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The effect of omega-3 fatty acids on alcohol-induced damage

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Alcohol is the most widely consumed psychoactive substance in the world that has a severe impact on many organs and bodily systems, particularly the liver and nervous system. Alcohol use during pregnancy roots long-lasting changes in the newborns and during adolescence has long-term detrimental effects especially on the brain. The brain contains docosahexaenoic acid (DHA), a major omega-3 (n-3) fatty acid (FA) that makes up cell membranes and influences membrane-associated protein function, cell signaling, gene expression and lipid production. N-3 is beneficial in several brain conditions like neurodegenerative diseases, ameliorating cognitive impairment, oxidative stress, neuronal death and inflammation. Because alcohol decreases the levels of n-3, it is timely to know whether n-3 supplementation positively modifies alcohol-induced injuries. The aim of this review is to summarize the state-of-the-art of the n-3 effects on certain conditions caused by alcohol intake, focusing primarily on brain damage and alcoholic liver disease.

KEYWORDS

polyunsaturated fatty acids, n-3, ethanol, brain damage, liver disease

1. Introduction

Alcohol is a worldwide-consumed drug and its use depends on gender, age and health status. In 2016, 43.0% of the global adult population were current drinkers and caused 5.3% of all deaths (1). The average intake in the world is 13.9 grams of pure alcohol per day. Its use is more common and the consumption is the highest in the European Region (59.9%), followed by the Region of the Americas (54.1%) and the Western Pacific Region (53.8%).

Chronic heavy consumption of alcohol causes injuries in the organism, notably in the digestive, immune and central nervous system (CNS). The liver alcohol dehydrogenase metabolizes the acetaldehyde of alcohol making this organ particularly susceptible to lesion (2). Alcohol intake during pregnancy can result in damage in newborns with detrimental effects on memory (3) due to hippocampal and prefrontal cortical alteration (3, 4). In addition, alcohol use commonly starts during adolescence disrupting brain maturation and key processes of development. Binge drinking during adolescence has a long-lasting impact on hippocampal neurogenesis increasing cell death (5, 6) as well as on parahippocampal and neocortical structures altering brain plasticity, cognition and behavior (7–10). Likewise, we observed deficits in recognition, spatial and associative memory in early adulthood after chronic ethanol intake during adolescence (11, 12). Cognitive impairment in adult brain after adolescent alcohol intake correlates with changes in white matter, disrupted gray

matter (13), reduced hippocampal volume and low levels of brain-derived neurotrophic factor in the adult hippocampus (14, 15). Furthermore, loss of prefrontal gray matter associates with motor, emotional and memory deficits (16) and the blood flow is altered in prefrontal and parietal regions of the female brain (17). Glial cells are also responsive to the adolescent binge drinking insult through the TLR4/NFκB signaling cascade with the consequent inflammatory response and the long-term impaired behavior and cognition (18, 19). Moreover, because dysfunctional swelled astrocytes with much less cannabinoid CB1 receptors is a key feature in adult hippocampus upon cessation of adolescent binge drinking (20), astroglial anti-inflammatory response mediated by cannabinoid receptors in astrocytes (21) is likely altered in alcohol conditions.

The brain is mainly composed of lipids, particularly docosahexaenoic acid (DHA) (22:6n-3), a n-3 long-chain polyunsaturated FA (PUFA), and eicosapentaenoic acid (EPA, 20:5n-3) and, at lower levels, by the omega-6 (n-6) arachidonic acid (AA) (22). The content of DHA varies among regions and between neurons and glial cell types (22), is essential for membrane structure and function, membrane-associated protein function, cell signaling, gene expression and lipid production (23, 24), having potent anti-inflammatory effects (22). The detrimental impact of alcohol on DHA (25–28) impairs synaptic plasticity (29–31), particularly N-methyl-D-aspartate (NMDA)-dependent long-term potentiation (LTP) in the hippocampus (31) and medial prefrontal cortex (30), two brain regions enriched with DHA (22). Also, adequate EPA levels are needed for a proper acute behavioral response to alcohol (32).

Compelling evidences have shown that n-3 protects against some brain conditions, such as multiple sclerosis, depression or schizophrenia (33). In Alzheimer's and Parkinson's disease, n-3 FAs ameliorate cognitive impairment related to synaptic plasticity disturbance (34), diminish oxidative stress (34, 35) and reduce neuronal death (35). They also decrease inflammatory cytokine levels in various pathologies (35, 36).

