was also mediated by the modulation of oxidative stress.

Skrzydlewska et al [175] studied the effect of green tea, which contains antioxidants called catechins, in rats that were chronically exposed to ethanol; they found that green tea protects cell membranes from lipid peroxidation and prevents the decrease of antioxidant activity. Luczaj et al [176] also studied the effect of black tea; they found that black tea prevented the detrimental effects of alcohol exposure in antioxidant activity in rats.

Protective effects of iron chelators

As mentioned above, iron overload in brain cells may be an important factor in ethanol-induced brain damage. The effect of iron chelators on alcoholic liver disease has been studied by Xiao et al [177]; they found that an iron chelator called M30 reduced ethanol-induced cell death and decreased production of ROS and pro-inflammatory cytokines. In a recent study by Zhang et al [178], it was shown that pretreatment of rats with the iron chelator deferoxamine attenuated the cognitive deficits induced by lipopolysacharide administration.

Vitamin and trace element supplementation

Tiwari et al [179] have shown that the administration of two isoforms of vitamin E (alpha-tocopherol and tocotrienol) to rats who were chronically exposed to ethanol prevented deficits in learning and behavior. However, they found that tocotrienol was more potent in preventing cognitive dysfunction. They attribute the differences between isoforms to the fact that tocotrienols have a better distribution in tissues such as brain and liver due to its unsaturated side chain. They suggest that vitamin E could be useful in treating patients with alcohol-induced cognitive dysfunction.

A class of antioxidants called lazaroids have been known for protecting cells from oxidative damage. A vitamin E derivative called U-83836E reduced lipid peroxidation in an animal model of myocardial ischemia/reperfusion injury [180]. However, Huang et al [181] have pointed out that lazaroid compounds are unable to modulate the late stages of cell injury and this may explain why lazaroids have not been effective in clinical and in vivo studies. In fact, Grisel

et al [182] studied the effect of U-83836E on cerebellar Purkinje cell injury in developing rat pups exposed to alcohol; they found that the antioxidant did not reduce the adverse effects on Purkinje cells.

Regarding trace elements, Menzano and Carlen [183] suggest that zinc supplementation can be used in the treatment of alcoholic encephalopathy due to the fact that zinc deficiency increases free radical formation and subsequently leads to neuronal injury. However, a study by Chen et al [184] showed that zinc supplementation in neonatal rats did not reduce cerebellar Purkinje cell loss induced by alcohol.

CONCLUSION

This review illustrates the main mechanisms by which ethanol ingestion alters brain structure and function. Confluence of several pathways, some of them closing positive feedback loops explain the devastating effects of chronic and binge ethanol consumption often exacerbated by nutritional alterations that impair antioxidant defensive mechanisms. Brain atrophy and ethanol-related brain dysfunction improve with ethanol abstinence. Alcohol abstinence, together with adequate nutrition, constitute the most effective therapeutic approach in these patients.

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