2. Alcohol damage to the nervous system and omega-3

Alcohol use during pregnancy can result in fetal alcohol spectrum disorder (FASD), characterized by long-lasting physical, mental, behavioral and learning deficits due to damage of the CNS (37). In the 1990s, first pieces of evidence provided a link between n-3 and FASD, as proper n-3 intake, particularly DHA and EPA, ameliorated newborn brain and body weight reduction caused by alcohol (38, 39). All the abnormalities of the developing brain elicited by prenatal ethanol exposure (PNEE) imply behavioral changes. N-3 intake improves locomotion and, although not at all ages, anxiety-like behavior in FASD (39, 40). Furthermore, DHA reverses the PNEE deficits in somatosensory performance, social behavior and vocalization (41).

Distinct protocols of ethanol administration result in different effects on brain phospholipid composition, ranging from a reduction in some saturated FA (12:0, 14:0, and 16:0) and a rise in 18:0 without diet effects (38), to unaffected levels of saturated FA (39). Furthermore, the ethanol-induced increase in n-6 and decrease in n-3 elevates the net n-6/n-3 ratio that can be reversed by a diet enriched in n-3 (38, 39, 42). N-3 increases the levels of 18:2n-6 and 20:3n-6 FA (38, 39), but more contradictory is the rise in 18:1n-9 achieved by ethanol intake (38) and a DHA-enriched diet (39). Although PNEE and diet do not alter the protein carbonyl levels detected by spectrophotometry, n-3 reduces lipid peroxidation in the dentate gyrus and prefrontal cortex after PNEE, thus preventing brain oxidative stress in FASD (43, 44). Furthermore, n-3 intake restores glutathione levels dampened by PNEE in adulthood (44), despite the fact that neither alcohol nor diet influence the activity of the superoxide dismutase and catalase. Glutathione regulates the thiol redox state of the cells positively affecting NMDA receptor function and plasticity disrupted by PNEE in the dentate gyrus of adult males, and recovered by a diet enriched with n-3 from birth to adulthood (45) (**Figure 1**). Also, n-3 lowers the increased caspase-3 and calpain activity detected by p-nitroanilin absorbance and calcium- and non-calcium-dependent fluorescence in ethanol conditions, reducing cell injury, neurodegeneration, brain hemorrhage, congestion, necrosis, leukocytosis and microglia activation (43).

Chronic ethanol impairs both basal and forskolin induced cAMP-dependent neurogenic differentiation of neural stem cells (NSC), by decreasing adenylyl cyclase (AC) mRNA, phosphodiesterases (PDEs) activity, as well as by downregulating Cyclic adenosine monophosphate (cAMP) production by reducing G-protein activation analyzed by [γ-^{35}S] GTP binding assays. Ethanol also reduces Tuj-1 expression, an early stage of neural differentiation marker, and protein kinase A (PKA) and cAMP-response element binding protein (CREB) phosphorylation. Noticeably, synaptamide, a DHA metabolite analog of the endocannabinoid anandamide, ameliorates cAMP signaling and boosts the NSC differentiation impaired by ethanol (46) (**Figure 2**).

Alcohol intake in adulthood promotes oxidative stress and neurodegeneration particularly in the hippocampus, entorhinal cortex and olfactory bulb (28, 47, 48). It also increases aquaporin-4 (AQP-4) involved in glial edema (28, 47), and poli ADP-ribose polymerase-1 (PARP-1) that favors necrosis through glial activation (28). In addition, a rise in phospholipase A2 (PLA2) which mobilizes AA from membrane phospholipids, a major reactive oxygen species (ROS) source in brain conditions, was revealed by immunoblotting and scintillation spectroscopy after binge

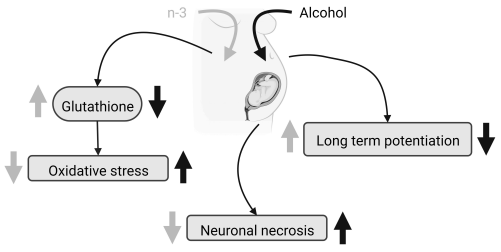

FIGURE 1
FASD and n-3 effects. Due to maternal ethanol intake, fetal glutathione decreases, oxidative stress augments, neuronal necrosis raises and LTP is impaired. Maternal n-3 enriched diet increases glutathione, decreases oxidative stress, reduces neuronal necrosis and rescues LTP, mitigating ethanol harmful effects. Created with www.Biorender.com.

ethanol (28, 48). Also, the ethanol-induced enhancement of 4-hydroxynonenal-adducted and 3-nitrotyrosinated (3NT) proteins, two oxidative footprints derived from AA and free radicals, were detected by immunoblot analysis (28). The ethanol-elicited DHA decrease shown by PI fluorescence labeling in cultures is detrimental, as this PUFA abolishes the changes in AQP-4, PLA2, PARP-1, and 3NT caused by alcohol with the consequent positive effects on neurodegeneration and oxidative stress (28, 47, 48). Likewise, DHA enrichment is able to counteract its own low brain levels due to alcohol (28).

3. Alcoholic liver disease and omega-3

In vitro investigations have shown opposite effects of the main n-3 FAs on hepatocyte damage caused by ethanol, with their more significant impact on lipid rafts (49, 50). Thus, EPA promotes membrane remodeling by phospholipase C (PLC) translocation into lipid rafts, enhancing the oxidative stress and cell death of ethanol that can be diminished by vitamin E and membrane stabilizers (49). In contrast, DHA prevents the harmful ethanol effects on hepatocytes by inhibiting PLC relocation into lipid rafts (50).

Oxidative stress causes membrane lipid peroxidation, impairs mitochondrial function and decreases antioxidant enzymatic activity, all together leading to liver damage (51). DHA mitigates PNEE-induced fetal liver enlargement and reduces alcohol rise of liver oxidative stress by normalizing the excess of glutathione reductase mRNA and the deficit in glutathione peroxidase mRNA, as detected by real-time quantitative polymerase chain reaction (52). Like in FASD, the increased liver-to-body weight ratio elicited by alcohol is reduced by n-3 in adulthood (53, 54). Ethanol increases ROS and reactive nitrogen species, thus rising lipid peroxidation measured by levels of hepatic malondialdehyde (55). The increase in CYP2E1 and, therefore, in ROS and acetaldehyde production (54, 55), as well as in inducible nitric oxide synthase that rises hydrogen peroxide and nitrite (55) point to the alcohol challenge of mitochondrial function. Also, conventional Oil Red O and hematoxylin and eosin staining revealed lipid droplets (54, 56, 57) and hepatocellular ballooning (54, 55) caused by alcohol disruption of the FA enzymatic metabolism (55). Compelling pieces of evidence have shown that n-3 reduces ROS (54, 55) and DHA supplementation promotes heme oxygenase-1 protein and mRNA against oxidative stress and cell death (54, 56).

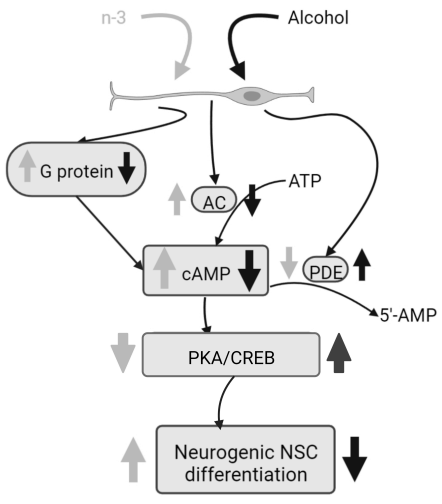

FIGURE 2
Alcohol damage of neurogenic NSC differentiation and n-3 effects. Alcohol decreases G protein and AC activation, consequently cAMP signaling is downregulated and PKA and CREB phosphorylation are increased, having a negative impact on NSC differentiation. PDE activity is upregulated by alcohol. However, n-3 intake improves cAMP signaling, decreasing PKA/CREB that promotes NSC differentiation. Also, n-3 downregulates PDE. Created with www.Biorender.com.

N-3 reduces adipose lipolysis and FA biosynthesis (53). DHA binds to the G protein-coupled receptor 40 in hepatocytes downregulating the sterol regulatory element-binding protein 1 (SRBEP-1) that controls gene expression of lipogenic enzymes (54, 57, 58), thus decreasing triglycerides and cholesterol accumulation in liver caused by alcohol consumption (55, 57). Furthermore, n-3 diminishes gene expression and activation of lipolytic enzymes and promotes adipose tissue storage (53) as well as FA oxidation by activation of peroxisome proliferator-activated receptor alpha (PPARα) (54, 57). This results in the decrease in lipid droplets and hepatocellular ballooning ameliorating liver steatosis (55, 57, 59) (**Figure 3**). In fact, DHA supplementation combined with extra virgin olive oil prevents the fall of PPARα mRNA and its target genes in animals fed in a high fat diet to induce hepatic steatosis (60). The n-3 enrichment also decreases alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin, lowers n-6/n-3 ratio and suppresses ethanol liver inflammation by reducing pro-inflammatory cytokines (53, 54, 56, 59, 61). Finally, lipolysis increase, high free FA flow to the liver, pro-inflammatory cytokines rise, FA oxidation dysregulation and *de novo* lipogenesis, are common features in both ethanol-induced liver injury and non-alcoholic fatty liver disease (NAFLD) (62). All these changes have been linked to the existence of a chronic detrimental low-grade inflammatory state in the adipose tissue (62). Lipid mediators generated from EPA (E series resolvins) and DHA (D series resolvins, protectins, maresins) (62) have anti-inflammatory properties contrary to n-6 derivatives (59). In fact, current pieces of evidence indicate that the antioxidant, anti-inflammatory and anti-apoptotic effects of DHA on metabolic diseases, including NAFLD, are mediated by resolvins (63–65).

4. Other organs damaged by alcohol and the effects of omega-3

DHA alleviates testosterone fall due to early ethanol exposure and recovers the low steroidogenic acute regulatory protein mRNA caused by PNEE in adolescence, responsible for cholesterol transport into mitochondria needed for testosterone synthesis. Also, DHA increases sperm number and morphology in adulthood (66). Diets enriched in both DHA and EPA modify phospholipid FA composition in rat gastric mucosal cells (67). Likewise, n-3 enriched diet (but not EPA alone) reduces the stomach lesion due to alcohol-induced gastric hemorrhage. Combined exposure to ethanol and palmitoleic acid (POA) increases

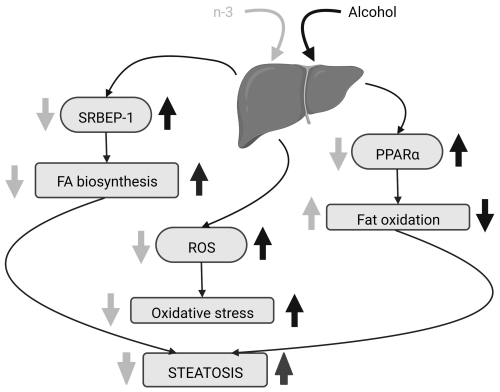

FIGURE 3
Alcohol-induced hepatic steatosis and n-3 effects. The increase in SRBEP-1 and ROS by alcohol elevates liver FA biosynthesis and oxidative stress, respectively, and alcoholic PPARα rise reduces liver fat oxidation. The consequence is steatosis. N-3 enriched diet lowers SRBEP-1 and ROS, decreasing liver FA biosynthesis and oxidative stress. It also promotes liver fat oxidation by downregulating activation of PPARα. Altogether, n-3 ameliorates steatosis. Created with www.Biorender.com.

intracellular and mitochondrial ROS in AR42J pancreatic cells that results in a significant increase in the necroptosis mediator receptor-interacting protein and mixed lineage kinase domain-like pseudokinase. EtOH/POA also promotes calcium overload and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activation. However, DHA suppresses EtOH/POA-induced ROS increase, necroptosis mediators and NADPH oxidase activity, thus dodging cell loss (68). Acute ethanol exposure decreases angiogenesis by reducing microvascular endothelial cell migration and tubulogenesis, as well as impairs wound healing measured by the relative epithelial gap and granulation tissue area. Interestingly, the DHA metabolite 14S, 21-diHDHA improves wound healing and increases vascularization, counteracting alcohol damage (69).

5. Conclusion

Alcohol elicits long-lasting body damage being one leading death cause surpassing diabetes, AIDS and tuberculosis (37). Compelling pieces of evidence have shown that n-3 intake, including maternal n-3 consumption, has beneficial effects in alcohol-elicited neurodegeneration, particularly in FASD, and alcoholic liver damage, also improving alcoholic gastric hemorrhage (67), pancreatitis (68) and angiogenesis (55) (**Supplementary Table 1**).

N-3, particularly EPA and DHA, and its derivatives reduce oxidative stress and inflammation, and decrease cell death in several pathological conditions (24, 33, 70, 71) through different mechanisms closely related to microglial activity. Thus, they modulate gene expression by surface and intracellular receptors, reducing pro-inflammatory cytokines and eicosanoids as well as promoting lipid mediators to resolve inflammation (72–74). Few receptors for DHA and EPA derivatives are known and most of them are highly expressed in microglial cells such as PPARs (75, 76). They also increase microglial phagocytic activity and their anti-inflammatory phenotype in various pathological conditions (77–79). The DHA rise in n-3 enriched diet promotes DHA incorporation into cell membranes. Membrane changes particularly in glial cells have consequences on pro-inflammatory receptor localization and related signaling cascades (80). Not the least, EPA lowers AA and DHA antagonizes the pro-inflammatory effects of AA products (81).

Despite the promising results described, more studies are needed in order to decipher the n-3 efficacy and dose required to alleviate the harmful effects of ethanol. Furthermore, the pathways by which n-3 PUFAs and their derivatives have their beneficial effects should be investigated in detail.

Author contributions

PG: article idea. MS: literature search, data analysis, and original draft preparation. MS, IR-B, and PG: writing—review and editing. IR-B and PG: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1068343/full#supplementary-material

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